

Hypertension Medication Recommendation via Synergistic and Selective Modeling of Heterogeneous Medical Entities: A Study

Ke Zhang, Zhichang Zhang, Yali Liang, Wei Wang, Xia Wang

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Hypertension Medication Recommendation via Synergistic and Selective Modeling of Heterogeneous Medical Entities: A Study

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Abstract

Background: Electronic health records (EHR) store rich data involving medical entities such as diagnoses, treatment procedures, and prescribed medications, offering valuable resources for developing automated systems for hypertension medication recommendations. The entities in EHR show significant synergies during treatment. However, existing medication recommendation methods mainly focus on homogeneous graphs, overlooking the crucial synergistic relationships among heterogeneous medical entities. Also, accurately modeling the progression of hypertension using EHR is essential for precise medication recommendations, but current approaches often lack comprehensive temporal modeling and don't fully meet clinical requirements.

Objective: To overcome the challenges in existing methods, introduce a novel model for hypertension medication recommendation that leverages the synergy and selectivity of heterogeneous medical entities.

Methods: First, use patient EHR to construct both heterogeneous and homogeneous graphs. Then, capture the inter-entity synergies with a multi-head graph attention mechanism to enhance entity-level representations. Next, apply a dual-layer temporal selection mechanism to calculate selective coefficients between current and historical visit records and aggregate them to form refined visit-level representations. Finally, determine medication recommendation probabilities based on these comprehensive patient representations.

Results: Experimental evaluations on the real-world dataset MIMIC-IV v2.2 show that the model achieves a Jaccard similarity coefficient of 55.82%, a precision-recall AUC of 80.69%, and an F1 score of 64.83%, outperforming baseline models.

Conclusions: The findings indicate the superior efficacy of the introduced model in medication recommendation, highlighting its potential to enhance clinical decision-making in the management of hypertension.

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Original Manuscript

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Abstract

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Keywords: hypertension medication recommendation; electronic health records; heterogeneous graph; multi-head graph attention mechanism; time series selective mechanism

Introduction

Hypertension represents a prevalent chronic condition and serves as a significant contributor to cardiovascular mortality, making timely pharmacological intervention for blood pressure management crucial [1]. With the increasing trend of an aging population, the rising number of hypertension patients has placed a significant burden on healthcare systems [2]. Consequently, automated medication recommendation systems for hypertension have been developed.

Early hypertension medication recommendation methods are primarily rule-based. For example, Wu et al. developed a hypertension ontology and reasoning rules to recommend appropriate antihypertensive medications to patients [3]. However, these methods relied only on predefined rules and a limited set of case data, neglecting other critical patient information, which resulted in recommendations that lacked flexibility and personalization. In recent years, numerous neural network models for recommending hypertension medications based on Electronic Health Records (EHR) have been proposed [4,5]. These models have shown improved outcomes and effectively address many limitations inherent in earlier algorithms.

Nevertheless, the complexity of EHR data continues to present significant challenges for medication recommendation tasks, particularly in two critical areas:

- **Insufficient Synergy Among Heterogeneous Medical Entities:** EHR generated during medical visits include various medical entities, including diagnoses, treatment procedures, and medication prescriptions, which have a significant synergistic effect during patient treatment. For example, diagnostic results often inform a patient's health status, which in turn guides the formulation of treatment plans. The selected treatment procedures and medications within these plans are expected to work synergistically to optimize treatment efficacy. Capturing this synergy between diverse medical entities is essential for effective medication recommendations. Current methods primarily use graph structures to address this issue, with models like MiME [6] and GCT [7] exploring potential causal relationships among different medical codes. Motivated by this perspective, MiME captures hierarchical and multi-layered representations from sequential medical data, whereas GCT simultaneously uncovers latent causal relationships among medical entities during the predictive modeling process. However, these studies focus only on homogeneous graphs and overlook the heterogeneity of medical entities in original health records.
- **Neglect of Temporal Dynamics in Patient Condition:** As a chronic disease, hypertension evolves over time. In clinical practice, physicians often synthesize both current and historical medical visit data to fully capture the progression of a patient's condition and tailor treatment plans accordingly. Therefore, effectively integrating visit information for temporal modeling of disease progression is another key issue in medication recommendation. Yang et al. modeled the time dependency of medications through two medical sequences but did not consider the correlation between these sequences [8]. Similarly, Liu and colleagues used three distinct LSTM-based architectures to simulate the correlation between various medical sequences while ignoring the impact of the patient's current status on therapeutic decision-making [9]. These existing techniques do not adequately represent the progression dynamics of patient conditions.

To overcome the limitations identified above, this study introduces CSRec, a recommendation framework for hypertension medication that leverages the collaborative interactions among diverse medical entities and incorporates selective modeling of temporal information. The proposed framework consists of two primary components: the Heterogeneous Synergy Module and the Temporal Selectivity Module. In the Heterogeneous Synergy Module, to capture the synergistic effects between different medical entities, the model first extracts data from individual medical visits to construct both heterogeneous and homogeneous graphs, then employs a Multi-Head Graph Attention Mechanism (GAT) to update nodes and obtain entity-level representations of medical entities. In the Temporal Selectivity Module, to effectively simulate the progression of hypertension, the model calculates selection coefficients for the current health status against historical medical visits for the same patient, selectively aggregating historical visit data to achieve visit-level medical entity representations. Finally, various types of medical entities are concatenated to form an inclusive patient representation, which serves as the basis for individualized medication recommendations for hypertension. Furthermore, to guarantee medication safety, the proposed model incorporates Drug-Drug Interaction (DDI) information into the recommendation process.

The primary contributions of this paper are summarized as follows:

- We propose a novel medication recommendation model, named CSRec, specifically designed for hypertension treatment. CSRec effectively integrates the synergistic interactions and selective characteristics among diverse medical entities. By constructing a heterogeneous medical entity graph derived from Electronic Health Records (EHR), our model utilizes a graph attention mechanism to generate enhanced collaborative embeddings among medical entities. Additionally, a temporal selection mechanism is incorporated to simulate hypertension progression, thereby producing a comprehensive patient representation to facilitate accurate medication recommendations.
- To better capture synergistic relationships between medical entities, we innovatively modify the traditional GAT to focus more on neighboring node information, thus obtaining a more

aggregated representation of the principal nodes.

- Extensive experiments conducted on the publicly available MIMIC-IV dataset [10] validate the superiority and effectiveness of our proposed method.

Related Work

Graph Neural Network-Based Medication Recommendation

Graph Neural Networks (GNN) are capable of learning node embeddings in a graph and effectively aggregating information from neighboring nodes. Therefore, researchers often utilize GNN to model EHR in medication recommendations. For instance, Shang et al. introduced GAMENet, a model uses graph convolutional networks to incorporate medical insights from EHR and DDI graphs, aiming to mitigate adverse side effects arising from medication interactions [11]. However, this model does not integrate knowledge from other medical entities such as diagnoses and procedures. To more comprehensively learn information from different medical entities, Shang et al. subsequently proposed the G-BERT model utilizing pre-training methods, but it overlooked the issue of medication safety [12]. Subsequently, Wang et al. introduced the CompNet model, which models medications in a graph in an unordered manner. However, this model incurs high learning costs and poor stability when dealing with large numbers of patients and a vast medication space [13]. Yang et al. attempted to model the molecular structures of medications as graphs to simulate interactions between medication molecules and their effects on diseases, thereby facilitating medication recommendations [14]. Meanwhile, Li et al. used graph contrastive learning to model differences between current and historical medical visits [15]. However, existing graph-based studies often struggle to ensure both effectiveness and safety in medication recommendation tasks.

