Panacea: Enhancing Graph Learning with Multimodal Semantics for Drug Repositioning

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Outline

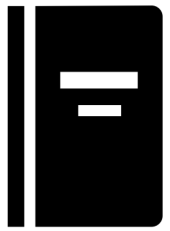
Background

Design

Experiment

Conclusion

Outline



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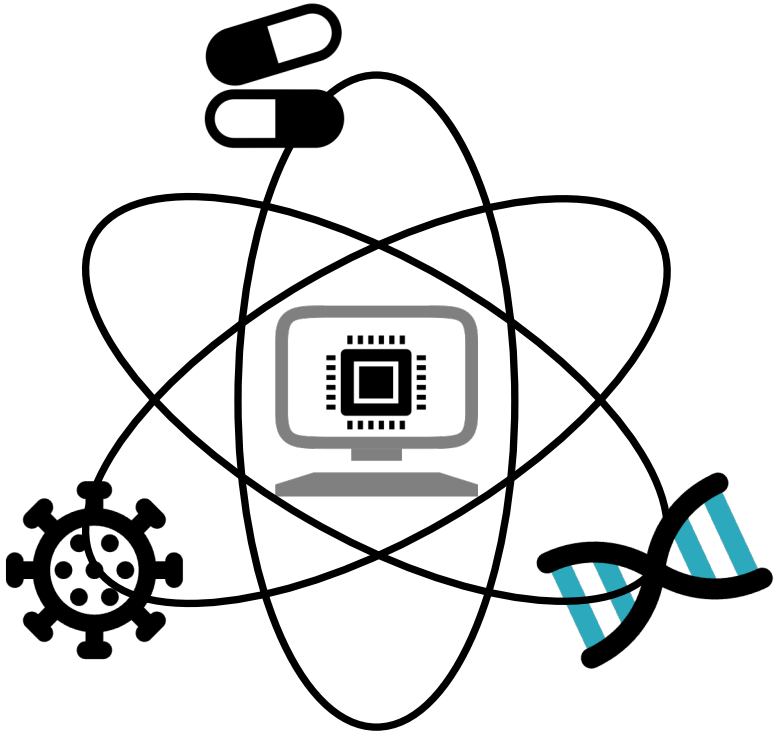
Modern Drug Development

Modern drug development is a multistage, high-risk process of discovering and testing new molecules to achieve regulatory approval for therapeutic use

The Problem

- Time-Consuming: 10-15 years
- Costly: Over $2 billion
- High Failure Rate: Over 90%

Drug Repositioning



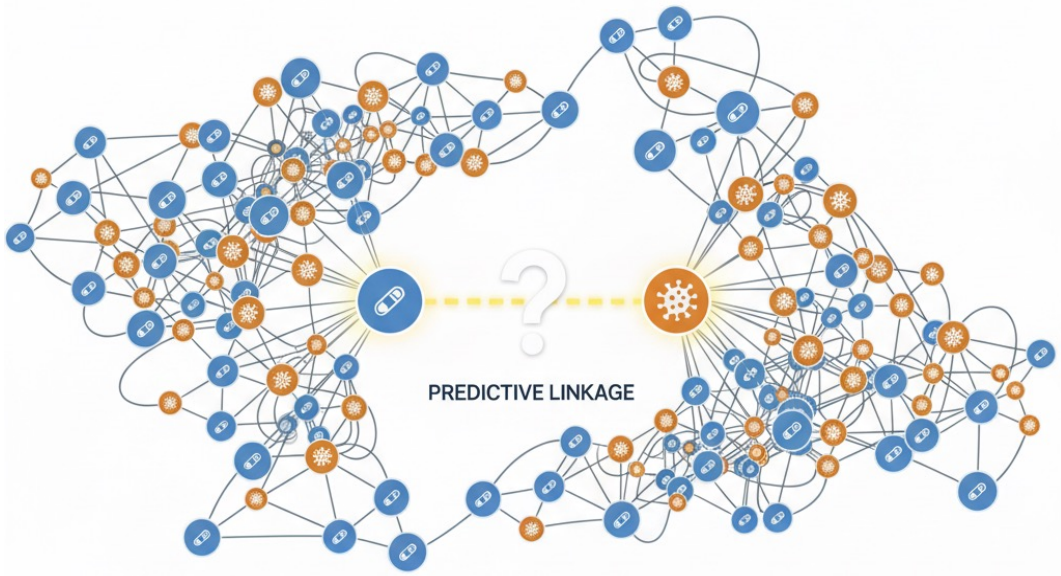
The Opportunity

- A New Paradigm: Drug Repositioning
- Definition: Identifying new therapeutic uses for existing, approved drugs ("old drugs, new tricks")
- Key Advantages:
  - Reduced Time & Cost: Bypasses early-stage discovery and pre-clinical testing
  - Lower Risk: Safety and pharmacokinetic profiles are already well-established

The Role of AI

- Computational approaches are crucial for systematically and efficiently identifying high-potential drug repositioning candidates from vast biomedical data

