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MMM: Quantum-Chemical Molecular Representation Learning for Combinatorial Drug Recommendation

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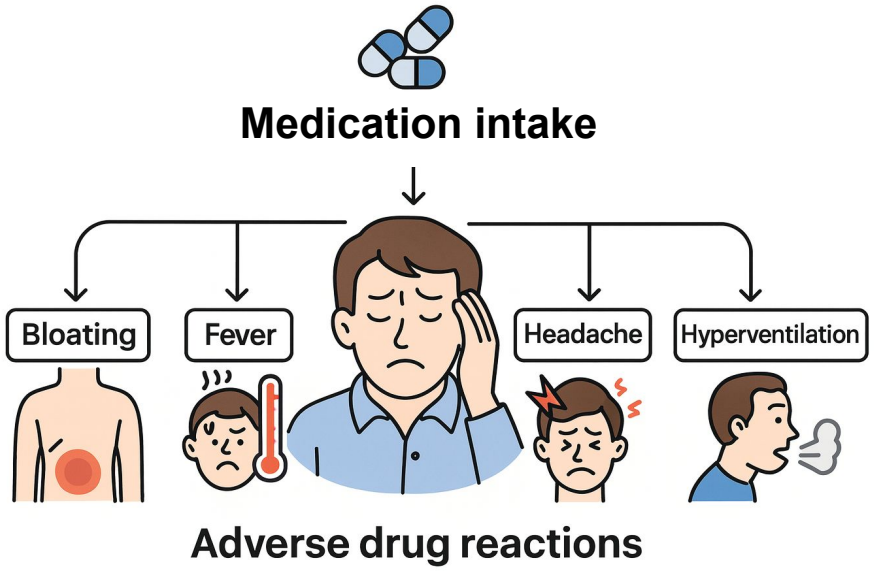
Background

- **Drug-Drug interaction (DDI)**
  - **6.3%** of reported DDIs resulted in patient mortality [FDA., 2024]
  - DDIs are a leading causes of adverse events and hospitalizations
  - Polypharmacy increase the likelihood of harmful interactions
  - Many DDIs remain underreported or undetected at prescription time [Spanakis et al., 2025]

    ➡ Need a model that reduces DDIs while preserving therapeutic effectiveness



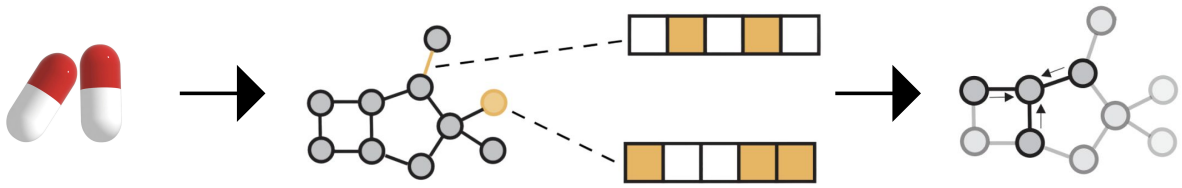
US Food and Drug Administration (FDA) (2024). FDA Adverse Event Reporting System (FAERS). 2024.
Spanakis et al., (2025). Artificial Intelligence Models and Tools for the Assessment of Drug–Herb Interactions.

Introduction

- **Approaches relying solely on longitudinal Electronic Health Records (EHRs) data** [Choi et al., 2016], [Pham et al., 2016]
  - Capture **temporal patterns of patient history** through sequential EHRs

    ➡ Limitations:
    - Completely ignore **molecular-level drug properties**
- **Approaches based on molecular graphs** [Yang et al., 2021], [Yang et al., 2023]
  - Incorporate structural information of drugs through **graph representations**

    ➡ Limitations:
    - Graph Neural Networks (GNN) [Scarselliet al., 2009] rely on local neighborhood aggregation
    - Difficult to capture **global molecular properties**



Choi et al., (2016). Retain: An interpretable predictive model for healthcare using reverse time attention mechanism.
Pham et al., (2016). Deepcare: A deep dynamic memory model for predictive medicine.
Yang et al., (2021). Safedrug: Dual molecular graph encoders for recommending effective and safe drug combinations.
Yang et al., (2023). Molerec: Combinatorial drug recommendation with substructure-aware molecular representation learning.
Scarselliet al., (2009). The Graph Neural Network Model

