

Original Research

ACDNet: Attention-guided Collaborative Decision Network for effective medication recommendation

Jiacong Mi, Yi Zu, Zhuoyuan Wang, Jieyue He *

School of Computer Science and Engineering, Key Lab of Computer Network and Information Integration, MOE, Southeast University, Nanjing, 210018, Jiangsu, China

ARTICLE INFO

Keywords:

Medication recommendation
Data mining
Electronic health record
Attention mechanism
Transformer

ABSTRACT

Medication recommendation using Electronic Health Records (EHR) is challenging due to complex medical data. Current approaches extract longitudinal information from patient EHR to personalize recommendations. However, existing models often lack sufficient patient representation and overlook the importance of considering the similarity between a patient's medication records and specific medicines. Therefore, an Attention-guided Collaborative Decision Network (ACDNet) for medication recommendation is proposed in this paper. Specifically, ACDNet utilizes attention mechanism and Transformer to effectively capture patient health conditions and medication records by modeling their historical visits at both global and local levels. ACDNet also employs a collaborative decision framework, utilizing the similarity between medication records and medicine representation to facilitate the recommendation process. The experimental results on two extensive medical datasets, MIMIC-III and MIMIC-IV, clearly demonstrate that ACDNet outperforms state-of-the-art models in terms of Jaccard, PR-AUC, and F1 score, reaffirming its superiority. Moreover, the ablation experiments provide solid evidence of the effectiveness of each module in ACDNet, validating their contribution to the overall performance. Furthermore, a detailed case study reinforces the effectiveness of ACDNet in medication recommendation based on EHR data, showcasing its practical value in real-world healthcare scenarios.

1. Introduction

Medication recommendation is an important part of healthcare, helping to find the best treatment plans by comparing patient histories, medicine information, and other data with medical knowledge. It uses technologies like machine learning, natural language processing, and data mining to improve treatment, reduce bad drug reactions, and boost patient well-being. Electronic health records (EHR) [1] have led to large, complex data sets with patient details, reports, and medication records. Medication records are key parts of EHR, providing vital info for doctors. As a result, using EHR data for medication recommendation is a main focus in recent medical studies.

In recent years, with the continuous development of machine learning and deep learning, medication recommendation models based on deep learning have attracted increasing attention [2]. These models can be divided into instance-based [3,4] and longitudinal-based [5–13] categories. Instance-based medication recommendation models solely rely on patients' current health information, neglecting past health data and medication records, which limits their effectiveness. In contrast, longitudinal-based models provide a more comprehensive understanding of patients' conditions, thereby improving the effectiveness of

medication recommendation. However, longitudinal-based medication recommendation models still face challenges and problems. Firstly, certain studies [7,11,12] utilize GRU or RNN to encode patients' EHR information, which makes it challenging to capture the comprehensive health information of patients from a global perspective. Secondly, some studies [6,9,10] disregard the importance of patients' medication records, overlooking the crucial combinations of medications that significantly impact patients' well-being.

To address these challenges, we propose the Attention-guided Collaborative Decision Network (ACDNet) model for medication recommendation. ACDNet utilizes attention mechanism and Transformer to effectively capture important information from the patient's historical visits and medication records at both the local and global levels, thereby providing more comprehensive medication recommendations. Firstly, ACDNet employs attention mechanism and Transformer to encode patients' visit information at both the local and global levels, generating representations for their health conditions and medication records. Secondly, it incorporates various domain-specific knowledge to comprehensively model medications. Finally, ACDNet utilizes

* Corresponding author.

E-mail address: jieyuehe@seu.edu.cn (J. He).

collaborative decision network to recommend the most suitable medications for patients based on their medical history and the similarity between their medication records and available medicines.

In addition to the widely used MIMIC-III dataset [14], we conducted experiments on the latest MIMIC-IV dataset [15]. Compared to MIMIC-III, MIMIC-IV offers more abundant medical data. The experimental results indicate that ACDNet model demonstrates significant improvements in accuracy and effectiveness compared to existing models in medication recommendation. Our main contributions are summarized as follows:

- We employ attention mechanism and Transformer to effectively capture the health conditions and medication records of a patient by modeling his historical visits at both local and global levels.
- We incorporate a collaborative decision mechanism to provide personalized medication recommendation by leveraging various medical information from a patient's history of visits, as well as diverse medicine information.
- We conduct extensive experiments on both the MIMIC-III and MIMIC-IV datasets, demonstrating the effectiveness of our proposed approach in comparison to existing methods.

2. Related works

In recent years, various medication recommendation methods [9, 11] have incorporated molecular information as external knowledge to improve the accuracy and effectiveness of medication recommendation. In this section, we discuss two research directions: medication recommendation and molecular representation.

2.1. Medication recommendation

Medication recommendation can be classified into instance-based and longitudinal-based categories. The former recommends medicines based on patients' current visit information, while the latter utilizes patients' historical visit information to predict future medication requirements. In instance-based medication recommendation, LEAP [4] employs RNN and attention mechanism to model current information, introducing reinforcement learning to prevent adverse drug combinations. SMR [3] uses EHR data and medical knowledge graphs to construct a heterogeneous graph, transforming the medication recommendation problem into a link prediction problem. In longitudinal-based medication recommendation, RETAIN [5] proposes a two-level neural attention model effectively capturing relevant information in patients' visits. GAMENet [7] uses RNN to model visit information, incorporating drug interaction information to represent medications. MICRON [10] employs residual networks to predict changes in health conditions, focusing on analyzing the differences between two consecutive visits. SafeDrug [11] is the first to model drug molecules and proposes a new loss function to reduce drug interaction rates. COGNet [16] employs Transformer to encode visit and medicine information, comparing current visit information with previous visits to make comprehensive judgments. DRMP [6] uses GRU and graph neural networks to capture relationships between visits, introducing a DDI Gating Mechanism to decrease drug interaction rates. FFBDNet [9] incorporates various external knowledge sources and employs a binary decision network for medication recommendation. OntoPath [17] is a novel framework that employs an ontology-aware hierarchical-attention model to predict suitable drug treatments. Despite the progress achieved by existing medication recommendation methods, challenges and shortcomings still persist in adequately representing patient information and providing effective medication recommendations for patients.

2.2. Molecular representation

Molecular representation transforms structures into numerical vectors for predicting properties and functions. Presently, graph neural network (GNN)-based methods [18–20] are considered effective means for learning high-quality molecular representations. Both MPNN [21] and Chemprop [22] are GNN methods based on message-passing mechanism. The former updates atomic embedding vectors by exchanging information between atoms and bonds, while the latter uses self-supervised learning to improve the quality of molecular representations, learning atom-level representations by predicting partial charges for each atom in the molecule and averaging or summing these representations to form molecule-level representations. D-GCAN [23] is a deep learning method based on graph convolutional attention networks, combining graph convolution and attention mechanism to extract feature vectors for atoms and bonds in molecular structures. D-GCAN uses graph convolution for molecular representation and then employs graph attention to calculate the importance of atoms and bonds within the molecule, ultimately forming the molecular representation. Current molecular representation techniques may encounter difficulties in capturing complex molecular features and interdependencies, necessitating further research to enhance the accuracy of predicting molecular properties and functions.