Problem Formulation

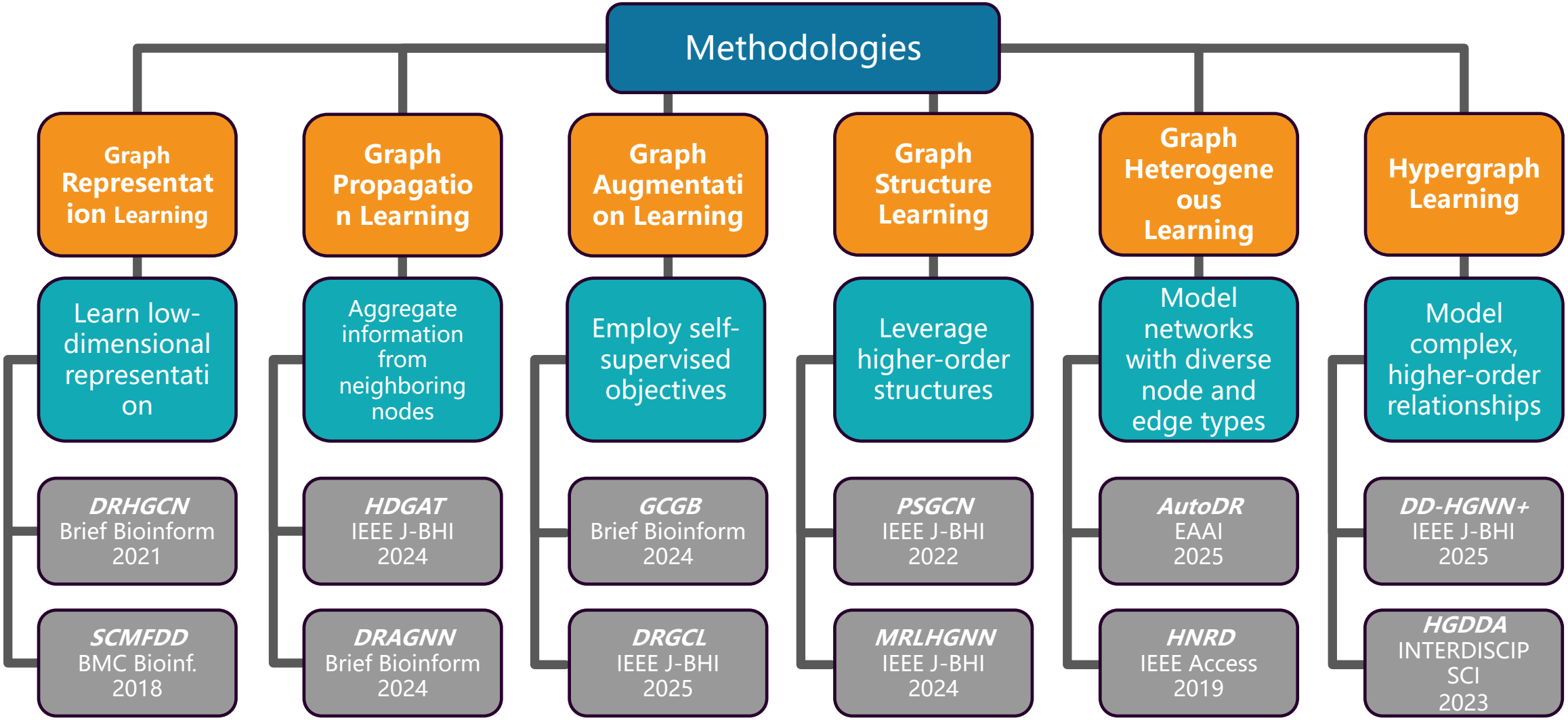


Formulation as a Graph

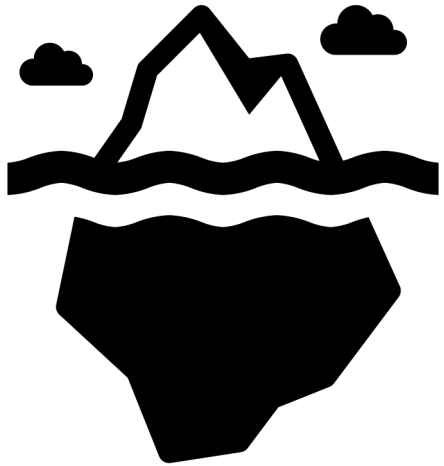
- Model: A general biomedical graph
  - Nodes represent the core entities, such as drugs and diseases
  - Edges denote known drug-drug, drug-disease, and disease-disease interactions
- Task: Predicting potential new drug-disease associations
- Existing approaches mainly rely on Graph Neural Networks (GNNs) for representation learning

Related Works

Taxonomy of graph-based learning methods for drug repositioning



Limitations



Data Sparsity

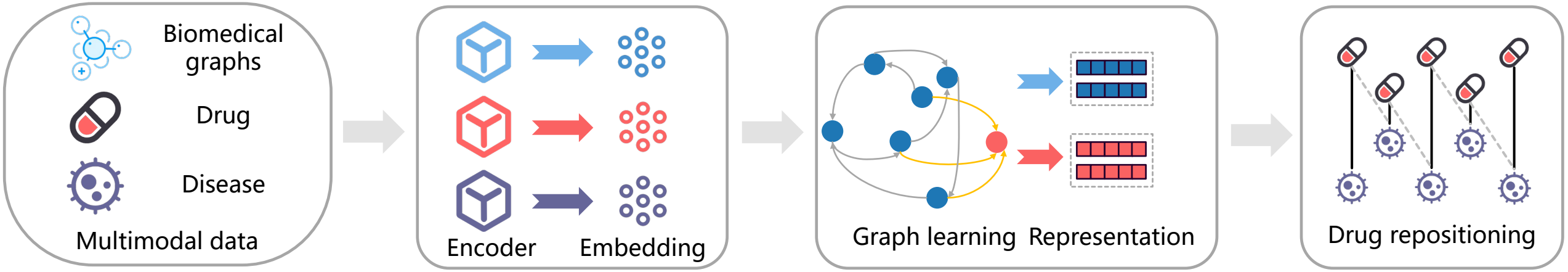
The scarcity of high-quality labeled drug-disease associations leads to weak input representations and undermines the foundation for effective graph learning

Over-smoothing

Multi-layer message passing in GNNs leads to indistinguishable node representations, severely degrading model performance and generalization.