Introduction

- **Insights**
  - **3D structural information of molecules** [Zhu et al., 2022], [Stärk et al., 2022], [Liu et al., 2021]
    - *"Molecules should be represented at the quantum-chemical level or in 3D to better capture their structure."*
  - **Probabilistic internal characteristics** [Fukui et al., 1952]
    - *"The probabilistic nature of molecular internal structure must be considered."*
  - **Energy distribution across molecular orbitals** [Yu et al., 2022]
    - *"Energy distribution within molecular orbitals must be utilized to identify reactive regions and predict binding affinity."*

Zhu et al., (2022). Unified 2D and 3D pre-training of molecular representations.
Stärk et al., (2022). 3D Infomax improves GNNs for molecular property prediction.
Liu et al., (2021). Pre-training molecular graph representation with 3D geometry.
Fukui et al., (1952). A molecular orbital theory of reactivity in aromatic hydrocarbons.
Yu et al. (2022)., Describing Chemical Reactivity with Frontier Molecular Orbitalets (FMOLs) for Large Systems.

Motivation

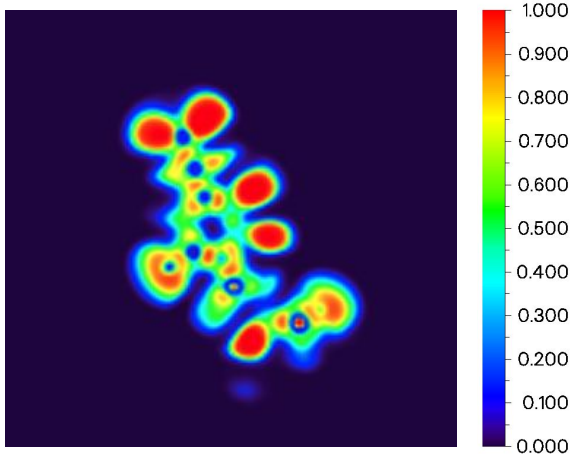
- **Research Questions**
  - Current models on EHR capture temporal patterns of patient history
  - But they often lack sufficient drug-level information for safe recommendations
  - **GNNs** introduced to include drug structure information
    - **Still, a key question remains: Are current approaches fully capturing drug information, and how can we do better?**

We propose **MMM: Multimodal DDI Prediction with Molecular Electron Localization Function Maps**

Motivation

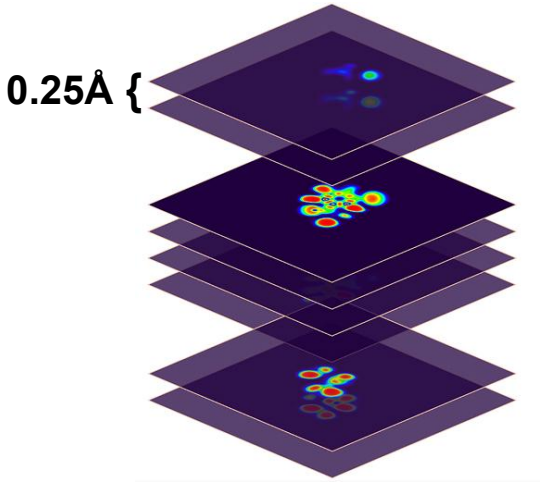
- **ELF maps** [Savin et al., 1997]
  - Provide **continuous 3-Dimensional (3D)** of electron pair localization
  - Capture **reactive sites** & **covalent bonds**
  - Generated by **Density Functional Theory (DFT)** [Dreizler et al., 2012] calculations

➡ *Enables a richer understanding of DDI mechanisms that were previously inaccessible through discrete graph-based structures.*