3. Problem formulation

In medication recommendation, we utilize patient EHR data and external medicine information to provide personalized medicine suggestions for patients. Below are the definitions of EHR data, medicine information, and medication recommendation.

3.1. Electronic health records (EHR)

In the EHR dataset, each patient is represented by sequential data $X^{(n)} = [x_1^{(n)}, x_2^{(n)}, \dots, x_{T(n)}^{(n)}]$. Each record $x_t = [c_t^d, c_t^p, c_t^m]$ ($t < T$) contains diagnosis codes c_t^d , procedure codes c_t^p , and medication codes c_t^m . The current medical record $x_T = [c_T^d, c_T^p]$ consists of diagnosis codes c_T^d and procedure codes c_T^p but excludes medication codes. For simplicity, medical code $c_i^* \in \mathbb{N}^{I_i^*}$ is utilized to represent the standardized definition of various medical code types where $\mathbb{N} \in [0, |C^*|]$, C^* is the medical code set and I_i^* is the number of medical codes in c_i^* .

3.2. EHR and DDI graph

The EHR graph $G^E = \{V^E, E^E\}$ and DDI graph $G^D = \{V^D, E^D\}$ both have node sets $V^E = C^M$ and $V^D = C^M$, representing all medicines. E^E corresponds to known medication combinations in the EHR database, while E^D represents known drug–drug interactions from an external knowledge base. The adjacency matrices $A^E, A^D \in \mathbb{R}^{|C^M| \times |C^M|}$ help clarify the construction of edge sets E^E and E^D , respectively.

3.3. Molecular graph

Molecular graph for medication $m_i \in C^M$ can be represented as $G^{m_i} = \{V^{m_i}, E^{m_i}\}$, where V^{m_i} is the node set consisting of all molecular units of medication m_i , and E^{m_i} is the edge set of known molecular structures of m_i . So the adjacency matrix for each medicine molecule can be represented as A^{m_i} .

3.4. Medication recommendation

Given the current time T , medical codes $x_T = [c_T^d, c_T^p]$ that only include diagnoses and procedures, as well as the medical records $X = [x_1, x_2, \dots, x_{T-1}]$ from the previous $T - 1$ times and graphs $G^E, G^D, \{G^{m_i}, i \in [1, \dots, |C^M|]\}$, the aim is to obtain a multi-class output $\hat{o} \in \{0, 1\}^{|C^M|}$ of medicines while minimizing the interactions between them.

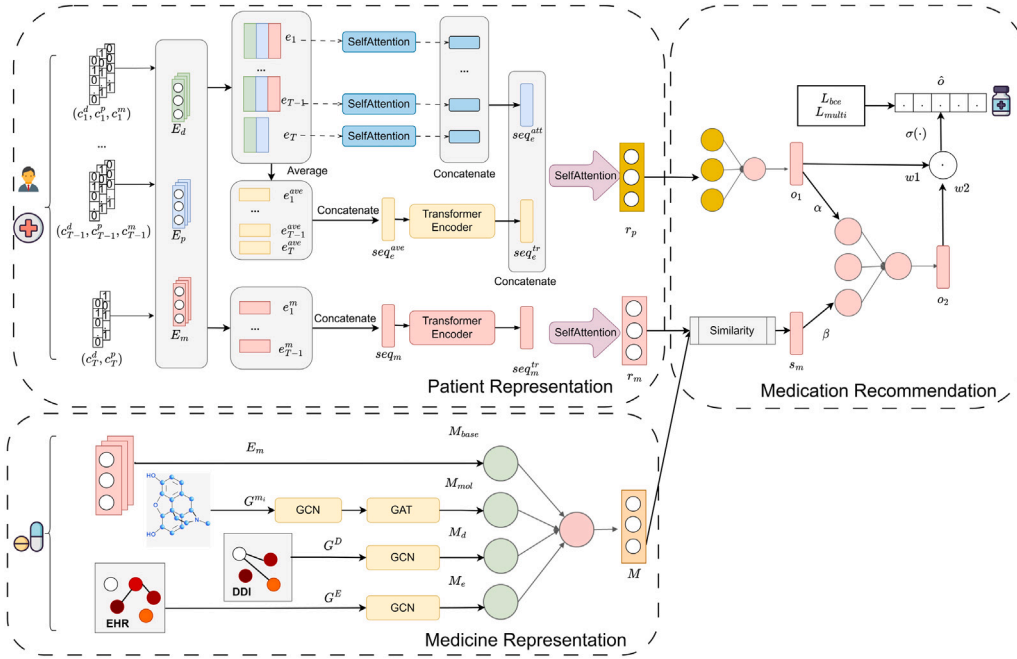


Fig. 1. The architecture of ACDNet.

4. Method

Our ACDNet model has three modules: a patient representation module, a medicine representation module, and a medication recommendation module. In the patient representation module, we utilize attention mechanism and Transformer encoder to extract essential information from historical medical records, creating the patient's representations of their past visits and medication history from both local and global perspectives. The medicine representation module encodes the medicine molecular graph and uses the EHR and DDI graphs to generate medicines' vector representation. Finally, the medication recommendation module employs a collaborative decision mechanism to determine the medication to recommend for the patient. The ACDNet model's architecture is shown in Figure 1.

4.1. Patient representation

By leveraging a patient's past health information and medication records, we can gather a significant amount of information related to their well-being. During the ongoing medical consultation, we further determine the patient's latest health condition. By integrating the collected data, we can conduct a thorough evaluation of the patient's health and provide customized medication recommendation. Specifically, we initially represent each visit as a vector using the EHR Embedding module. Following this, with the application of techniques such as attention mechanism and Transformer encoder, we obtain encoded representations of visit sequences and medication records sequences. Finally, by employing the self-attention mechanism, we generate a vector representation of the patient's historical health and medication records, establishing a foundation for subsequent personalized recommendation.

4.1.1. Attention module

We employ the Self-Attention mechanism to effectively capture valuable information from a sequence vector of length L . This mechanism allows us to focus on the most relevant parts of the sequence, considering the relationships and dependencies among different elements, ultimately enhancing our ability to extract significant insights from the sequence data.

$$\text{SelfAttention}(v) = \text{softmax}(\tanh(v \cdot W_{a1})W_{a2})^T \cdot v \quad (1)$$

where $v \in R^{L \times \text{dim}}$ represents the new input sequence, $W_{a1} \in R^{\text{dim} \times \text{dim}}$, $W_{a2} \in R^{\text{dim} \times 1}$. The output dimension of the sequence is R^{dim} .