Our Goal

Our goal is to design an automated ***multimodal semantics-enhanced*** graph learning framework for drug repositioning



- Collect multimodal biomedical data: including drug, disease, and biomedical graphs
- Encode modality-specific information: generate unified embeddings for each modality
- Perform graph learning: capture structural and semantic relationships
- Predict novel drug-disease associations: enable automated drug repositioning

Key Challenges

Limitation 1
Data sparsity

Challenge 1

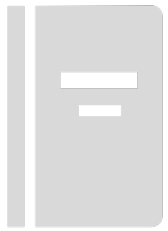
Multimodal semantic integration: How to effectively integrate heterogeneous biomedical modalities, such as biomedical graphs, molecular structures, and textual symptoms descriptions

Limitation 2
Over-smoothing

Challenge 2

Structural expressiveness under sparse inputs: How to preserve representation diversity and maintain expressive power as the number of graph layers increase

Outline



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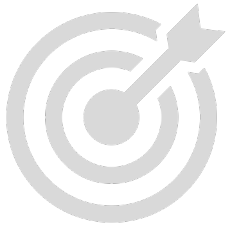
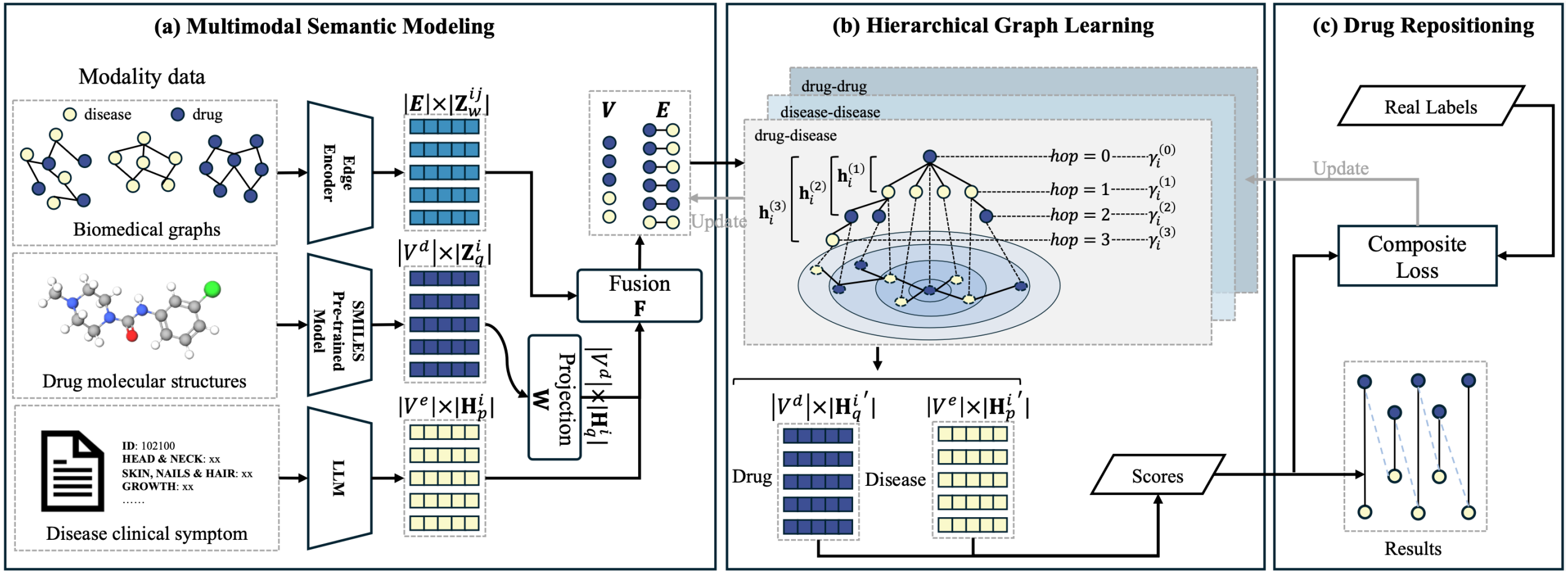


Conclusion

Model Overview



Panacea is an automated multimodal semantics-enhanced graph learning framework for drug repositioning. It mainly includes (a) Multimodal Semantic Modeling, (b) Hierarchical Graph Learning, and (c) Drug Repositioning