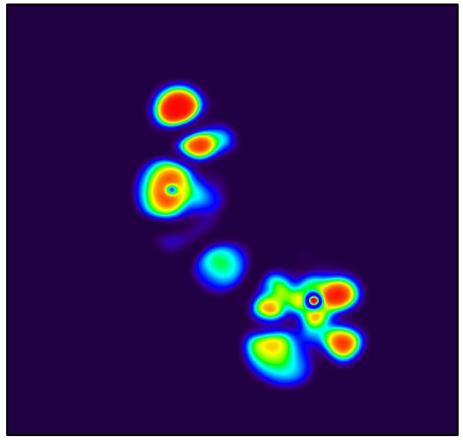


ELF ≈ 1: Region of strong electron localization

ELF ≈ 0: Region of delocalized electron



Stacked ELF maps

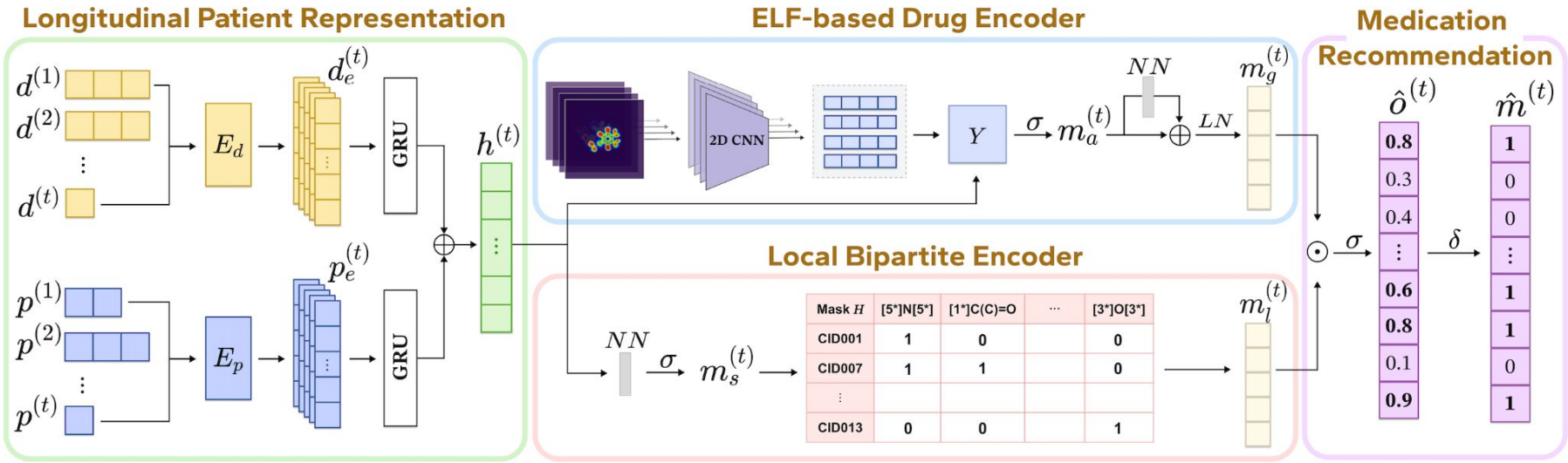


Slices From the 3D Structure

Savin et al., (1997). Elf: The electron localization function.
Dreizler et al, (2012). Density functional theory: an approach to the quantum many-body problem.

Proposed Framework

- A **combinatorial drug recommendation framework** for **personalized multi-drug recommendations**
  - **Longitudinal Patient Representation** for summarizing a patient's clinical status
  - **ELF-based Drug Encoder** for capturing the intrinsic electronic behavior of each drug
  - **Local Bipartite Encoder** for identifying the importance of drug substructures
  - **Medication Recommendation** for computing each drug's final prescription probabilities



d **:** diagnosis
p **:** procedure

Figure 1. Proposed model architecture.