4.1.2. Transformer encoder module

During the encoding process, the Transformer encoder [24] can capture important information from the historical visit records and medication records. The Transformer encoder consists of L Transformer encoder Layers, and for the i th layer, its output is:

$$Z^{(i)} = \text{LayerNorm}(\text{MultiHeadAttention}(seq^{(i)}, seq^{(i)}, seq^{(i)}) + seq^{(i)}) \quad (2)$$

$$F^{(i)} = \text{LayerNorm}(\text{FeedForward}(Z^{(i)}) + Z^{(i)}) \quad (3)$$

Describing MultiHeadAttention, we have the following expressions:

$$\text{MultiHeadAttention}(Q, K, V) = \text{Concat}(\text{head}_1, \text{head}_2, \dots, \text{head}_h)W^O \quad (4)$$

$$\text{Attention}(Q, K, V) = \text{softmax}\left(\frac{QK^T}{\sqrt{d_k}}\right)V \quad (5)$$

Here, $\text{head}_i = \text{Attention}(Q_i, K_i, V_i)$ denotes the computation for each attention head, where $\sqrt{d_k}$ serves as the scaling factor, and W^O represents the output weight matrix utilized for the linear transformation and aggregation of results from various attention heads to yield the ultimate output.

The final output of the Transformer encoder is:

$$\text{TransformerEncoder}(seq) = \text{LayerNorm}(seq + \text{sum}(F^{(1)}, \dots, F^{(L)})) \quad (6)$$

where sum is the pooling operation that involves adding up the results.

4.1.3. Local representation module

Based on the previous context, the vector $x_i = [c_i^d, c_i^p, c_i^m]$ represents the representation of a visit. To refine the processing of these vectors, we have devised three embedding operations, $E_d: \mathbb{N}^{l^d} \rightarrow R^{l^d \times \text{dim}}$, $E_p: \mathbb{N}^{l^p} \rightarrow R^{l^p \times \text{dim}}$, and $E_m: \mathbb{N}^{l^m} \rightarrow R^{l^m \times \text{dim}}$, facilitating their mapping into the embedding space. Explicitly, upon querying each vector within

the embedding operations, we obtain the respective embedded vectors, culminating in the subsequent result:

$$\begin{aligned} e_t^d &= E_d(c_t^d) \\ e_t^p &= E_p(c_t^p) \\ e_t^m &= E_m(c_t^m) \end{aligned} \quad (7)$$

To obtain the sequential representation of the visit x_t , we concatenate the following three vectors:

$$e_t = [e_t^d \parallel e_t^p \parallel e_t^m] \quad (8)$$

where $e_t \in R^{l \times dim}$, l is the sum of l_t^d, l_t^p and l_t^m . Consequently, by executing an averaging operation on this vector, we ascertain the current visit's average representation:

$$e_t^{ave} = average(e_t) \quad (9)$$

where $e_t^{ave} \in R^{dim}$ and *average* denotes the vector's averaging operation.

Our goal is to enhance the performance of the model by capturing the interaction information between medical codes. To achieve this, we employ self-attention mechanism to calculate the interdependencies among the medical code features within the current input sequence, in order to capture the important information from each patient visit. Thus, by applying the self-attention mechanism, we can model the information of a patient's visit at time t and obtain a local representation of the patient's visit history:

$$v_t^{att} = SelfAttention(e_t) \quad (10)$$

where $v_t^{att} \in R^{dim}$. Subsequently, we concatenate vectors to acquire the attention representation sequence for the patient's T visits:

$$seq_e^{att} = [v_1^{att} \parallel v_2^{att} \parallel \dots \parallel v_T^{att}] \quad (11)$$

where $seq_e^{att} \in R^{T \times dim}$.

4.1.4. Global representation module

Although ACDNet and COGNet [16] both utilize Transformer encoders, they exhibit significant differences in how they encode patient information. In COGNet, the model employs the Transformer to encode medical records for individual visits, with a specific focus on capturing the relationships between various medical codes within each visit. In contrast, ACDNet treats each visit as a vector, arranging all visits into a sequence processed through a Transformer encoder to emphasize the relationships between distinct visits.

We handle the complete set of patient visit and medication records separately, enabling the capture of essential information at a global level throughout the patient's entire visit history. The patient's health status and medication records after T visits can be represented as:

$$seq_e^{ave} = [e_1^{ave} \parallel e_2^{ave} \parallel \dots \parallel e_T^{ave}] \quad (12)$$

$$seq_m = [e_1^m \parallel e_2^m \parallel \dots \parallel e_{T-1}^m] \quad (13)$$

where $seq_e^{ave} \in R^{T \times dim}$ and $seq_m \in R^{(T-1) \times dim}$. Then, we input them into the Transformer encoder separately to obtain the encoded vectors:

$$seq_e^{tr} = TransformerEncoder(seq_e^{ave}) \quad (14)$$

$$seq_m^{tr} = TransformerEncoder(seq_m) \quad (15)$$

where $seq_e^{tr} \in R^{T \times dim}$ and $seq_m^{tr} \in R^{(T-1) \times dim}$.

4.1.5. Represent module

After processing with the attention mechanism and the Transformer encoder, we can obtain the representations of the patient's health status and medication records after T medical visits. For the patient's health information representation, we concatenate the two patient health status sequences and perform a self-attention operation:

$$r_p = SelfAttention(seq_e^{att} \parallel seq_e^{tr}) \quad (16)$$

where $r_p \in R^{dim}$. Similarly, we perform a self-attention operation on the medication records sequence:

$$r_m = SelfAttention(seq_m^{tr}) \quad (17)$$

where $r_m \in R^{dim}$.

4.2. Medicine representation

To improve the effectiveness of medication recommendation and better express medicine information, we employ various methods to model medicines, including EHR graph, DDI graph, and molecular graphs. First, we use a basic embedding table to represent all medicines. Then, we introduce graph neural networks to encode the graph information. Finally, we aggregate all representation information to obtain the final medicine representation. As shown in Eq. (7), we use the learned Embedding table E_m as the base representation for all medicines:

$$M_{base} = E_m(C^M) \quad (18)$$

where $M_{base} \in R^{|C^M| \times dim}$.

As mentioned earlier, we obtained the EHR Graph and DDI Graph with their adjacency matrices represented as A^E and A^D , respectively. Inspired by the use of GCN [25] to encode graph information in GAMENet [7], we apply GCN separately to the EHR graph and DDI graph, given the graph adjacency matrix A^* :

$$\tilde{A}^* = \tilde{D}^{-\frac{1}{2}} (A^* + I) \tilde{D}^{-\frac{1}{2}} \quad (19)$$

where \tilde{D} is a diagonal matrix of A^* and I are identity matrices. Then, we can obtain the graph representation:

$$M^* = \tilde{A}^* \sigma(\tilde{A}^* W_{g1}^*) W_{g2}^* \quad (20)$$

where σ is a nonlinear activation function, $W_{g1}^* \in R^{|V^*| \times dim}$, $W_{g2}^* \in R^{dim \times dim}$ are learnable parameters. Based on the above formula, we obtain the EHR Graph representation $M_e \in R^{|C^m| \times dim}$ and DDI Graph representation $M_d \in R^{|C^m| \times dim}$.