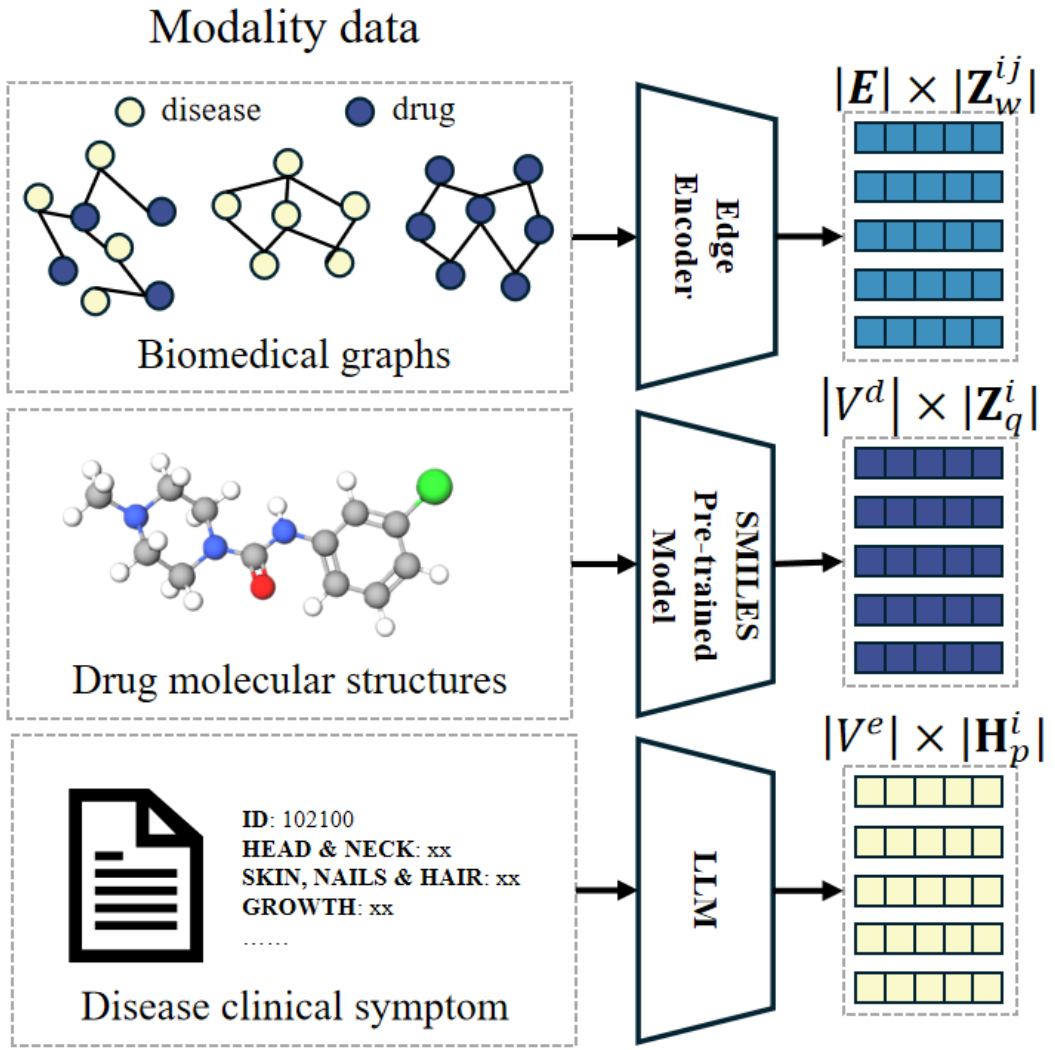
Multimodal Semantic Modeling

Modality Data

- Biomedical graphs (drug, disease)
- Drug SMILES strings from PubChem
- Disease symptom descriptions from OMIM

Encoding

- Graph Edge → Edge encoder → Topology embedding
- SMILES → MolBERT → Structure-aware embedding
- Symptom Text → ChatGPT-4o → compress and standardize → Qwen2.5-7B-Instruct → Textual embedding



Multimodal Semantic Modeling

Prompt Case

- Motivation: Clinical symptom descriptions exhibit varying lengths and inconsistent quality
- Example: Overly long descriptions may contain redundant or irrelevant information
- Method: Leverage ChatGPT-4o to compress and standardize the symptom texts, ensuring semantic consistency and uniform length distribution

Example

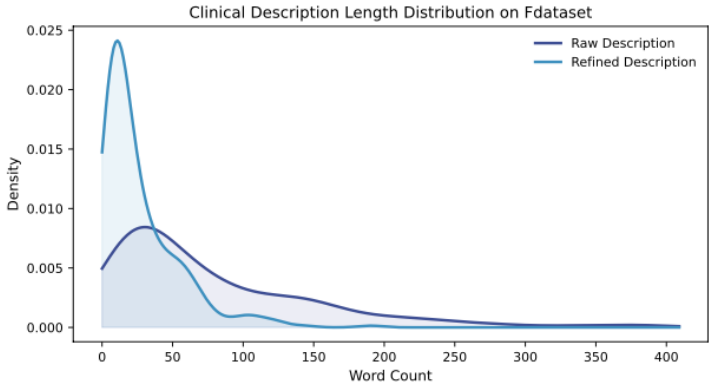
Input:
INHERITANCE - Autosomal recessive GROWTH Height - Short stature HEAD & NECK Head - Microcephaly - Brachycephaly - Turribrachycephaly - Plagiocephaly (in some patients) - Wide fontanelles Face – Craniofacial dysplasia - Prominent forehead - Midface hypoplasia - 'Fishlike' facies - Choanal atresia or choanal stenosis - Micrognathia - Prognathism (in some patients) Ears - Low-set ears - Dysplastic ears (in some patients) - Posteriorly rotated ears (in some patients) - Protruding ears (in some patients) - Hearing loss, mixed (in some patients) Eyes - Exophthalmos - Downslanting palpebral fissures - Hypertelorism (in some patients) - Arched eyebrows (in some patients) Nose - Hypoplastic nose - Depressed nasal bridge Mouth - Gingival hyperplasia - Cleft palate - High palate - Small mouth - Wide mouth (in some patients) - Large protruding tongue Teeth - Abnormal teeth (in some patients) - Natal teeth (in some patients) - Small teeth (in some patients) - Enamel dysplasia (in some patients)

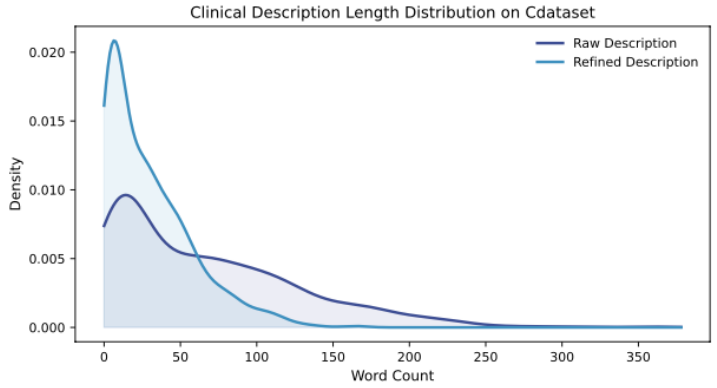
Prompt:
Please rewrite the clinical symptom description into a concise and standardized format suitable for structured clinical NLP tasks. Focus on key abnormal findings, remove redundancies, and maintain medical accuracy.