Proposed Framework

- **Longitudinal** Patient Representation
  - Generate a **patient-specific vector** summarizing **past diagnoses and procedures** at the current time step ➡ The foundation for personalized medication
  - Take **diagnoses and procedures** as inputs
  - Capture longitudinal clinical history with **Gated Recurrent Unit (GRU)** [Dey et al., 2017] to produce patient embedding

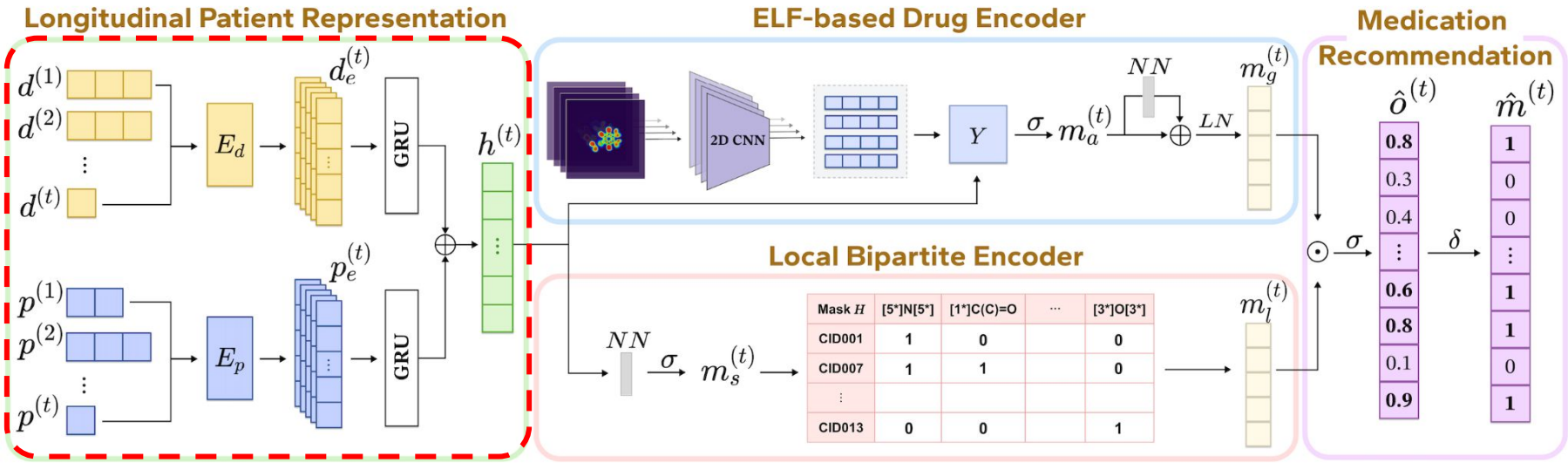


Figure 1. Proposed model architecture.

Dey et al., (2017) Gate-variants of gated recurrent unit (GRU) neural networks.

Proposed Framework

- **ELF**-based Drug Encoder
  - Capture **3D molecular structure** and **electron density distribution**

  ➡ To better capture **molecular-level interaction mechanisms**
  - From **Simplified Molecular Input Line Entry System (SMILES)** [Weininger et al., 1988]
  - Extract features using **pretrained Convolutional Neural Networks (CNN)** [LeCun et al., 2002]
  - Capture the relationship between patient status and drug features