Therefore, this paper proposes modeling EHR as complete heterogeneous graphs and extending the conventional Graph Attention Network (GAT) to learn within this framework.

Temporal Modeling-Based Medication Recommendation

Research on temporal modeling of EHR for medication recommendations has been extensive. For example, the RETAIN model proposed by Choi et al. utilized an attention-based mechanism to precisely identify historical medical visits and key clinical variables that have significant impacts on the treatment process [16]. An et al. proposed an interactive Long Short-Term Memory (LSTM) architecture designed to capture temporal dependencies and hierarchical relationships among multiple sequences, effectively simulating physician decision-making processes [17]. Hung et al. adopted a memory-enhanced neural network framework to simulate complex interactions and long-term dependencies between two asynchronous sequential views [18]. Yang et al. focused on the prescription medications from the most recent visit and captured changes in patient health status between consecutive visits through a residual mechanism [19]. Wu et al. used the Transformer architecture to model the temporal relationships among a patient's historical diagnoses, medications, and current diagnosis, and introduced a copying or generate mechanism to dynamically decide whether to reuse previous prescriptions or generate new ones [20].

Inspired by previous research, this paper designs a Temporal Selectivity Module to effectively simulate the progression of diseases.

Problem Formulation

Electronic Health Records

Electronic Health Records (EHR) encompass a variety of medical visit information collected from patients. For a specific patient, EHR can be structured a sequence comprising multiple clinical visit records, represented as $V = [V^1, V^2, \dots, V^T]$, where V^t represents the t -th visit and T indicates the total

number of visits for that patient. Specifically, each clinical visit V^t can be represented as $V^t = [V_d^t, V_p^t, V_m^t]$, in which $V_d^t \in [0,1]^{|D|}$, $V_p^t \in [0,1]^{|P|}$, and $V_m^t \in [0,1]^{|M|}$ represent multi-hot encoded vectors corresponding to diagnosis, procedures, and medications, respectively. Here, the notation $|i|$ indicates the total number of distinct categories within each respective medical entity type.

Heterogeneous Medical Entities

In this paper, distinct medications are modeled as medication entities. Each medication recorded in the EHR corresponds to a unique medication entity, identified by a specific identifier denoted as $[m_1, m_2, \dots]$, and each entity is independently embedded within the model using embeddings of identical dimensionality. Likewise, diagnoses and procedures are categorized into diagnostic entities and procedural entities, respectively. Collectively, these three categories of entities are termed heterogeneous medical entities.

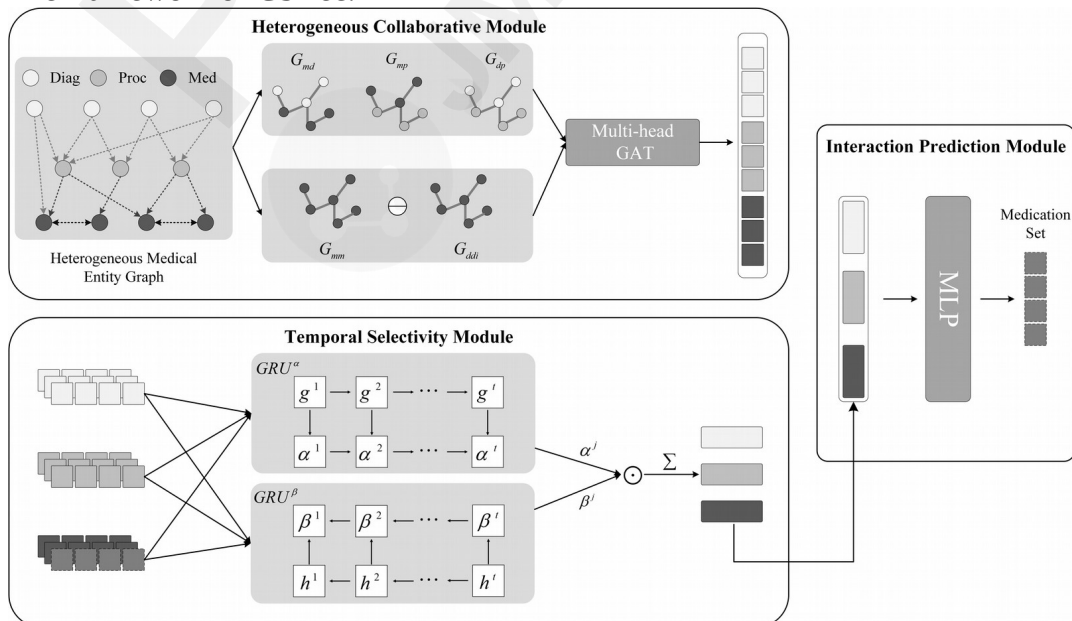
Hypertension Medication Recommendation

Based on the patient's current diagnostic information V_d^t , procedural data V_p^t , historical visit sequence $V = [V^1, V^2, \dots, V^{T-1}]$, and the heterogeneous medical entity graph G , the model recommends appropriate antihypertensive medications $\hat{y}_t \in [0,1]^{|M|}$ to the patient.

Methods

In this section, we present a comprehensive description of the CSRec model's structure. As depicted in Figure 1, our model comprises three core modules: (1) The Heterogeneous Collaborative Module, where we design both heterogeneous and homogeneous graph networks, focusing on aggregating the collaboration between different entities to update the entity-level representations. (2) In the Temporal Selectivity Module, we calculate the selection coefficients of the current visit against previous visit records through a bidirectional selection mechanism, and then integrate these into a visit-level representation. (3) The Interaction Prediction Module is used for integration and output. We concatenate the visit-level representations of heterogeneous medical entities into the final patient representation, which is then transformed into probabilities of medication recommendation. Medications exceeding the threshold are outputted as results.

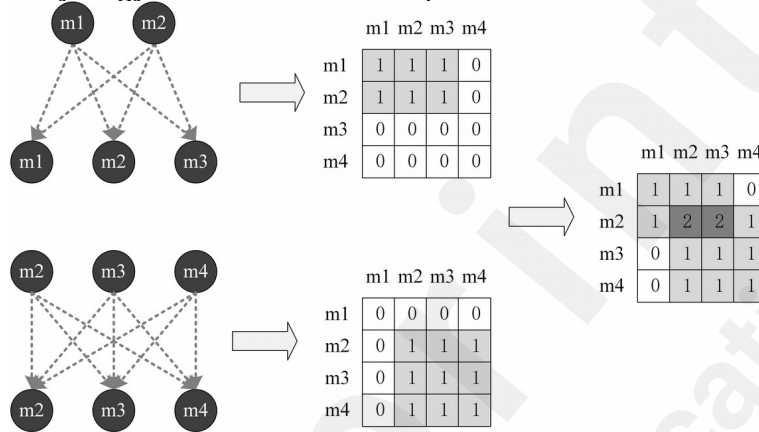
Figure 1. The framework of CSRec.