Medicine molecules can be represented in the form of molecular graphs, where nodes represent atoms and edges represent chemical bonds between atoms. Inspired by D-GCAN [23], we adopt GCN [25] and GAT [26] to represent molecules. For each molecule G^{m^i} with adjacency matrix A^{m^i} , we first obtain $M_g^{m^i} \in R^{|V^{m^i}| \times dim}$ through Eqs. (19) and (20). Then, using GAT and Readout function, we get:

$$M^{m^i} = READOUT(GAT(M_g^{m^i})) \quad (21)$$

where $M^{m^i} \in R^{dim}$ is the vector representation of the i th medicine molecule. Finally, we obtain the representations of all molecules:

$$M_{mol} = [M^{m^1} \parallel M^{m^2} \parallel \dots \parallel M^{m^{|C^M|}}] \quad (22)$$

where $M_{mol} \in R^{|C^M| \times dim}$ represents the molecular graph information of all drugs. Ultimately, we obtain the final medicine representation:

$$M = NN_{med}(M_{base} \parallel M_e \parallel M_d \parallel M_{mol}) \quad (23)$$

where $NN_{med}(\cdot) : R^{4dim} \rightarrow R^{dim}$ is a fully connected feedforward neural network, and $M \in R^{|C^M| \times dim}$ incorporates various medicine information, which is beneficial for similarity calculations with the patient's medication information.

4.3. Medication recommendation

Drawing inspiration from FFBDNet [9], our medication recommendation system incorporates two modules that work collaboratively to provide medication suggestions for patients. The direct module primarily focuses on the patient's representation to recommend suitable medicines. On the other hand, in contrast to FFBDNet, the indirect

module takes into account the similarity between the patient's medication records and medicine representation. By integrating the patient's medication history, which contains valuable information about relevant medicines, we aim to simulate the decision-making process of a prescribing doctor. This integration enables us to generate comprehensive personalized medication recommendation based on the patient's specific medication history.

In the direct recommendation module, we use the patient representation and a feedforward neural network to recommend suitable medicines directly:

$$o_1 = \text{NN}_{o_1}(r_p) \quad (24)$$

where $o_1 \in R^{|C^m|}$ is the result of the direct recommendation, and $\text{NN}_{o_1}(\cdot) : R^{\text{dim}} \rightarrow R^{|C^m|}$ is a learnable feedforward neural network.

The indirect recommendation module integrates the patient's medication records in EHR with the representations of medicines and calculates the similarity between them. This similarity calculation mimics the prescribing behavior of healthcare professionals, selecting the most important combination of medications from all the patient's medication records.

$$s_m = \text{Cosine Similarity}(r_m, M) = \frac{r_m \cdot M^T}{\|r_m\| \cdot \|M\|} \quad (25)$$

where $s_m \in R^{|C^m|}$ is the similarity between medication records and medicines.

Then, we concatenate the direct recommendation o_1 and similarity results and input them into a neural network to obtain the indirect recommendation result:

$$o_2 = \text{NN}_{o_2}(\alpha o_1 \parallel \beta s_m) \quad (26)$$

where $o_2 \in R^{|C^m|}$ is the output result of indirect recommendation based on similarity, $\text{NN}_{o_2}(\cdot) : R^{2 \times |C^m|} \rightarrow R^{|C^m|}$ is a fully connected feedforward neural network, and $\alpha, \beta \in R^1$ are trainable parameters.

In the collaborative decision-making recommendation process, direct patient EHR-based recommendations take precedence, constituting the primary component, whereas similarity-based recommendations assume a supplementary role. Consequently, we use these two modules to derive the ultimate recommendation result:

$$\hat{o} = \sigma(w_1 \odot o_1 + w_2 \odot o_2) \quad (27)$$

where σ is a nonlinear activation function, $w_1, w_2 \in R^{|C^m|}$ are learnable parameters to adjust the two recommendation modules, and $\hat{o} \in R^{|C^m|}$ is the output medication recommendation result.

4.4. Training and inference

To suggest medicine combinations, we treat this task as a multi-label prediction problem. During training, we use two common multi-label loss functions: binary cross-entropy loss (L_{bce}) and multi-label margin loss (L_{multi}). Binary cross-entropy loss handles multi-label binary classification problems by calculating binary cross-entropy loss for each label and summing them up. Multi-label margin loss accounts for label correlations, producing smoother predictions.

$$L_{bce} = -\sum_i^{|C^m|} y_i \log(\hat{o}_i) + (1 - y_i) \log(1 - \hat{o}_i) \quad (28)$$

$$L_{multi} = \sum_{i,j: y_i=1, y_j=0} \frac{\max(0, 1 - (\hat{o}_i - \hat{o}_j))}{|y|} \quad (29)$$

where $y \in \{0, 1\}^{|C^m|}$ is the true label set of recommended medicines. Therefore, the final Loss is represented as:

$$L = \lambda L_{bce} + (1 - \lambda) L_{multi} \quad (30)$$

where $\lambda \in R$ is a predefined parameter.

In ACDNet training, we combine these loss functions for better prediction performance, as detailed in **Algorithm 1**.

Algorithm 1: One training epoch of ACDNet

Input: Training set $X^{(n)} = [x_1^{(n)}, x_2^{(n)}, \dots, x_{T(n)}^{(n)}]$, EHR graph A^E , DDI graph A^D , molecular graph $\{A^{m_i}, i \in [1, \dots, |C^m|]\}$

- 1 Generate the medicine representation M according to Eqs. (18)–(23);
- 2 **for** patient $i = 1$ to N **do**
- 3 Read the patient i 's history x_1, x_2, \dots, x_T ;
- 4 **for** history visit $t = 1$ to T **do**
- 5 Read the historical diagnoses, procedures, medicines of the patient at the t^{th} visit
 $[c_1^d, c_2^d, \dots, c_t^d], [c_1^p, c_2^p, \dots, c_t^p], [c_1^m, c_2^m, \dots, c_{t-1}^m]$;
- 6 Generate embeddings e_t and e_t^{ave} by Eqs. (7)–(9);
- 7 Generate visit v_t^{att} using self-attention by Eq. (10);
- 8 Generate sequences $seq_e^{att}, seq_e^{tr}, seq_m^{tr}$ by Eqs. (11)–(15);
- 9 Generate patient representation r_p and medication records representation r_m by Eqs. (16)–(17);
- 10 Generate similarity s_m by Eq. (25);
- 11 Generate output \hat{o} by Eqs. (24), (26)–(27);
- 12 Generate and accumulate L_{bce}, L_{multi} in Eqs. (28)–(29);
- 13 Optimize the combined loss L in Eq. (30)

Table 1

Statistics of the datasets.