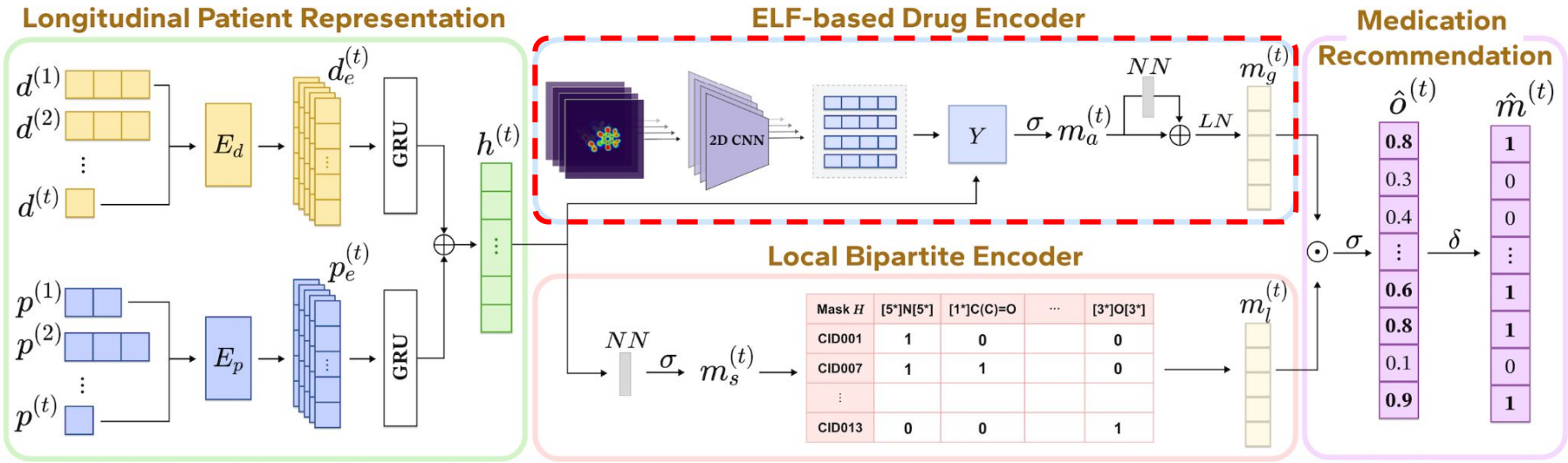


Figure 1. Proposed model architecture.

Weininger et al., (1988) Smiles, a chemical language and information system. 1. introduction to methodology and encoding rules.
LeCun et al., (2002) Gradient-based learning applied to document recognition.

Proposed Framework

- **Local Bipartite** Encoder [Yang et al., 2021]
  - Identifies the importance of **drug substructures** depending on **patient conditions**
  - Segments each drug into substructures using Breaking Retrosynthetically Interesting Chemical Substructures (**BRICS**) [Degen et al., 2008] decomposition
  - Encodes inclusion relationships with a **binary mask matrix *H***

➡ Leverages patient-specific substructure information to avoid **DDI risk**

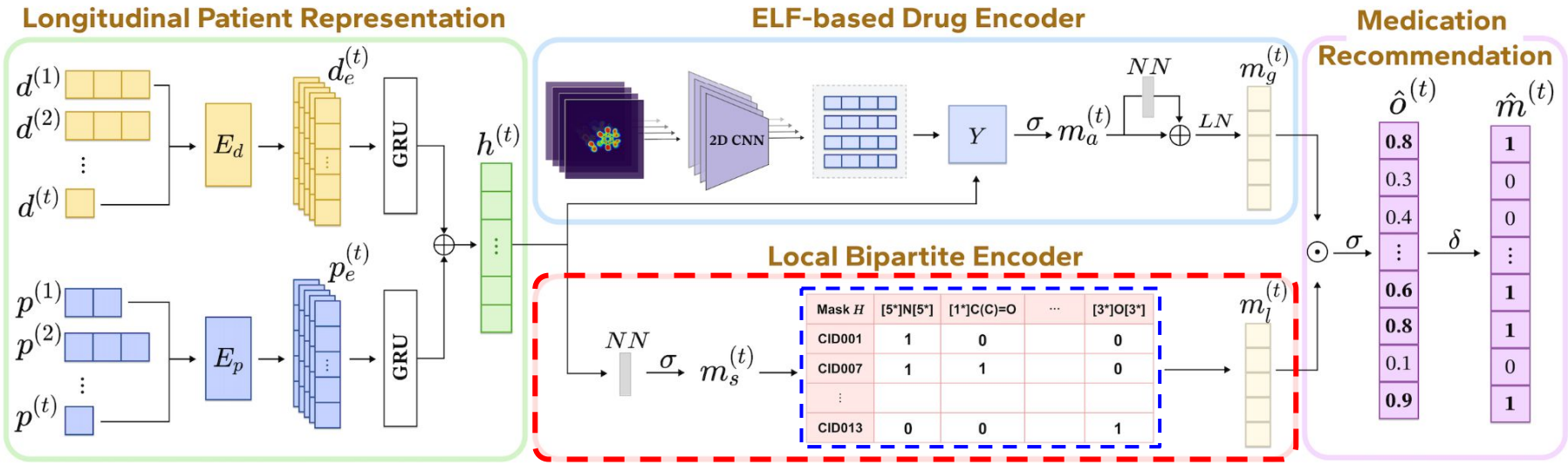


Figure 1. Proposed model architecture.