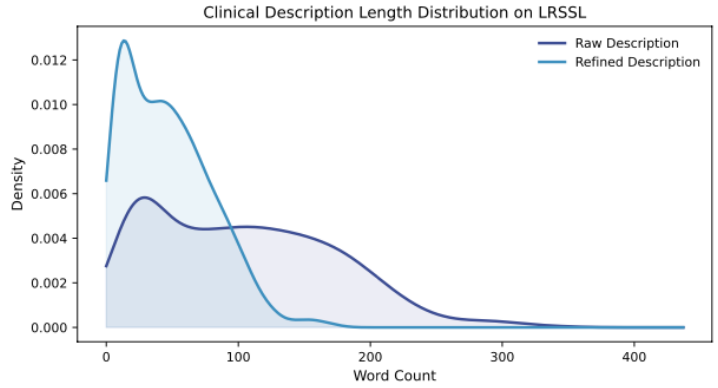
Refinement:
Autosomal recessive disorder characterized by **short stature, craniofacial dysplasia, midface hypoplasia, microcephaly, low-set dysplastic ears, hearing loss, exophthalmos, cleft or high palate, wide fontanelles, and dental abnormalities.**

Multimodal Semantic Modeling

Distribution Experiment





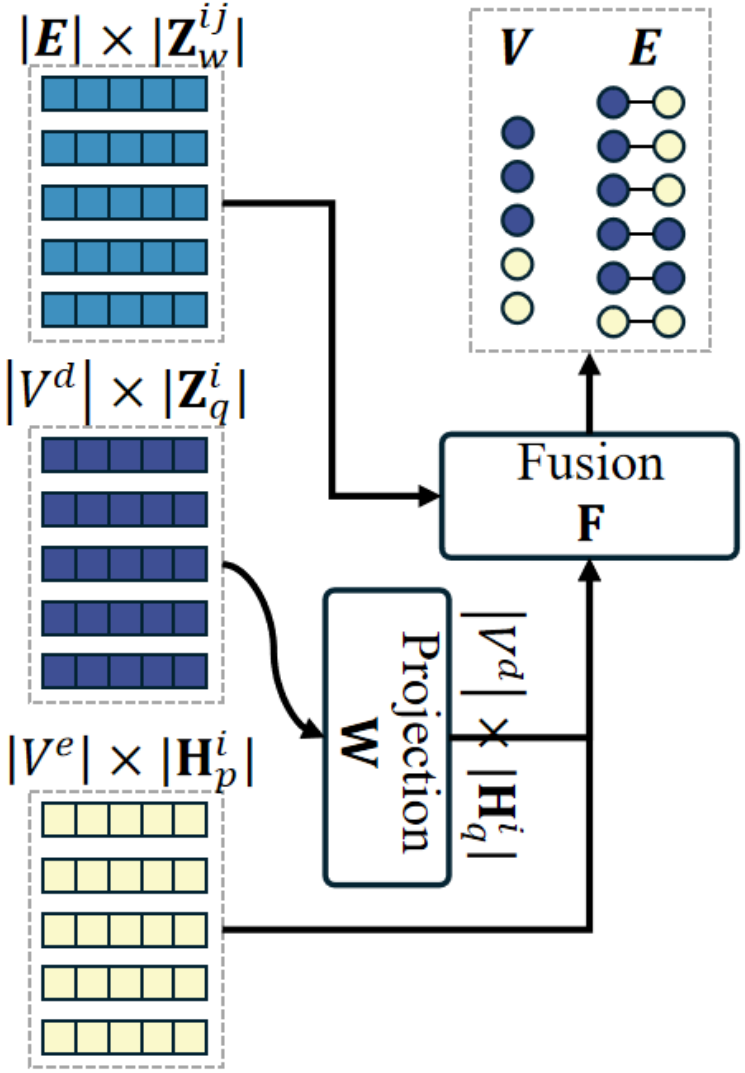


- Experiment result: After refinement, clinical description lengths are shortened and standardized to a more uniform length