	MIMIC-III	MIMIC-IV
# patients	6350	64 462
# clinical events	15 032	171 295
# diagnoses	1958	2000
# procedures	1430	1500
# medicines	131	131
Avg/max # of visits	2.37/29	2.66/66
Avg/max # of diagnoses	10.51/128	8.54/228
Avg/max # of procedures	3.84/50	2.22/72
Avg/max # of medicines	11.44/65	6.54/72
Total # of DDI pairs	448	448

5. Experiment

To validate the effectiveness of ACDNet, we conducted experiments on two publicly available datasets, which can be divided into the following three sections:

- In comparative experiments, we assessed the performance of ACDNet and baselines on both datasets.
- In the parameter experiments, we explore different parameter combinations in the parameter experiments to find the optimal model configuration for ACDNet.
- In ablation experiments, we separately verified the effectiveness of each module in ACDNet.
- Additionally, we performed case validation, demonstrating the practical application of ACDNet in real-world scenarios.

5.1. Dataset

We employed MIMIC-III [14] and MIMIC-IV [15] as sources for our experimental data. For the MIMIC-IV dataset, diagnoses and procedures are based on ICD-9 and ICD-10 codes. To process this information, we initially converted ICD-10 coded data to ICD-9 coded data [27]. In accordance with the data processing methods utilized in GAMENet [7] and SafeDrug [11], we processed the datasets, resulting in the data presented in **Table 1**.

5.2. Baselines and metrics

We compare our model with the baselines below.

- LR is a instance-based classifier with L2 regularization.
- ECC [28] is an ensemble model for multi-label classification with correlated labels.
- RETAIN [5] is an interpretable healthcare model using reverse time attention.
- LEAP [4] captures label dependencies and prevents adverse drug interactions with reinforcement learning.
- GAMENet [7] recommends safe medication combinations using graph-augmented memory networks.
- SafeDrug [11] is a DDI-controllable drug recommendation model utilizing molecular structures.
- MICRON [10] predicts medication changes based on patient health using recurrent residual networks.
- COGNet [16] generates medicine sets for patients based on diagnoses with a copy-or-predict mechanism.
- DRMP [6] is a drug recommendation model using message propagation and DDI gating mechanism.
- FFBDNet [9] is a feature fusion and bipartite decision network for medication combination recommendation.

We evaluate the prediction performance using several metrics, including DDI rate, Jaccard similarity score (Jaccard) [29], Average F1 score (F1), PR-AUC [30], precision@k and nDCG@k, to assess the safety, accuracy, and effectiveness of our model.

5.3. Implementation details

In line with previous research efforts [7,11], we divided the dataset into training, validation, and test sets at a 4:1:1 ratio. Our model is implemented using Python 3.9.15 and PyTorch 1.12.1 [31], with training and testing conducted on Intel Xeon CPU and NVIDIA 3080Ti GPU. After conducting parameter experiments, optimal hyperparameters were selected within the model, with the embedding dimension size set at 64 and λ set at 0.97. For the Transformer encoder, we selected a configuration with 8 attention heads and 6 layers. Due to varying dataset sizes, a learning rate of 0.0015 was established for the MIMIC-III dataset, and 0.0002 for the MIMIC-IV dataset. We utilized the Adam optimizer to refine the model. For all baseline models, we used the optimization parameters mentioned in the literature for training and testing on the MIMIC-III dataset. Similarly, for the MIMIC-IV dataset, we re-optimized the parameters for all baseline models to ensure their optimal performance. According to SafeDrug [11], in the evaluation process, instead of conducting cross-validation, we apply bootstrapping sampling. Specifically, we randomly sample 80% of the data points from the test set for one round of evaluation. We perform 10 rounds of sampling and evaluation, and report the mean and standard deviation values.

5.4. Performance comparison

Table 2 presents the performance of various models on the MIMIC-III dataset. ACDNet outperforms the baseline models in terms of Jaccard, PR-AUC, and F1 metrics, demonstrating its effectiveness in capturing both local and global patient information and facilitating collaborative decision-making. The results suggest that longitudinal-based models are more accurate than instance-based approaches, as they can better capture patients' historical health information, leading to improved patient representations. In terms of reducing the drug-drug interaction (DDI) rate, SafeDrug performs well due to its utilization of DDI loss to minimize the DDI rate. However, it is important to note that the actual DDI rate is 0.08379, and ACDNet's results closely resemble the real dataset, indicating its reliability and alignment with the genuine data.

Table 3 presents the performance of various models on the MIMIC-IV dataset. Similar to the MIMIC-III dataset, longitudinal-based models prove more accurate than instance-based approaches on the MIMIC-IV

dataset. Although the LEAP model performs well in DDI, its accuracy is inferior to other models. To enhance SafeDrug's accuracy, we set its DDI threshold to 0.1. The results reveal that despite SafeDrug's lower DDI value, its accuracy remains subpar compared to other models. The MICRON model primarily focuses on differences between adjacent visits and performs poorly on the more complex MIMIC-IV dataset. COGNet, DRMP, and FFBDNet exhibit satisfactory performance on the MIMIC-IV dataset, yet still fall short of ACDNet. ACDNet excels in Jaccard, PR-AUC, and F1 metrics, signifying its superior capability in obtaining patient health information and medication representations compared to other models.

Tables 4 and 5 display the precision and nDCG results on the MIMIC-III and MIMIC-IV datasets. Since the average number of recommended medications in the MIMIC-III and MIMIC-IV datasets is 11.44 and 6.54, respectively, we opted for K values of 5 and 10. From the results, it is evident that ACDNet outperforms other models in all metrics except precision@10, confirming its effectiveness in recommendations. DRMP, which uses GNN and GRU to model patient information, has shown promising results in precision@k. However, its use of message-passing mechanisms to capture information between adjacent visits requires a longer training period. LEAP does not perform well, possibly because its reinforcement learning process for sequential decisions may not effectively meet the requirements of recommendations. Similarly, the information capture between adjacent visits in MICRON does not yield strong results.

5.5. Parameter influence

In this section, we will evaluate the performance of ACDNet on the MIMIC-III dataset using various parameter settings. Specifically, we will explore different combinations of λ values and embedding dimensions to identify the optimal configuration that yields the best results.

Firstly, with a fixed embedding dimension of 64, we explored different λ values. As shown in Fig. 2, the Jaccard, PR-AUC, and F1 scores reach their peak when λ is set to 0.97.