Heterogeneous Collaborative Module

For a specific patient, we initially construct a complete medication graph $G_{mm}(t-1) = \{M(t-1), A^{mm}\}$, where $M(t-1)$ denotes the collection of all prescribed medications from the patient's previous visits, and A^{mm} signifies the adjacency matrix representing collaborative interactions among medications. Each entry within this adjacency matrix indicates the initial collaboration weight between the respective medication nodes. The detailed procedure for generating this matrix is illustrated in Figure 2. Initially, A^{mm} is set as a zero matrix. If medication i and medication j co-occur during a specific visit, $A[i, j] = 1$; if medication i and j co-occur across multiple visits, the corresponding value in A^{mm} is incremented, with higher values indicating stronger collaboration between the medications.

Figure 2. The med-med synergy matrix construction process.



Each medication node $m \in M(t-1)$ in the graph corresponds to its initial embedding vector.

$$e_m = V_m^{t-1} E_m \quad (1)$$

Moreover, some medications may have harmful interactions (DDI) and should be avoided when used together. To address this, we integrate the medication collaboration graph G_{mm} with the medication safety graph G_{ddi} , enhancing the comprehensive representation of the medication nodes.

$$G_m = G_{mm} - \lambda G_{ddi} \quad (2)$$

Subsequently, we adopt a GAT-based graph neural approach to obtain embeddings for medication nodes within the medication graph G_m .

1. Utilize the attention mechanism to calculate the attention coefficients between a node and its neighbors, followed by normalization

$$\alpha_{ij}^{(m)} = \frac{\exp(g_{ij}^{(m)})}{\sum_{k \in N_i^{(m)}} \exp(g_{ik}^{(m)})} \quad (3)$$

Where $g_{ij}^{(m)} = \text{LeakyReLU}(\beta^{(m)\top} (h_i^{(m)} \parallel h_j^{(m)}))$, $N_i^{(m)}$ represents the neighboring node set of node m_i in the graph G_m , $\beta^{(m)}$ represents the learnable attention parameter vector, and $\parallel$ indicates concatenation.

2. Employ the calculated attention coefficients to perform weighted aggregation of neighbor nodes, thereby obtaining the representation of node m_i :

$$e_i^{(m)} = \sigma \left(\sum_{j \in N_i^{(m)}} \gamma_{ij}^{(m)} h_j^{(m)} \right) \quad (4)$$

3. To overcome the limitations posed by single-view attention, we further introduce a multi-head attention mechanism, using a linear layer to map node representations into multiple subspaces, and then aggregate representations under each subspace. Formally, this operation is expressed as:

$$e_i^{(m)} = \parallel_{h=1}^H \sigma \left(\sum_{j \in N_i^{(m|h)}} \gamma_{ij}^{(m|h)} h_j^{(m|h)} \right) \quad (5)$$

In the above equation, H denotes the total number of attention heads, the superscript $[h]$ indicates the current attention head index, and $\parallel$ represents concatenating outputs from different heads. Through this strategy, distinct node-specific information is captured across various dimensions and integrated from multiple subspaces, thereby significantly improving the precision and robustness of the learned node representations.

During the training process, each medication entity is updated according to the above steps, resulting in an aggregated representation of the medication set $V_m = [v_m^1, v_m^2, \dots, v_m^{t-1}]$.

Similarly, we define three heterogeneous complete graphs: the diag-pro graph $G_{dp}(t) = [D(t), P(t), A^{dp}]$, the med-diag graph $G_{md}(t) = [M(t-1), D(t), A^{md}]$, and the med-pro graph $G_{mp}(t) = [M(t-1), P(t), A^{mp}]$. Following a similar learning approach to the medication graph G_m , we first initialize the diagnosis and procedure nodes in the three heterogeneous graphs.

$$e_d = V_d^t E_d, e_p = V_p^t E_p \quad (6)$$

Then, we learn from the diag-pro graph according to steps (3)-(5) to obtain aggregated sets of diagnosis codes $V_d = [v_d^1, v_d^2, \dots, v_d^t]$ and procedure nodes $V_p = [v_p^1, v_p^2, \dots, v_p^t]$.

Finally, based on the aggregated medication nodes from the medication graph G_m and the learned diagnosis and procedure nodes from the diag-pro graph G_{dp} , we learn from the med-diag graph G_{md} and the medication-procedure graph G_{mp} , updating to obtain entity-level representations of the medication, diagnosis, and procedure sets:

$$\begin{aligned} V_D &= [V_d^1, V_d^2, \dots, V_d^t] \\ V_P &= [V_p^1, V_p^2, \dots, V_p^t] \\ V_M &= [V_m^1, V_m^2, \dots, V_m^{t-1}] \end{aligned} \quad (7)$$

It is noteworthy that this study adopts a multi-head Graph Attention Network (GAT) mechanism to learn and update nodes within the graph. While traditional GAT models consider intrinsic features and aggregate neighboring features, our proposed heterogeneous graph-based method places greater emphasis on enhancing the embeddings of medications, diagnoses, and procedures by explicitly modeling interactions among diverse medical entities. Consequently, our model focuses more intensively on neighboring nodes to prevent excessive node information merging. To this end, we have modified the standard GAT approach to explicitly focus on information derived from neighboring nodes within the heterogeneous graph learning process.

Temporal Selectivity Module

To effectively model the temporal evolution of patient health conditions, this paper introduces a dual-layer temporal selection mechanism utilizing Gated Recurrent Units (GRU). Compared to traditional Recurrent Neural Networks (RNN), GRU demonstrates superior modeling capability and effectively captures temporal dependencies inherent in sequential medical data. It mitigates common issues such as gradient vanishing and the extensive parameterization typical of Long Short-Term Memory networks (LSTM) architectures. The relatively simplified structure and faster training efficiency of GRU make it particularly advantageous for medication recommendation applications.

Specifically, we first utilize GRU^α to learn the diagnostic sequence, generating forward diagnostic selection coefficients.

$$g^1, g^2, \dots, g^t = GRU_d^\alpha(V_d^1, V_d^2, \dots, V_d^t) \quad (8)$$

$$\alpha^j = \tanh(W^\alpha g^j + b^\alpha), j = 1, \dots, t \quad (9)$$

Concurrently, GRU^β is employed in the reverse temporal order to learn the diagnostic sequence, thereby ensuring that the backward selection coefficients are generated at different time steps, which enhances the computational stability.

$$h^t, h^{t-1}, \dots, h^1 = GRU_d^\beta(V_d^t, V_d^{t-1}, \dots, V_d^1) \quad (10)$$

$$\beta^j = \tanh \text{shrink}(W^\beta h^j + b^\beta), j = t, \dots, 1 \quad (11)$$

Based on the generated dual-layer diagnostic selection coefficients, we can capture key visit information and entity information within the visit sequence, thereby obtaining a diagnostic representation that integrates historical visit information.

$$d^t = \sum_{j=1}^t \alpha^j \beta^j \odot V_d^j \quad (12)$$

After a series of similar processing steps, we obtain the patient's final procedural and medication representations.

$$p^t = \sum_{j=1}^t \alpha^j \beta^j \odot V_p^j, m^{t-1} = \sum_{j=1}^{t-1} \alpha^j \beta^j \odot V_m^j \quad (13)$$

Interaction Prediction Module

Based upon the outputs generated by the aforementioned modules, for the patient's t -th visit, we concatenate the medical entity sequence to make medication recommendations:

$$\hat{y}^t = \sigma([d^t; p^t; m^{t-1}]) \quad (14)$$

In our approach, the medication recommendation task is formulated as a multi-label classification problem[21,22]. During the model training process, the binary cross-entropy loss function is minimized by employing the Adam optimization algorithm[23].