Yang et al., (2021). Safedrug: Dual molecular graph encoders for recommending effective and safe drug combinations.
Degen et al., (2008) On the art of compiling and using drug-like chemical fragments spaces.

Proposed Framework

- Medication **Recommendation**
  - Fuse the **global 3D molecular** and **local substructure** information using element-wise product
  - Predict prescription probability per drug
  - Output **multi-label** drug recommendations

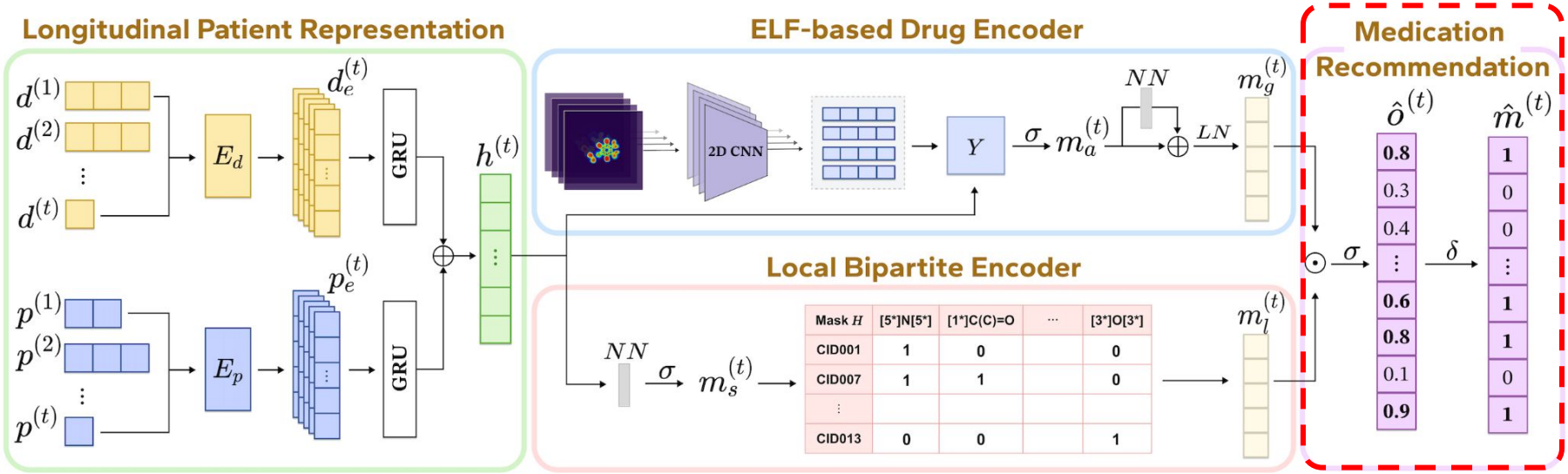


Figure 1. Proposed model architecture.

Experiment

- Experimental Setting
  - Dataset
    - **MIMIC-III** dataset [Johnson et al., 2016]
      - **Multi-label medication recommendation** task using longitudinal EHRs
      - Data components: Diagnosis codes, Procedure codes, and Medication records

Table 1. Data Statistics. (D: Diagnosis, M: Medication, P: Procedure)

Items	Size	Items	Size
# of visits/# of patients	14,057 / 5,413	avg./max # of visits	2.60 / 29
D. / P. / M. space size	1,942 / 1,399 / 250	avg./max # of D. per visit	10.38 / 128
total # of DDI pairs	4,918	avg./max # of P. per visit	3.85 / 50
total # of substructures	442	avg./max # of M. per visit	7.67 / 68

  - Evaluation Metrics
    - To evaluate the performance of medication recommendation,
      - **DDI rate** : prescription safety, evaluated at the **compound level**
      - **F1-score** : predictive effectiveness, evaluated at the **Anatomical Therapeutic Chemical third-level codes (ATC3)** [WHO., 2000]
      - **Jaccard similarity** : therapeutic relevance, evaluated at the **ATC3 code level**

Johnson., (2016). Mimic-iii, a freely accessible critical care database.
WHO., (2000). Collaborating centre for drug statistics methodology, guidelines for atc classification and ddd assignment

Experiment

- Can **quantum-chemical ELF features** improve medication recommendation safety and accuracy?
  - Result
    - **MMM** significantly outperforms all baseline models
    - **MMM** reduces the DDI Rate by 9.3%
    - **MMM** improves the F1-score and Jaccard by 1.6% and 0.76%, respectively

➡ *Demonstrating drug safety by reducing the DDI while recommending medications that correspond to therapeutic objectives.*

Table 2. Performance Comparison on MIMIC-III (recorded DDI rate is 0.2509).