Subsequently, with a fixed learning λ value of 0.97, we examined the impact of different embedding dimensions. The results, depicted in Fig. 3, indicate that an embedding dimension of 64 yields the highest Jaccard, PR-AUC, and F1 scores.

5.6. Ablation study

In the section, we removed some components of the ACDNet model to observe their impact on model performance.

- ACDNet $w/o M_e, M_d$: We remove the EHR graph and DDI graph from input.
- ACDNet $w/o M_{mol}$: We remove the medicine molecular from input.
- ACDNet $w/o att$: We change the all self-attention to mean operation.
- ACDNet $w/o seq_e^{att}$: We remove the patient representations that have undergone self-attention.
- ACDNet $w/o seq_e^{tr}$: We remove the patient representations that have undergone Transformer Encoder.
- ACDNet $w GRU$: We replace the Transformer encoder with GRU.
- ACDNet $w RNN$: We replace the Transformer encoder with RNN.
- ACDNet $w o_1$: We remove vectors related to the medication record, such as seq_m^{tr}, r_m, M, s_m , and o_2 , retaining only the patient EHR representation for recommendation.

The results from Table 6 indicate that, while the removal of the EHR graph and DDI graph has a relatively minor impact on the final results, their importance may become more pronounced in specific use cases or lay the foundation for future enhancements, thus making them integral to the model's comprehensive design. Furthermore, the inclusion of medication molecular structure information also contributes to

Table 2

Performance comparison on MIMIC-III.

Models	Jaccard	PR-AUC	F1	DDI	Avg_Med
LR	0.4865 ± 0.0021	0.7509 ± 0.0018	0.6434 ± 0.0019	0.0829 ± 0.0009	16.1773 ± 0.0942
ECC	0.4996 ± 0.0049	0.6844 ± 0.0038	0.6569 ± 0.0044	0.0846 ± 0.0018	18.0722 ± 0.1914
RETAIN	0.4887 ± 0.0028	0.7556 ± 0.0033	0.6481 ± 0.0027	0.0835 ± 0.0020	20.4051 ± 0.2832
LEAP	0.4521 ± 0.0024	0.6549 ± 0.0033	0.6138 ± 0.0026	0.0731 ± 0.0008	18.7138 ± 0.0666
GAMENet	0.5067 ± 0.0025	0.7631 ± 0.0030	0.6626 ± 0.0025	0.0864 ± 0.0006	27.2145 ± 0.1141
SafeDrug	0.5213 ± 0.0030	0.7647 ± 0.0025	0.6768 ± 0.0027	0.0589 ± 0.0005	19.9178 ± 0.1604
MICRON	0.5100 ± 0.0033	0.7687 ± 0.0026	0.6654 ± 0.0031	0.0641 ± 0.0007	17.9267 ± 0.2172
COGNet	0.5336 ± 0.0011	0.7739 ± 0.0009	0.6869 ± 0.0010	0.0852 ± 0.0005	28.0900 ± 0.0950
DRMP	0.5312 ± 0.0015	0.7757 ± 0.0016	0.6854 ± 0.0011	0.0865 ± 0.0006	22.7300 ± 0.2300
FFBDNet	0.5292 ± 0.0020	0.7777 ± 0.0010	0.6833 ± 0.0017	0.0717 ± 0.0016	19.6900 ± 0.3000
ACDNet	0.5433 ± 0.0027	0.7904 ± 0.0021	0.6957 ± 0.0021	0.0859 ± 0.0010	20.4900 ± 0.1197

Table 3

Performance comparison on MIMIC-IV.

Models	Jaccard	PR-AUC	F1	DDI	Avg_Med
LR	0.4510 ± 0.0013	0.7290 ± 0.0014	0.6007 ± 0.0013	0.0762 ± 0.0004	8.9866 ± 0.0374
ECC	0.4233 ± 0.0010	0.7284 ± 0.0012	0.5680 ± 0.0019	0.0771 ± 0.0003	8.1070 ± 0.0235
RETAIN	0.4239 ± 0.0017	0.6798 ± 0.0018	0.5791 ± 0.0017	0.0939 ± 0.0015	10.8602 ± 0.0736
LEAP	0.4287 ± 0.0012	0.5506 ± 0.0015	0.5820 ± 0.0012	0.0592 ± 0.0004	11.5198 ± 0.0459
GAMENet	0.4507 ± 0.0013	0.7174 ± 0.0012	0.6043 ± 0.0014	0.0890 ± 0.0003	18.4426 ± 0.0474
SafeDrug	0.4651 ± 0.0016	0.7118 ± 0.0016	0.6117 ± 0.0014	0.0740 ± 0.0004	14.4705 ± 0.0575
MICRON	0.4554 ± 0.0026	0.6842 ± 0.0025	0.6088 ± 0.0032	0.0637 ± 0.0016	15.6963 ± 0.2875
COGNet	0.4884 ± 0.0009	0.7087 ± 0.0008	0.6367 ± 0.0009	0.0894 ± 0.0003	19.7235 ± 0.0242
DRMP	0.4913 ± 0.0015	0.7338 ± 0.0021	0.6435 ± 0.0018	0.0872 ± 0.0013	15.0512 ± 0.0365
FFBDNet	0.4970 ± 0.0010	0.7435 ± 0.0012	0.6454 ± 0.0009	0.0838 ± 0.0004	11.2906 ± 0.0658
ACDNet	0.5077 ± 0.0015	0.7501 ± 0.0017	0.6564 ± 0.0013	0.0849 ± 0.0005	12.7024 ± 0.0005

Table 4

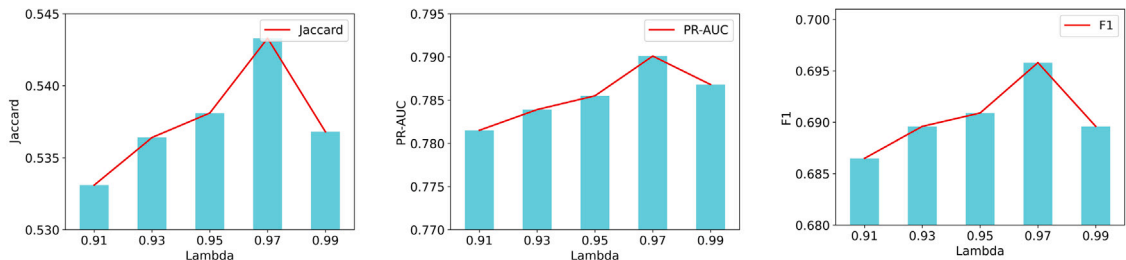
Recommendation performance comparison on MIMIC-III.