$$L = - \sum_{t=1}^T \sum_{i=1}^{|M|} y_i^t \log \hat{y}_i^t + (1 - y_i^t) \log (1 - \hat{y}_i^t) \quad (15)$$

Results

Dataset Description

Our experiments were conducted using the MIMIC-IV v2.2 dataset¹ [10], provided by the Massachusetts Institute of Technology. This dataset comprises medical records collected from patients admitted to intensive care units during the period from 2008 to 2019. The experiments primarily utilized the HOSP module of the dataset, which includes data on diagnoses, procedures, and medications. The diagnostic and procedural information employ the ICD-9 coding system², while medication records utilize the NDC (National Drug Code) system in the United States³. To study medication recommendations for patients with hypertension, this paper extracted corresponding data based on the ICD-9 codes for hypertension from the dataset and selected patients who had at least two visits, following previous studies [4,19,20], while filtering out medications that appeared less than 2000 times. Subsequently, the dataset was partitioned into training, validation, and testing subsets according to a ratio of $\frac{2}{3} : \frac{1}{6} : \frac{1}{6}$.

Detailed information about the dataset used in the experiments and examples of patient are shown in Error: Reference source not found and Error: Reference source not found.

Table 1. The detailed information of experimental dataset.

Item	Number
# patients	19,609
# visits	55,239
# diagnosis	2,000
# procedure	5,488
# medication	14

¹ <https://physionet.org/content/mimiciv/2.2/>

² https://en.wikipedia.org/wiki/List_of_ICD9_codes

³ http://www.whocc.no/atc/structure_and_principles

avg # of visits	2.8169
avg # of diagnosis	9.3666
avg # of procedure	2.5492
avg # of medication	1.0804

Table 2. The samples of Electronic Health Records.

Sub_ID	Hadm_ID	Diagnoses	Procedures	Medications
10001217	24597018	3240,3484,3485,5180, 340,04109,3051,4019, V168,V161	139,331,3897	HydrALAzine, LeVETiracetam, Vancomycin , Bisacodyl, Meropenem,...
10001217	27703517	3240,3485,340,04102, 04184,4019,3051	139	HydrALAzine, Vancomycin, Meropenem, Bisacodyl, Lidocaine,...

Evaluation Metrics

To validate the effectiveness of CSRec, the following evaluation metrics are used:

- **Jaccard Similarity Coefficient (Jaccard).** A higher Jaccard coefficient reflects greater overlap between the predicted medication set and the actual medication set.

$$Jaccard = \frac{1}{T} \sum_{t=1}^T \frac{|y^t \cap \hat{y}^t|}{|y^t \cup \hat{y}^t|} \quad (16)$$

- **Precision-Recall AUC (PRAUC).** A high PRAUC indicates that the model recommends appropriate medications while keeping a low error rate.

$$PRAUC = \frac{1}{T} \sum_{t=1}^T \sum_{i=1}^{|M|} Precision^t \quad (15)$$

- **F1 Score (F1).** The elevated F1 metrics in medication recommendations signify an optimal equilibrium between minimizing false negatives and maintaining classification specificity.

$$Precision^t = \frac{|y^t \cap \hat{y}^t|}{|\hat{y}^t|}, Recall^t = \frac{|y^t \cap \hat{y}^t|}{|y^t|} \quad (15)$$

$$F1 = \frac{1}{T} \sum_{t=1}^T \frac{2 \times Precision^t \times Recall^t}{Precision^t + Recall^t} \quad (15)$$

- **Drug-Drug Interaction Rate (DDI).** A lower DDI rate ensures that the recommended combination of medications is safer in clinical practice.

$$DDI = \frac{1}{T} \sum_{t=1}^T \frac{\sum_{i=1}^{|\hat{y}^t|} \sum_{j=i+1}^{|\hat{y}^t|} 1[A_d[\hat{y}_i^t, \hat{y}_j^t]]}{\sum_{i=1}^{|\hat{y}^t|} \sum_{j=i+1}^{|\hat{y}^t|} 1} \quad (15)$$

Comparative Models

The following baseline models are selected for comparison with proposed CSRec:

- **LR:** Logistic Regression with L2 regularization.
- **ECC [24]:** Enhances predictions by connecting multiple classifiers, typically applied to multi-

label classification scenarios for performance optimization.

- **RETAIN** [16]: Implements dual-layer temporal attention architecture, designed for sequential clinical prediction tasks like treatment recommendation.
- **LEAP** [25]: Utilizes Recurrent Neural Networks (RNNs) to extract meaningful representations during current medical visits and generate medication sequences.
- **DMNC** [18]: Incorporates dual-memory neural components to model asynchronous therapeutic pattern interactions.
- **GAMENet** [11]: Adopts graph-based memory architecture combining medication interaction knowledge, querying longitudinal EHR data for medication retrieval.
- **MICRON** [19]: Analyzes EHR temporal dynamics to adaptively optimize medication combinations upon symptom evolution.
- **SafeDrug** [8]: Evaluates molecular-level medication-patient compatibility to suggest safer therapeutic regimens.
- **COGNet** [20]: Implements medication copy or predict strategy integrating historical effective prescriptions into current recommendations.

Performance Comparison

In this section, we conduct an extensive comparative analysis between CSRec and the previously described baseline medication recommendation models to evaluate its effectiveness. Experimental results on the MIMIC-IV 2.2 dataset are shown in Error: Reference source not found (bold indicates optimal data, ↑ indicates a preference for larger values, ↓ indicates a preference for smaller values).

Table 3. The comparison experimental results.

Model	Jaccard↑	PRAUC↑	F1↑	DDI↓
LR	0.4248	0.7426	0.5125	0.2821
ECC	0.4389	0.7498	0.5305	0.3064
RETAIN	0.5349	0.7964	0.6356	0.3431
LEAP	0.4186	0.5047	0.5326	0.0104
DMNC	0.5139	0.7678	0.5392	0.2801
GAMENet	0.5151	0.7781	0.6069	0.2884
MICRON	0.4297	0.7543	0.5151	0.2866
SafeDrug	0.5173	0.7770	0.6109	0.3084
COGNet	0.5087	0.7448	0.5948	0.3261
CSRec	0.5582	0.8069	0.6483	0.2760

After detailed analysis, we can observe several key findings:

- The CSRec model proposed in this paper outperforms most comparative models across multiple evaluation metrics, fully demonstrating its significant effectiveness in hypertension medication recommendation.
- LR and ECC performed poorly, primarily because these methods focus only the patient's current clinical condition, neglecting the influence of historical medical data on present treatment decisions. In contrast, the model presented in this paper, along with RETAIN, GAMENet, and other models integrating longitudinal medical histories, performed better, highlighting the importance of capturing historical medical information in hypertension medication recommendations.
- Compared with longitudinal models like RETAIN, GAMENet, and COGNet, CSRec still outperforms other methods, thanks to the model's accurate simulation of patient disease progression and effective capture of the relationships between heterogeneous medical entities.
- Although the CSRec model introduced in this study does not achieve the highest score on the DDI metric, it still ranks as suboptimal. This is mainly because the best performing LEAP model only considers the patient's present health status, resulting in the recommendation of fewer