Model	DDI Rate	Jaccard	F1-score	Avg. # Drugs
Random Forest	0.3652 ± 0.0018	0.3123 ± 0.0019	0.4628 ± 0.0023	4.8476 ± 0.0113
RETAIN	0.3325 ± 0.0098	0.4882 ± 0.0129	0.6319 ± 0.0114	5.7883 ± 0.1757
MoleRec	0.0760 ± 0.0031	0.7384 ± 0.0127	0.8353 ± 0.0094	14.9414 ± 1.1696
SafeDrug	0.0742 ± 0.0026	0.7488 ± 0.0081	0.8434 ± 0.0064	13.4697 ± 1.4838
	- 9.30%	+ 1.6%	+ 0.76%	
MMM	$0.0673 \pm 0.0049^*$	$0.7608 \pm 0.0066^*$	$0.8498 \pm 0.0046^*$	12.5239 ± 0.9008

Conclusion

- Proposed a **multimodal drug recommendation MMM framework** to reduce DDI risks
- **By combining patient EHRs with quantum-chemical ELF maps and a bipartite substructure encoder,**
  - Capture both **global reactivity** and **patient-specific safety signals**
- **MIMIC-III Dataset Experiment**
  - **MMM** achieved significantly **better accuracy and lower DDI rates** compared to existing GNN-based models
- **Future Directions**
  - Model DDI severity more clearly
  - Expand evaluation to a broader range of drugs, moving closer to real-world clinical use

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Thank you for your attention

Title **MMM: Quantum-Chemical Molecular Representation Learning for Combinatorial Drug Recommendation**

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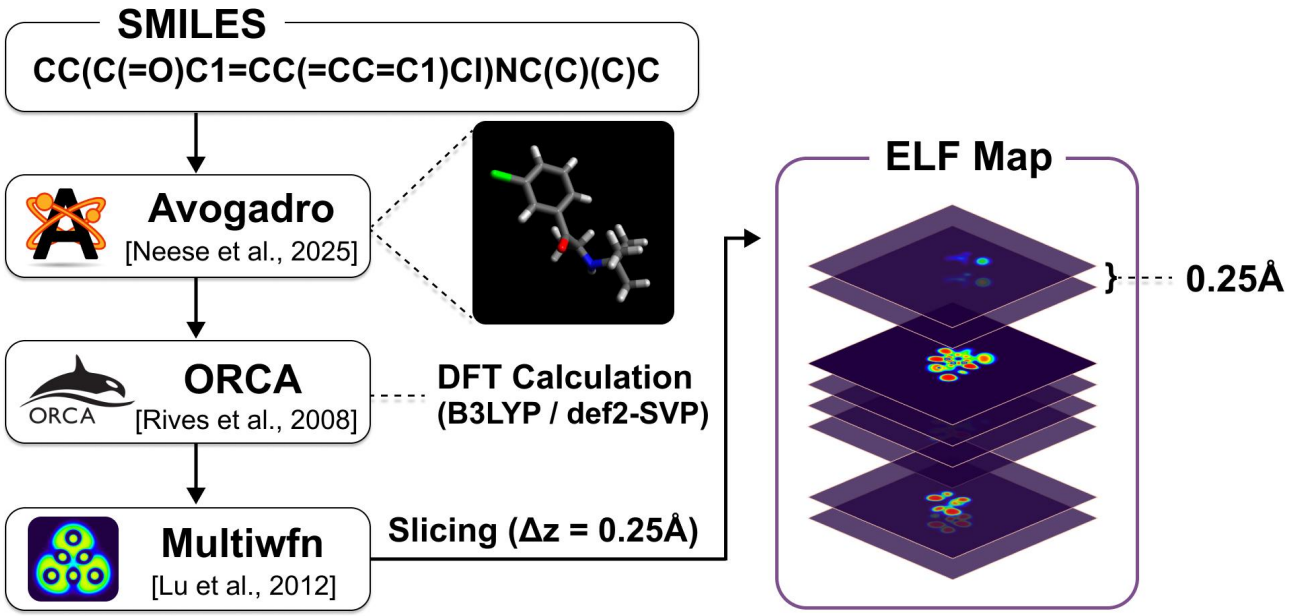
ELF-based Molecular Representation