Model	precision@5	precision@10	nDCG@5	nDCG@10
LR	0.8852 ± 0.0043	0.8075 ± 0.0035	0.8982 ± 0.0045	0.8404 ± 0.0038
ECC	0.8851 ± 0.0033	0.8111 ± 0.0024	0.8993 ± 0.0038	0.8433 ± 0.0026
RETAIN	0.8913 ± 0.0046	0.8126 ± 0.0033	0.9016 ± 0.0040	0.8436 ± 0.0030
LEAP	0.7211 ± 0.0042	0.6772 ± 0.0040	0.7411 ± 0.0041	0.7033 ± 0.0039
GAMENet	0.8953 ± 0.0054	0.8224 ± 0.0051	0.9079 ± 0.0049	0.8534 ± 0.0046
SafeDrug	0.8964 ± 0.0040	0.8200 ± 0.0023	0.9088 ± 0.0037	0.8518 ± 0.0022
MICRON	0.8655 ± 0.0061	0.8131 ± 0.0040	0.8740 ± 0.0054	0.8354 ± 0.0039
COGNet	0.8913 ± 0.0037	0.8114 ± 0.0030	0.9045 ± 0.0027	0.8450 ± 0.0024
DRMP	0.9003 ± 0.0032	0.8290 ± 0.0028	0.9097 ± 0.0024	0.8575 ± 0.0021
FFBDNet	0.9029 ± 0.0042	0.8349 ± 0.0041	0.9136 ± 0.0043	0.8633 ± 0.0040
ACDNet	0.9061 ± 0.0034	0.8400 ± 0.0026	0.9137 ± 0.0026	0.8660 ± 0.0021

Table 5

Recommendation performance comparison on MIMIC-IV.

Model	precision@5	precision@10	nDCG@5	nDCG@10
LR	0.7910 ± 0.0019	0.6581 ± 0.0016	0.8156 ± 0.0019	0.7154 ± 0.0016
ECC	0.7858 ± 0.0017	0.6571 ± 0.0013	0.8105 ± 0.0014	0.7132 ± 0.0012
RETAIN	0.7374 ± 0.0036	0.6109 ± 0.0029	0.7594 ± 0.0035	0.6645 ± 0.0029
LEAP	0.5571 ± 0.0023	0.5139 ± 0.0023	0.5567 ± 0.0027	0.5275 ± 0.0024
GAMENet	0.7722 ± 0.0014	0.6398 ± 0.0011	0.7944 ± 0.0016	0.6954 ± 0.0011
SafeDrug	0.7740 ± 0.0018	0.6379 ± 0.0019	0.7974 ± 0.0019	0.6955 ± 0.0019
MICRON	0.7583 ± 0.0022	0.6236 ± 0.0021	0.7801 ± 0.0023	0.6796 ± 0.0022
COGNet	0.7609 ± 0.0012	0.6359 ± 0.0014	0.7870 ± 0.0011	0.6918 ± 0.0011
DRMP	0.7938 ± 0.0016	0.6692 ± 0.0013	0.8150 ± 0.0017	0.7218 ± 0.0014
FFBDNet	0.7931 ± 0.0011	0.6546 ± 0.0017	0.8157 ± 0.0010	0.7125 ± 0.0014
ACDNet	0.8005 ± 0.0020	0.6647 ± 0.0020	0.8235 ± 0.0019	0.7221 ± 0.0019

**Fig. 2.** Impact of λ values on MIMIC-III Dataset.

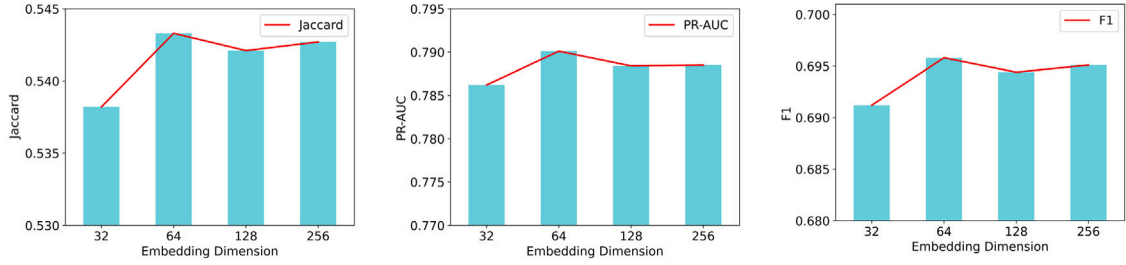


Fig. 3. Impact of Embedding Dimensions on MIMIC-III Dataset.

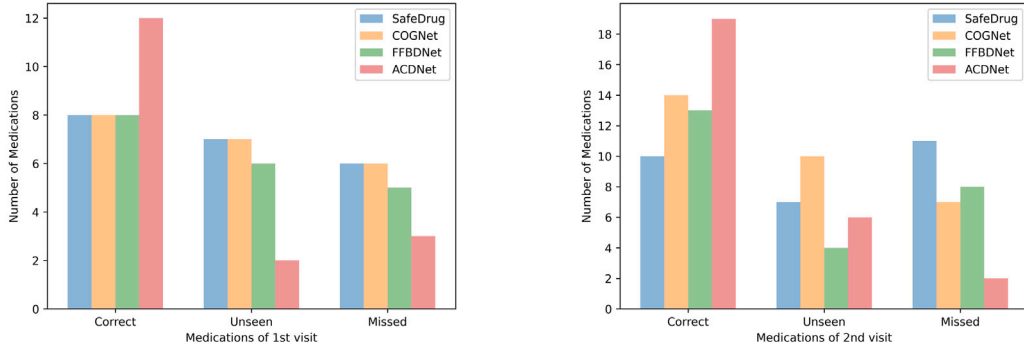


Fig. 4. Recommended Medications of Patient A.

Table 6
Ablation study on MIMIC-III.

Models	Jaccard	PR-AUC	F1	DDI	AVG_Med
ACDNet <i>w/o</i> M_e, M_d	0.5423 \pm 0.0015	0.7888 \pm 0.0022	0.6947 \pm 0.0022	0.0861 \pm 0.0009	20.4650 \pm 0.1077
ACDNet <i>w/o</i> M_{mol}	0.5398 \pm 0.0022	0.7861 \pm 0.0024	0.6927 \pm 0.0021	0.0817 \pm 0.0008	20.8585 \pm 0.1200
ACDNet <i>w/o</i> att	0.5350 \pm 0.0016	0.7845 \pm 0.0020	0.6887 \pm 0.0016	0.0815 \pm 0.0009	20.7952 \pm 0.1420
ACDNet <i>w/o</i> seq_e^{att}	0.5001 \pm 0.0029	0.7430 \pm 0.0029	0.6568 \pm 0.0026	0.0914 \pm 0.0007	22.0030 \pm 0.1511
ACDNet <i>w/o</i> seq_e^{ir}	0.5357 \pm 0.0020	0.7834 \pm 0.0014	0.6893 \pm 0.0019	0.0814 \pm 0.0007	21.2701 \pm 0.1517
ACDNet <i>w</i> GRU	0.5355 \pm 0.0022	0.7814 \pm 0.0023	0.6888 \pm 0.0020	0.0861 \pm 0.0009	21.1938 \pm 0.1440
ACDNet <i>w</i> RNN	0.5323 \pm 0.0024	0.7762 \pm 0.0025	0.6860 \pm 0.0022	0.0844 \pm 0.0010	21.2428 \pm 0.1564
ACDNet <i>w</i> o_1	0.5297 \pm 0.0025	0.7789 \pm 0.0024	0.6840 \pm 0.0023	0.0889 \pm 0.0008	20.0775 \pm 0.0993
ACDNet	0.5433 \pm 0.0027	0.7904 \pm 0.0021	0.6957 \pm 0.0021	0.0859 \pm 0.0010	20.4900 \pm 0.1197