Multimodal Semantic Modeling

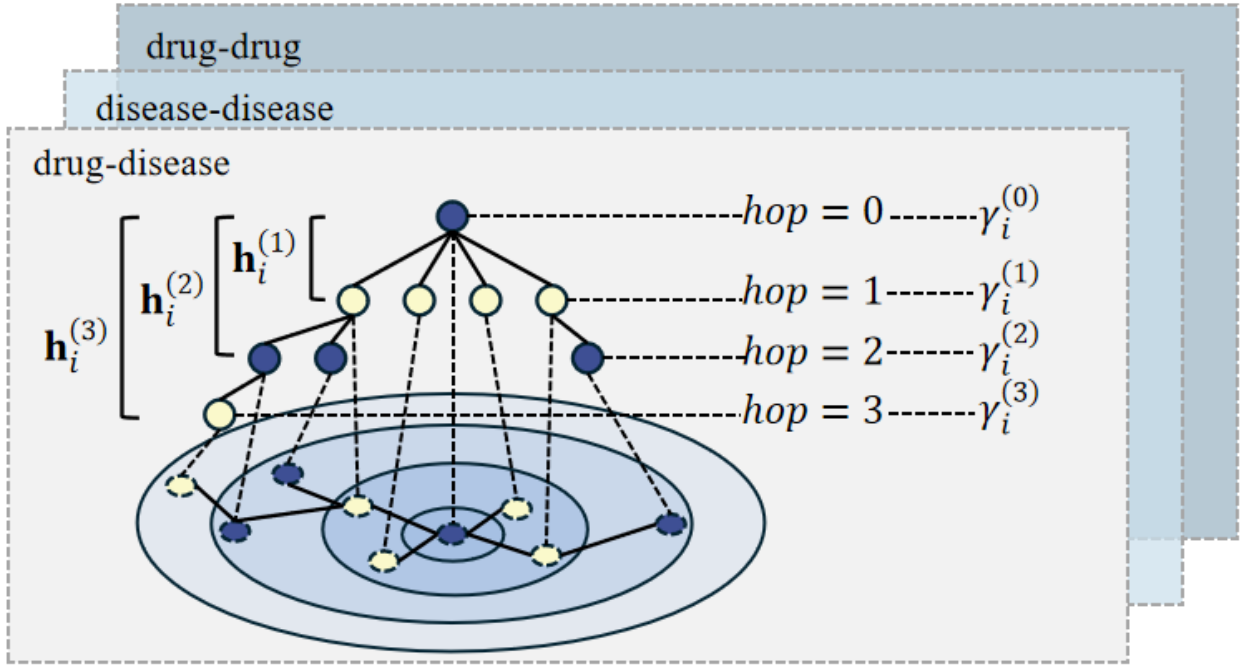
Alignment and Fusion

- Motivation: Enable effective alignment and produce modality-compatible representations
- Introduce a lightweight linear projection layer, mapping the drug molecular embeddings into the latent space of textual modality
  - $\boldsymbol{H}_q = W \cdot \boldsymbol{Z}_q$
- Compute a semantic-aware similarity $\boldsymbol{w}_{ij}$ score using cosine similarity
- Obtain adaptive edge embedding by fusing structure- and semantics-aware components
  - $\boldsymbol{H}_w = \boldsymbol{Z}_w + \beta \cdot \boldsymbol{MLP}(\boldsymbol{w}_{ij})$



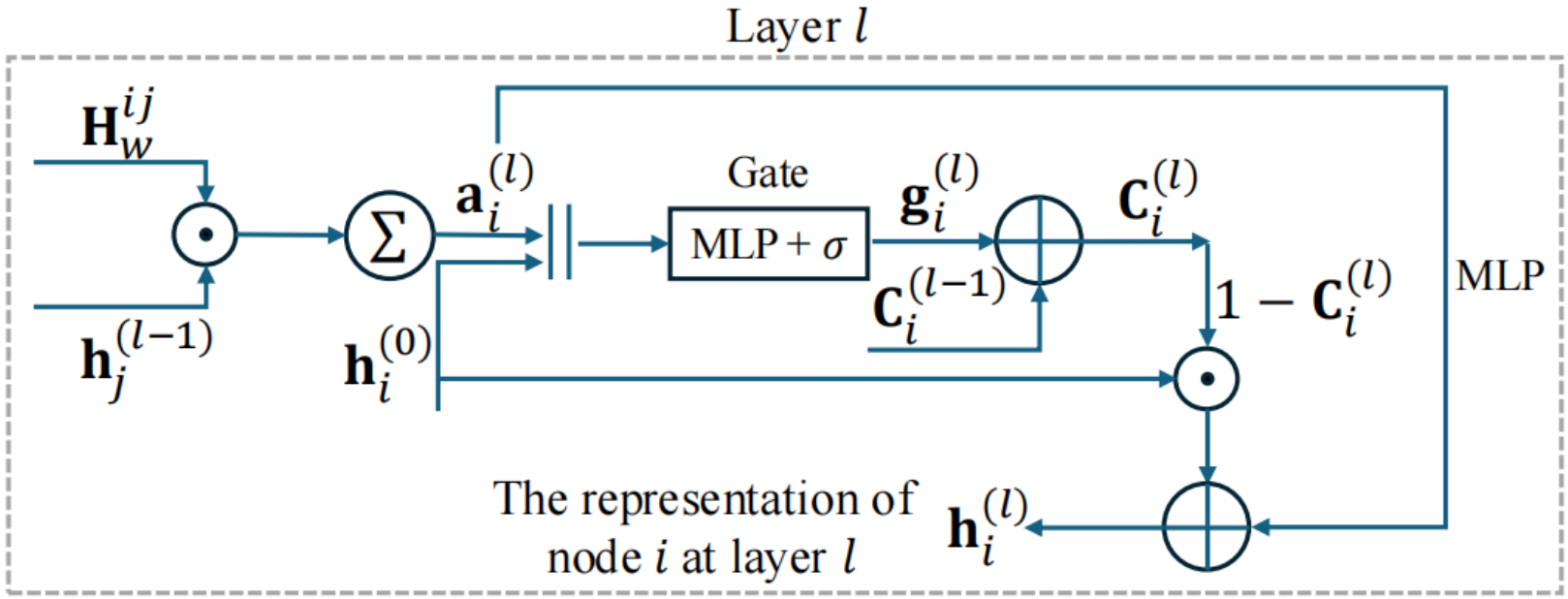
Hierarchical Graph Learning

- Goal: Captures higher-order dependencies and alleviates the over-smoothing problem
- Method: Employs a novel Graph Isomorphism Network with gated mechanisms and residual connections
- Builds hierarchical receptive fields across k-hop neighborhoods
- Progressively integrate structural signals from near to distant nodes, enhancing the representation capacity