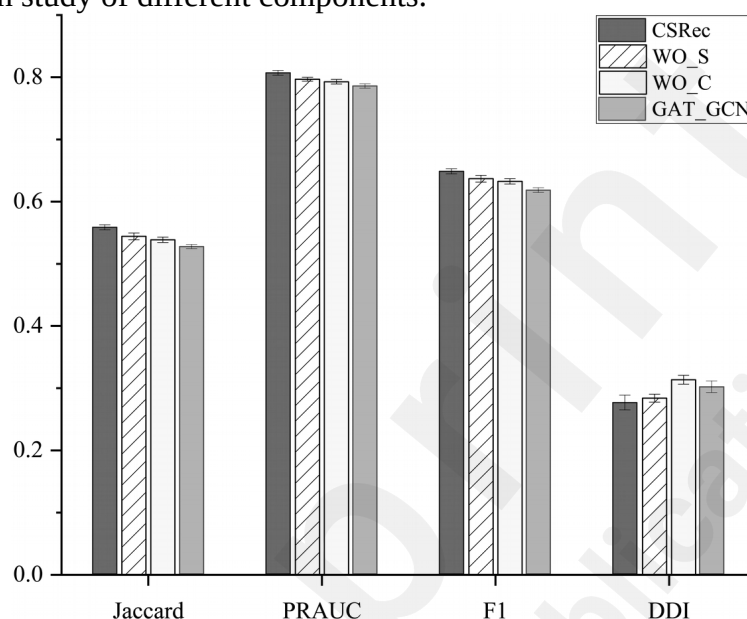
medications and consequently yielding the lowest DDI scores.

Ablation Study

To systematically assess the contribution and validity of each module within CSRec, ablation experiments were conducted by comparing CSRec with its variants.

- **WO_S**: Removes the selection module based on the cyclic mechanism.
- **WO_C**: Removes the collaborative module based on the heterogeneous graph.
- **GAT_GCN**: Replaces the multi-head GAT in the collaborative module with a GCN.

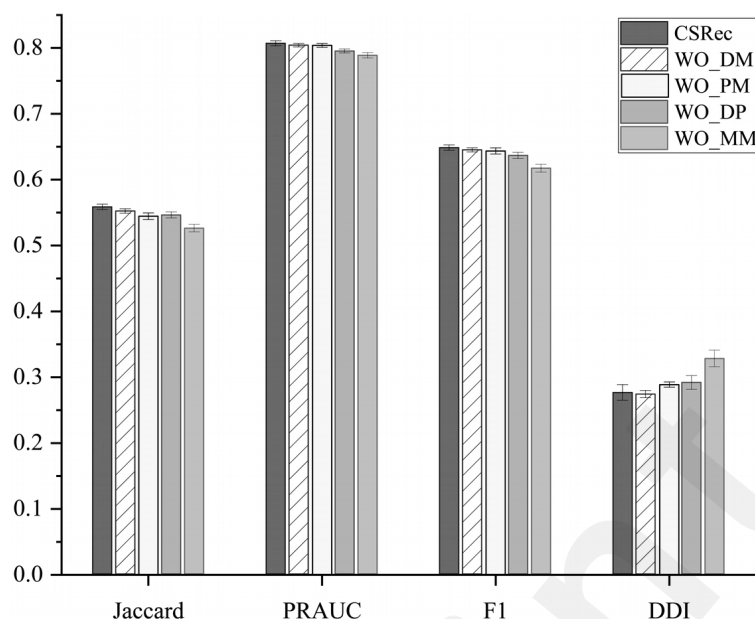
Figure 3. The ablation study of different components.



The results displayed in Error: Reference source not found indicate that the performance of CSRec declines when any module is removed or replaced, demonstrating that each component of CSRec is indispensable. The collaborative module effectively models the correlations between different medical events during each visit, enhancing the representation of medical entities; the selective module globally models the patient's historical medical data, emphasizing the influence of each historical time point on the current health status, thereby accurately simulating the progression of hypertension in patients; and the multi-head attention mechanism aggregates richer information in the heterogeneous graph compared to the convolutional network, accurately representing the nodes and edges of medical entities.

Additionally, this study investigates how different categories of medical entity information (including diagnoses, procedures, and medication interaction data) affect hypertension medication recommendations, with detailed results illustrated in Figure 4. Experimental results show that the performance of CSRec declines when any type of medical entity is removed (WO_DM, WO_PM, WO_DP), indicating that different types of medical entities are highly relevant to medication recommendation. Moreover, removing medication co-occurrence and interaction information (WO_MM) significantly reduces the safety of the recommended medications, indicating that DDI information is also essential.

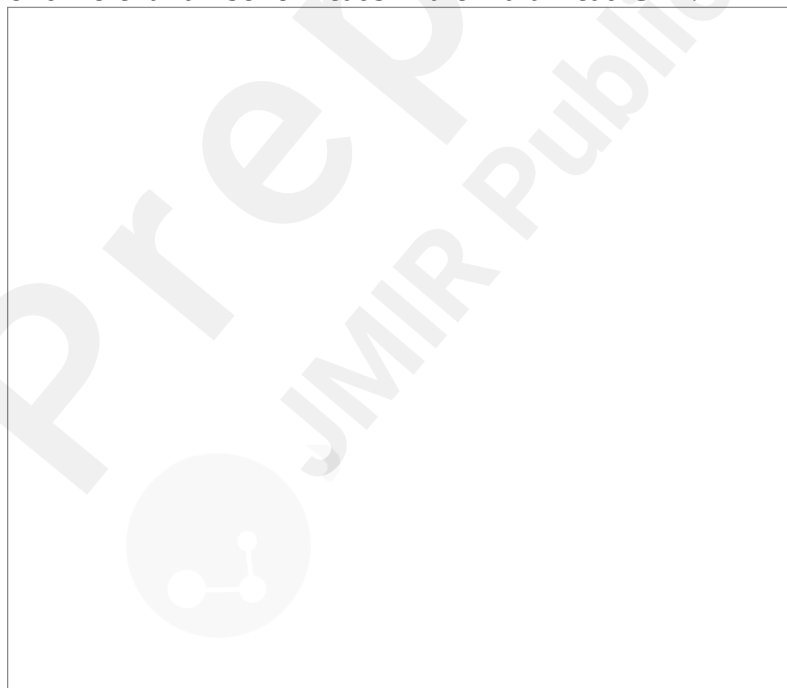
Figure 4. The ablation study of different medical entities.



Parameter Sensitivity

To examine how varying the number of attention heads in the multi-head graph attention mechanism within the heterogeneous collaborative module impacts model efficacy, multiple experiments were conducted. The outcomes of these experiments, comparing different head counts, are presented in Figure 5.

Figure 5. The effect of different number of heads in the multi-head GAT.



It was found that a setting of three attention heads (head=3) achieves optimal performance. Consequently, this configuration (head=3) is adopted consistently throughout the remaining experiments in this study. Moreover, experimental results illustrate that variations in the number of attention heads lead to minimal performance differences, highlighting the stability and reliability of the proposed model.

Case Study

To visualize the learning process of the model presented in this paper, a patient was randomly

selected from the test set for a case study. Taking diagnosis and medication entities as examples, the entire learning process is shown in Error: Reference source not found.

Figure 6. Case Study.