the effectiveness of medication representation. When the self-attention mechanism is eliminated from the ACDNet model, a noticeable decline in performance is observed, underscoring the critical role of the attention mechanism in the model. After removing patient representations processed by self-attention, the model's performance significantly deteriorated. This indicates the vital role of self-attention in capturing each visit in a patient's history. The results obtained by removing the Transformer or replacing it with RNN or GRU in ACDNet emphasize the superiority of the Transformer encoder in comprehensively capturing essential information from patients' visit records and medication records. Moreover, when the collaborative decision-making component is removed, leaving only the direct recommendation part, a significant reduction in performance is evident. This emphasizes the significance of similarity-based collaborative decision-making in the model's overall effectiveness.

Overall, these findings demonstrate the importance of incorporating EHR and DDI graphs, attention mechanism, Transformer encoder, and collaborative decision-making in ACDNet to achieve superior performance in medication recommendation tasks.

5.7. Case study

To investigate the effectiveness of ACDNet under different numbers of visits, we selected two patients, one with 2 visit records and the other with 5 visit records. We employed four models, namely

SafeDrug, COGNet, FFBDNet, and ACDNet, for medication recommendations. Figs. 4 and 5 display the recommendation results, where "Correct" refers to medications that were accurately recommended. "Unseen" denotes medications predicted by the model but not found in the actual data, while "Missed" indicates medications present in the actual data that the model failed to predict.

For patient A, who had only two visit records, ACDNet displayed remarkable precision in medication recommendations, and the occurrence of unseen medications was notably minimal. This underscores the robust effectiveness of ACDNet in medication recommendations, as it consistently minimizes the occurrence of erroneous medication suggestions.

In the scenario of patient B, who had a more extensive medical history with five visit records, ACDNet maintained its exceptional performance. It delivered a considerably higher number of accurate medication recommendations when compared to other models. This emphasizes the model's consistent excellence in catering to patients with a richer medical journey, establishing ACDNet as a reliable choice for medication recommendation across diverse patient profiles.

6. Conclusion

Medication recommendation constitutes a crucial application of data mining within the biomedical domain. However, existing models grapple with inadequacies concerning patient information and medicine representation. To address these issues, this study introduces

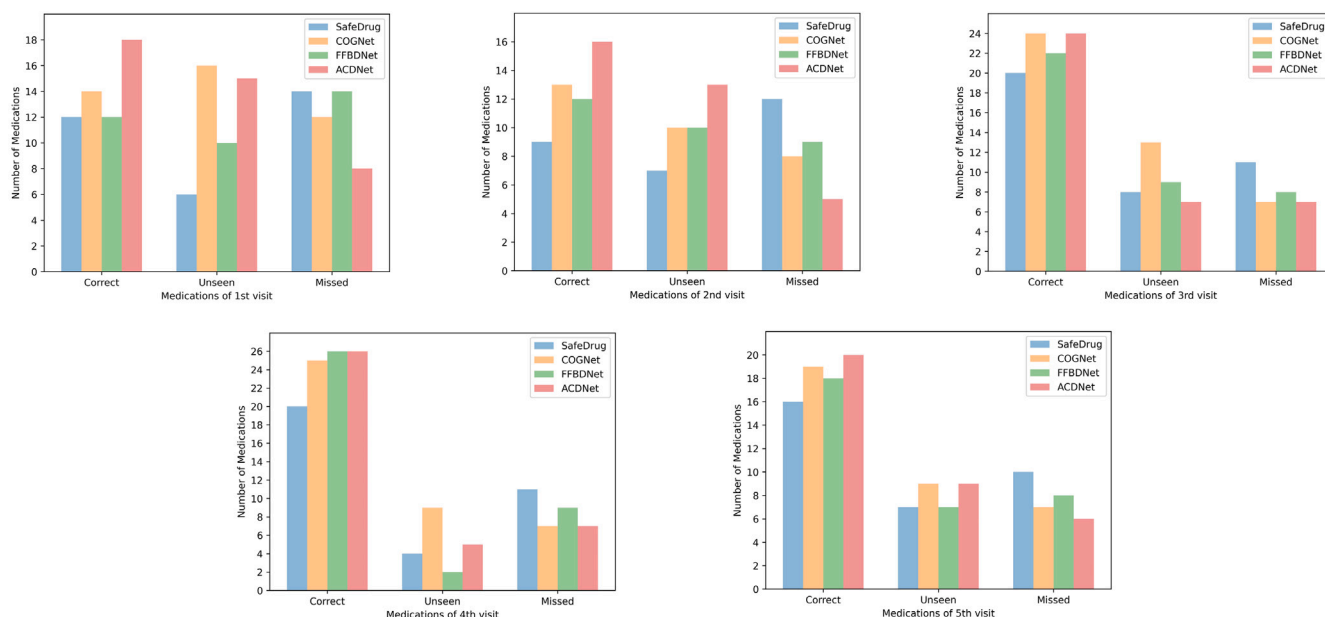


Fig. 5. Recommended Medications of Patient B.

the ACDNet model for modeling and predicting patients' health and medicine information. The model employs attention mechanism and Transformer to encode patients' EHR data and incorporates various external knowledge sources to represent medicine information. By combining the collaborative decision mechanism based on medication record similarity, we have successfully achieved personalized medication recommendation. We experimented with MIMIC-III and MIMIC-IV datasets, comparing ACDNet to other models. Results show ACDNet outperforms in Jaccard, PR-AUC, and F1 metrics, proving its efficacy in acquiring patient health data and medication representations. In future work, we will strive to reduce the interaction rate between drugs to avert potential adverse reactions and side effects.

CRedit authorship contribution statement

Jiacong Mi: Conceptualization, Methodology, Software, Validation, Writing – original draft. **Yi Zu:** Data curation, Writing – review & editing. **Zhuoyuan Wang:** Data curation, Writing – review & editing. **Jieyue He:** Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by National Key R&D Program of China (2019YFC1711000) and Collaborative Innovation Center of Novel Software Technology and Industrialization.

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