Hierarchical Graph Learning

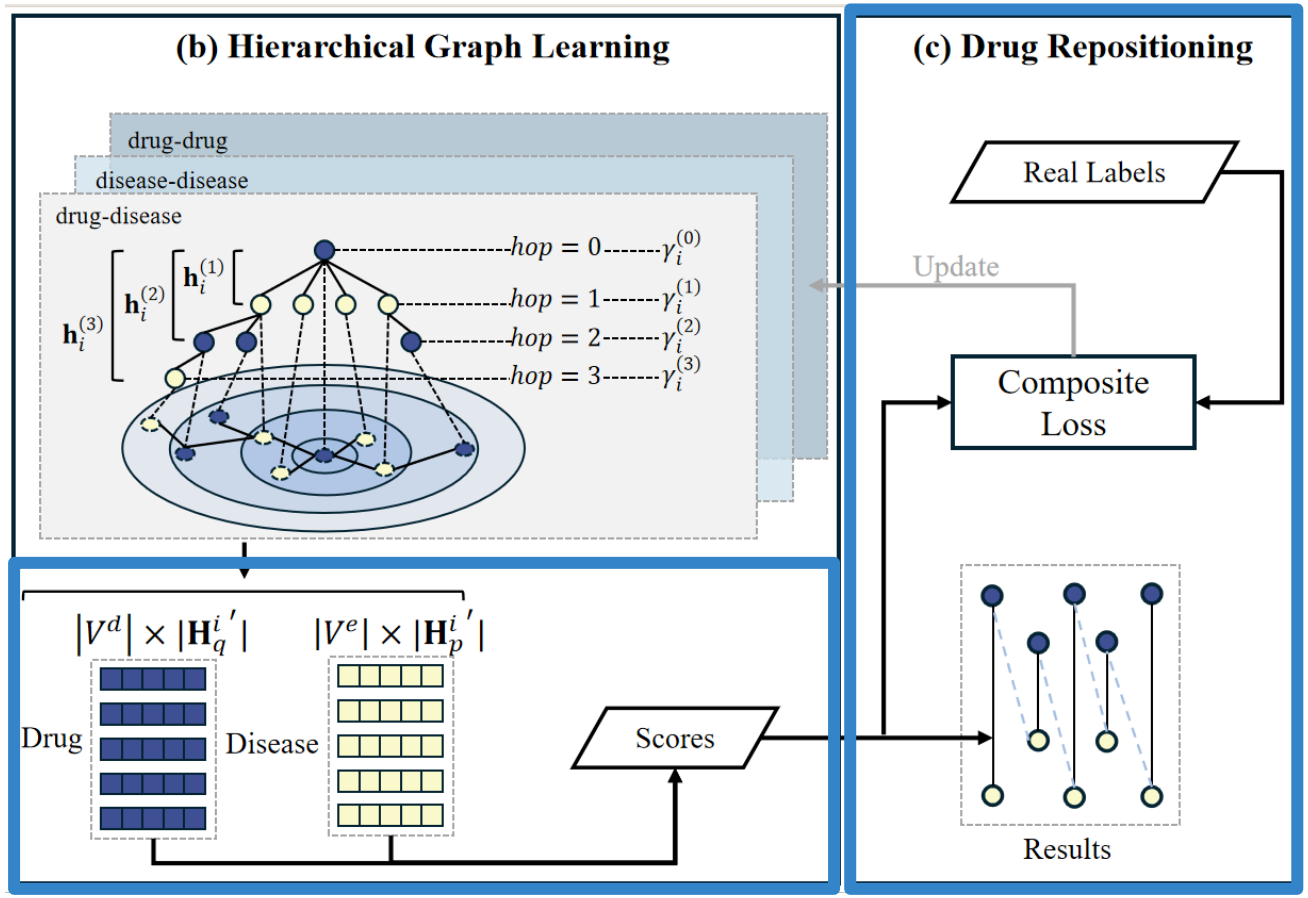
GIN Layer



- the message passing within each GIN layer proceeds in three stages
  - weighted neighborhood aggregation, incorporating structure-aware and semantics-aware edge weights → $\mathbf{a}_i^{(l)} = \sum_{j \in \mathcal{N}(i)} \boldsymbol{H}_w^{ij} \odot \mathbf{h}_j^{(l-1)}$
  - adaptive gating mechanism, control the integration of newly aggregated information and the original semantics → $\mathbf{g}_i^{(l)} = \sigma\left(\mathrm{MLP}\left(\left[\mathbf{a}_i^{(l)} \parallel \mathbf{h}_i^{(0)}\right]\right)\right),\ \mathbf{C}_i^{(l)} = \mathbf{C}_i^{(l-1)} + \mathbf{g}_i^{(l)}$
  - residual update, compute the candidate representation → $h_i^{(l)} = MLP\left(a_i^{(l)}\right) + \left(1 - C_i^{(l)}\right) \odot h_i^{(0)}$

Downstream Task: Drug Repositioning

- Input: Final drug and disease embeddings
- Scoring:
  - Dot-product
    - $s_{ij} = \mathbf{H}_q^{i'} \cdot \mathbf{H}_p^{j'} = \sum_{k=1}^{d} \left(\mathbf{H}_q^{i'}\right)_k \cdot \left(\mathbf{H}_p^{j'}\right)_k$
  - Sigmoid
    - $y_{ij} = \sigma(s_{ij}) = \frac{1}{1+\exp(-s_{ij})}$
  - association probability
- Loss: Composite loss which jointly optimizes multimodal semantic modeling and hierarchical graph learning



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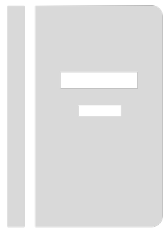

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Research Questions

RQ1: Effectiveness of Drug Repositioning

Does Panacea achieve superior performance on drug repositioning compared to existing SOTA methods?