DC	DS	MC	MS	DC	DS	MC	MS	DC	DS	Rec	True
5533	0.023	C07A	0.599	E8786	0.084	C09A	0.245	57451	0.063	C09A	C09A
1682	0.047	C08C	0.401	78060	0.115	C07A	0.437	5184	0.094	C03C	C03C
496	0.209			42731	0.112	C08C	0.318	4019	0.178	C07A	C07A
4019	0.233			4019	0.140			42731	0.123	C08C	C08C
2449	0.172			2449	0.127			V1254	0.152		
42731	0.168			V1254	0.095			V5861	0.140		
V1254	0.148			496	0.131			2449	0.134		
V4364	0.000			79092	0.087			496	0.116		
				V5861	0.109						
Visit 1				Visit 2				Visit 3			

DC: Diagnosis Code

MC: Medication Code

Rec: Recommended Medication

DS: Diagnosis Selection Coefficient

MS: Medication Selection Coefficient

True: Prescribed Medication

Initially, in the collaborative process (a), the model interacts between diagnostic codes (DC column) and medication codes (MC column) at the visit level, enhancing the effect of diagnostic information on medication information. Furthermore, given the inherent temporal dependencies present in EHR, the suggested medications are influenced not only by the diagnosed diseases at the current (third) visit (DC column), but also significantly by prior prescriptions and the progression of past illnesses. Hence, as depicted in step (c), medication codes from historical visits are assigned higher selection coefficients, emphasizing their importance in the recommendation process. Similarly, in process (b), diagnostic codes from previous visits receive more attention, with higher selection coefficients. In each DC column, hypertension diseases are consistently assigned a higher selection coefficient, aligning with the data characteristics of hypertension treatment records.

Results

This paper presents the CSRec model for hypertension medication recommendation, which is based on the collaboration and selection of heterogeneous medical entities. By effectively capturing relationships among diverse medical entities and combining the temporal evolution characteristics of clinical entities, the model provides more precise and effective medication guidance for hypertension treatment. Future research will focus on three main areas: 1) further investigating the model's performance on the cold start problem; 2) attempting to use other methods to comprehensively model the correlations and collaboration between medical entities; 3) exploring recommendations for medication dosages alongside medication types.

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analysis, decision-making regarding publication, or manuscript preparation.

Conflicts of Interest

The authors affirm that there are no financial or personal relationships posing potential conflicts of interest that could have influenced the research outcomes presented in this manuscript.

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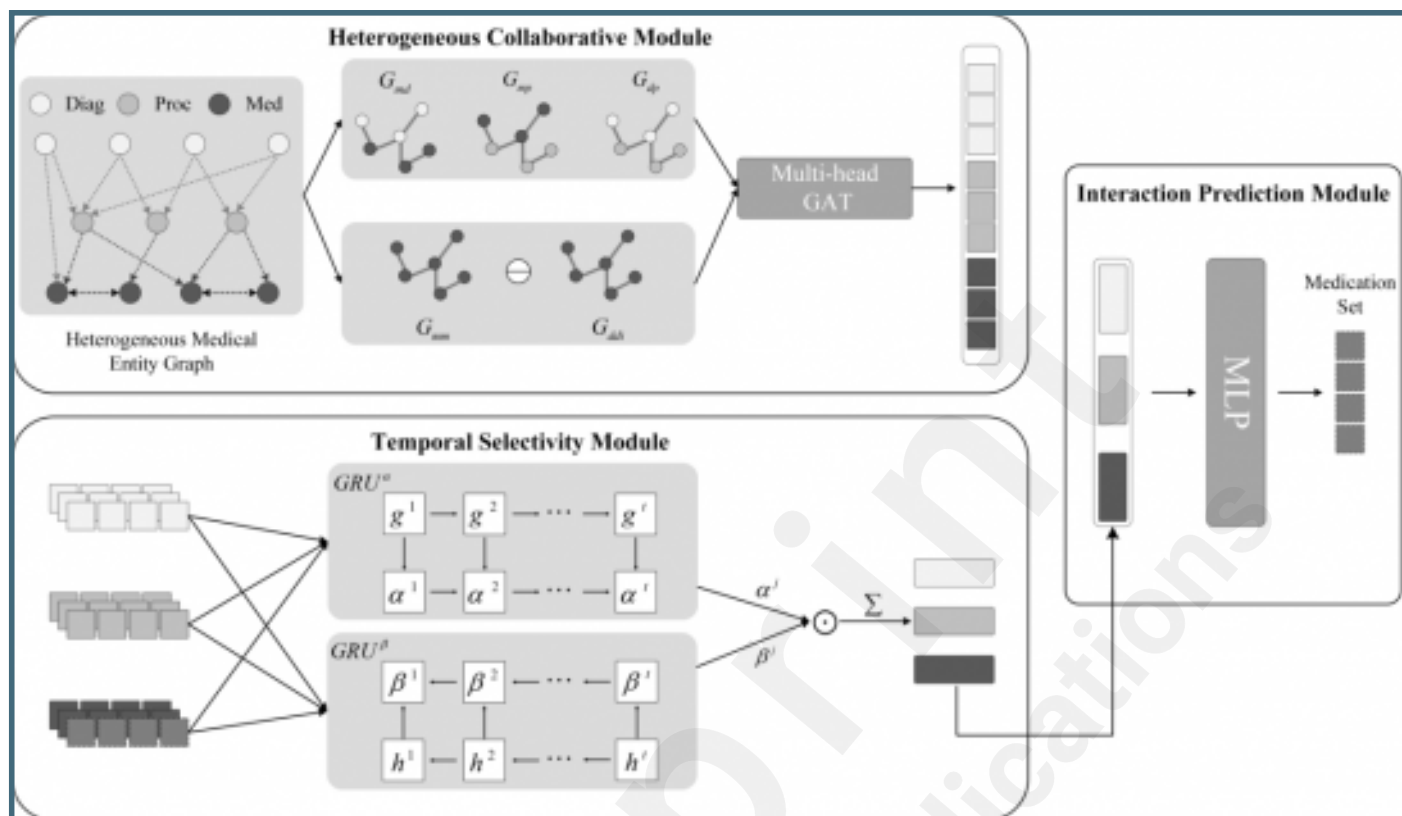
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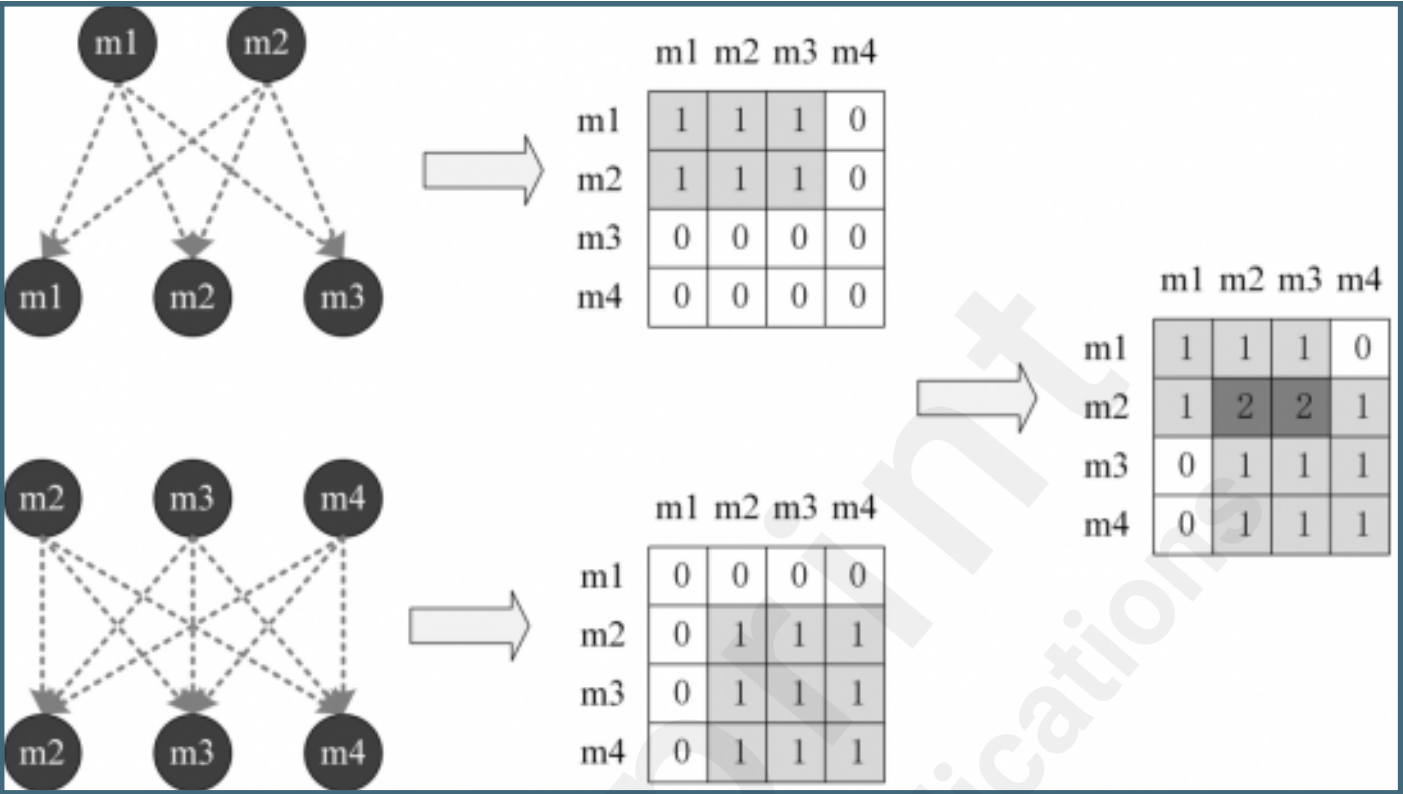
Supplementary Files