- Molecular planes were sliced at **0.25Å** to correspond to **the spatial scale of the smallest hydrogen atoms**.
- ELF maps were generated for all **250 drugs** using an **AMD Ryzen Threadripper PRO 3955WX CPU**, taking approximately **30 hours in total**.
- This **cost** is incurred **only once** during preprocessing, and the generated ELF maps can be **stored** and **reused during inference**.



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Experiment

- Do ELF and Bipartite encoders complement in drug recommendation?
  - We Found
    - Removing bipartite encoder keeps therapeutic metrics high but increases DDI risk
    - Removing ELF encoder lowers DDI risk slightly but reduces therapeutic similarity and effectiveness
    - **Complete MMM** combines both to **maintain low DDI risk** and **achieve the best Jaccard** and **F1-score**

Table 3. Ablation Study: Effect of Each Component on Model Performance

Model	DDI Rate	Jaccard	F1-score	Avg. # Drugs
w/o Bipartite Encoder	0.0776 ± 0.0023	0.7450 ± 0.0132	0.8363 ± 0.0104	15.2948 ± 1.0907
w/o ELF Encoder	0.0610 ± 0.0068	0.7182 ± 0.0297	0.8195 ± 0.0231	15.2336 ± 1.8888
MMM	0.0673 ± 0.0049	0.7608 ± 0.0066	0.8498 ± 0.0046	12.5239 ± 0.9008

Experiment

- The recorded prescriptions in the dataset resulted in a DDI rate of 0.3214, whereas SafeDrug, MoleRec, and MMM achieved lower DDI rates of 0.0833, 0.0909, and 0.0667, respectively.
- Red color indicates interacting medications.

Table 3. Case Study: Patient from MIMIC-III with multiple diagnoses

		Patient 1
Diagnosis		Morbid obesity, Hypertension, Osteoarthrosis, Disorders of circulatory system, Accidental hemorrhage
Prescribed Medications		Gabapentin, Warfarin, Argatroban, Midazolam, Cefazolin, Pantoprazole, Metoprolol, Furosemide
Recommended Medications	**SafeDrug**	Bisacodyl, Docusate, Acetaminophen, Hydromorphone, Metoprolol, Warfarin, Pantoprazole, Lisinopril, Morphine, Oxycodone
	MoleRec	Acetaminophen, Bisacodyl, Furosemide, Docusate, Hydromorphone, Pantoprazole, Lisinopril, Warfarin, Morphine
	MMM	Acetaminophen, Bisacodyl, Docusate, Hydromorphone, Metoprolol, Pantoprazole, Clopidogrel, Lisinopril, Ondansetron, Morphine, Oxycodone, Famotidine

Experiment

- Can **quantum-chemical ELF features** improve medication recommendation safety and accuracy?
  - Result
    - **MMM** significantly outperforms all baseline models
    - **MMM** achieves the lowest DDI Rate, indicating the highest level of safety
    - **MMM** achieves the highest Jaccard and F1-scores

Table 2. Performance Comparison on MIMIC-III (recorded DDI rate is 0.2509).

Model	DDI Rate	Jaccard	F1-score	Avg. # Drugs
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MMM	$0.0673 \pm 0.0049^*$	$0.7608 \pm 0.0066^*$	$0.8498 \pm 0.0046^*$	12.5239 ± 0.9008

MMM achieves a **9.3% reduction** in DDI Rate compared to SafeDrug and a **73% reduction** compared to the recorded DDI rate (0.2509).