Figures

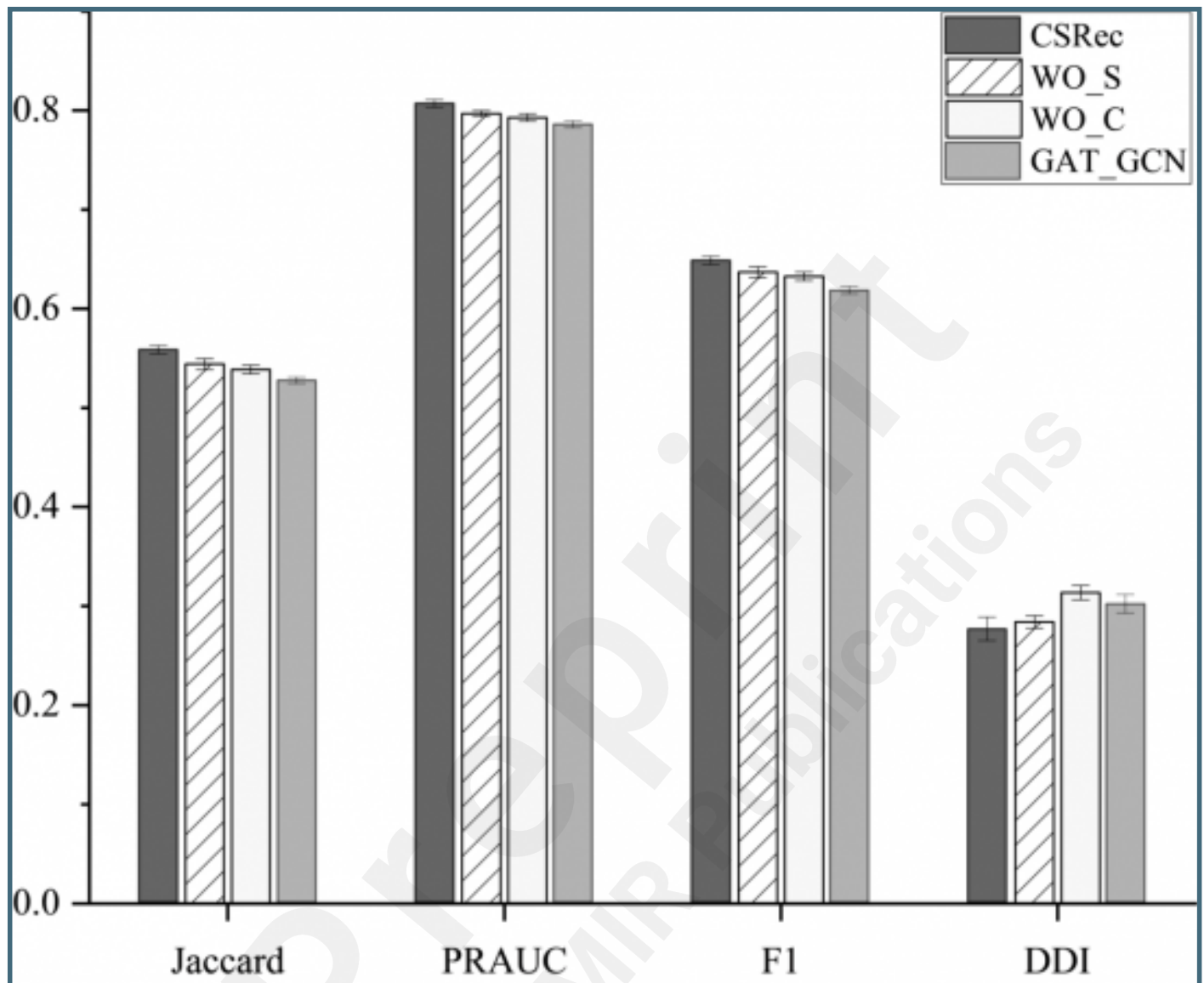
The framework of CSRec.



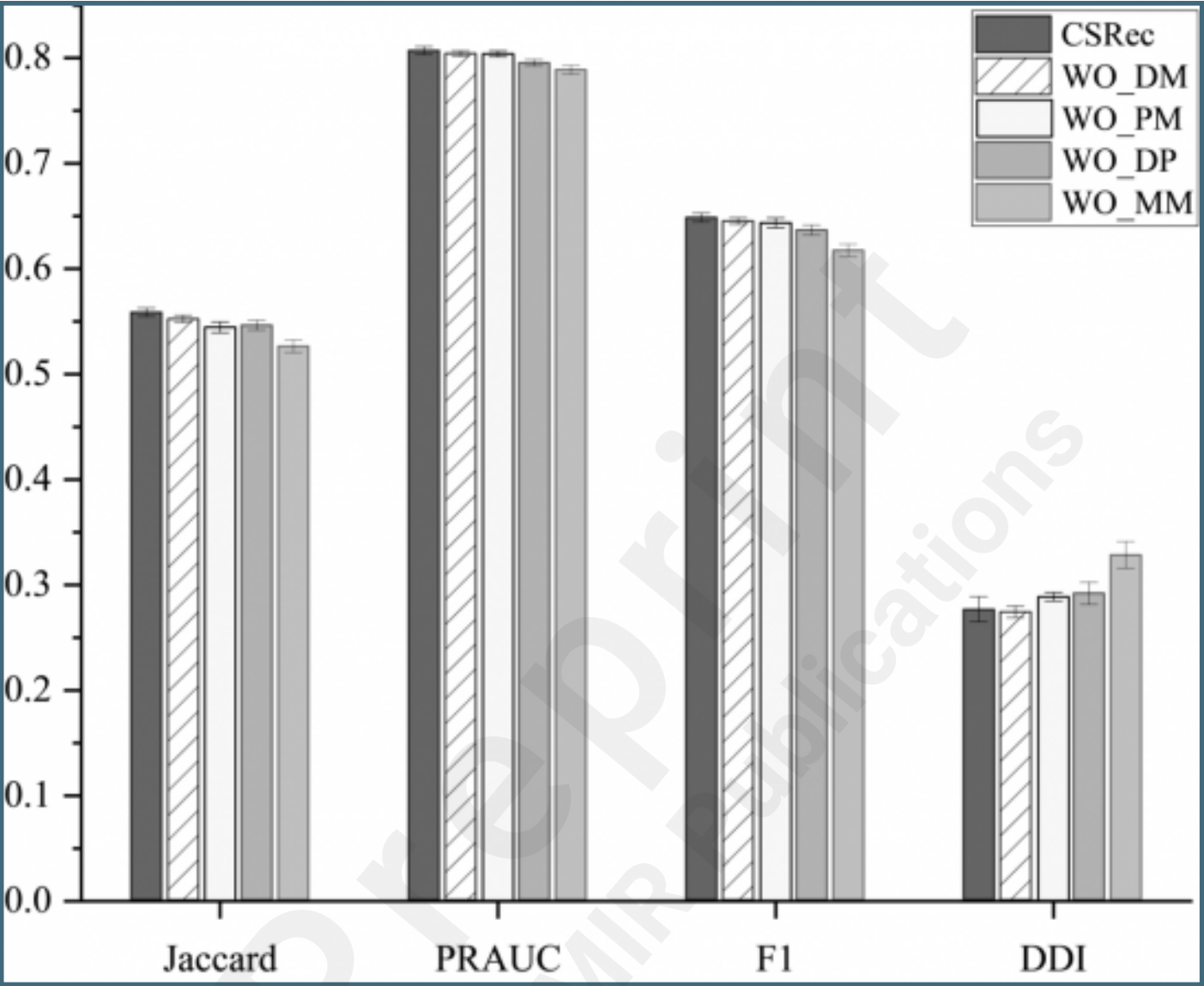
The med-med synergy matrix construction process.



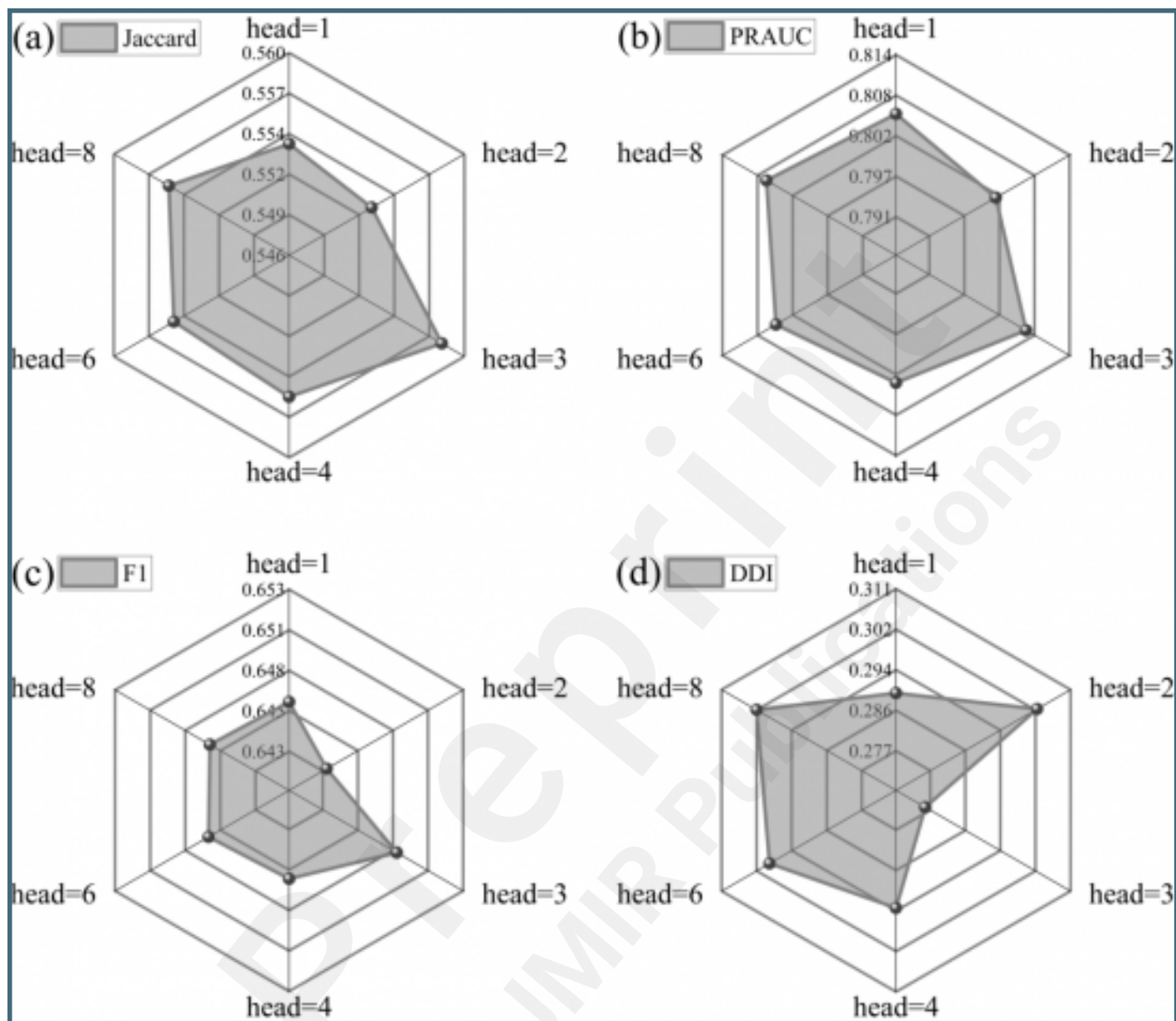
The ablation study of different components.



The ablation study of different medical entities.



The effect of different number of heads in the multi-head GAT.



Case Study.

(a)				(b)				(c)			
DC	DS	MC	MS	DC	DS	MC	MS	DC	DS	Rec	True
5533	0.023	C07A	0.599	E8786	0.084	C09A	0.245	57451	0.063	C09A	C09A
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DC: Diagnosis Code MC: Medication Code Rec: Recommended Medication
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