RQ2: Ablation Study

How effective are Panacea's core design components?

RQ3: Multimodal Representation Analysis

What does Panacea learn through multimodal graph representation learning?

RQ4: Over-smoothing Mitigation Verification

Does Panacea effectively mitigate the over-smoothing issue commonly observed in graph learning?

RQ5: Hyperparameter Robustness Evaluation

How do hyperparameter configuration affect the performance of Panacea?

RQ6: Case Study

Can Panacea discover clinically relevant drug-disease associations supported by literature evidence?

Experiment Settings

Baselines

- Graph representation learning
  - DRHGCN, SCMFDD, SCPMF
- Graph propagation learning
  - HDGAT
- Graph heterogeneous learning
  - AutoDR, HNDR

Datasets

Dataset	No.of drugs	No.of diseases	No.of associations	Sparsity
Fdataset [8]	593	313	1933	1.04%
Cdataset [9]	663	409	2352	0.87%
LRSSL [10]	763	681	3051	0.59%

Metrics

- **AUROC**, **AUPRC**: assess the model's overall ranking performance
- **F1-score**, **Precision**, **Recall**: measure the prediction reliability at different decision thresholds
- For all metrics, higher values indicate better performance

Results

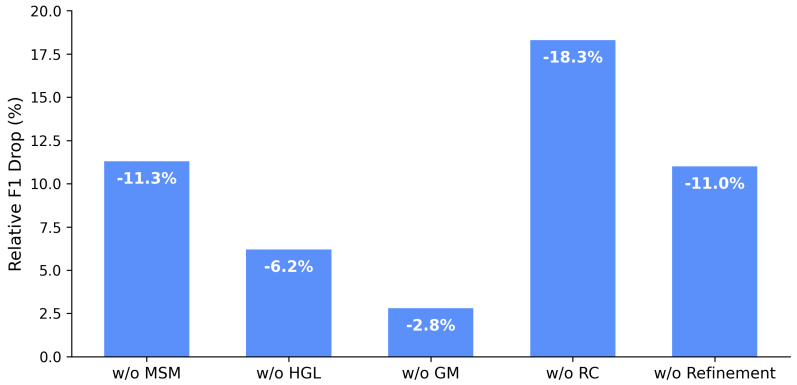
RQ1: Effectiveness of Drug Repositioning

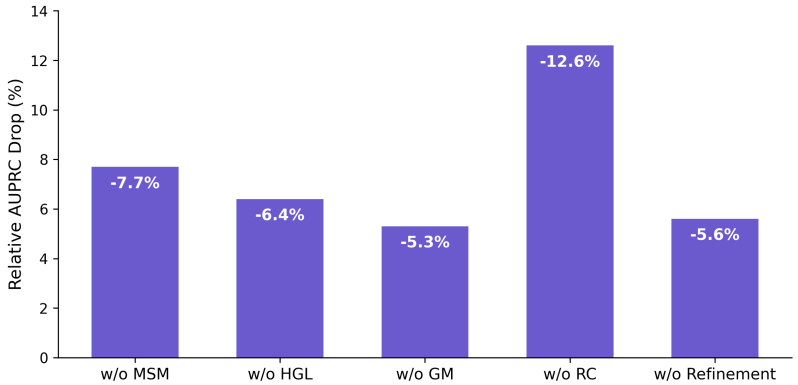
Dataset	Metric	Model						
		HDGAT	DRHGCN	SCPMF	SCMFDD	HNRD	AutoDR	Ours
Fdataset	F1-score	0.493 ± 0.004	0.516 ± 0.007	0.418 ± 0.006	0.364 ± 0.004	0.469 ± 0.008	0.502 ± 0.005	**0.518 ± 0.006**
	Precision	0.734 ± 0.006	0.690 ± 0.008	0.556 ± 0.008	0.515 ± 0.004	0.701 ± 0.008	0.667 ± 0.007	**0.788 ± 0.007**
	Recall	0.371 ± 0.006	**0.404 ± 0.006**	0.335 ± 0.007	0.282 ± 0.003	0.352 ± 0.011	0.402 ± 0.006	0.386 ± 0.006
	AUROC	0.911 ± 0.001	**0.944 ± 0.002**	0.893 ± 0.001	0.776 ± 0.001	0.881 ± 0.004	0.943 ± 0.002	0.943 ± 0.001
	AUPRC	0.303 ± 0.002	0.543 ± 0.006	0.349 ± 0.006	0.005 ± 0.000	0.350 ± 0.006	0.539 ± 0.008	**0.562 ± 0.005**
Cdataset	F1-score	0.572 ± 0.007	0.624 ± 0.006	0.551 ± 0.007	0.466 ± 0.003	0.557 ± 0.007	0.564 ± 0.005	**0.638 ± 0.006**
	Precision	0.634 ± 0.006	0.730 ± 0.007	0.572 ± 0.007	0.608 ± 0.005	0.597 ± 0.008	**0.803 ± 0.007**	0.726 ± 0.007
	Recall	0.521 ± 0.006	0.545 ± 0.007	0.531 ± 0.006	0.378 ± 0.004	0.521 ± 0.007	0.435 ± 0.005	**0.553 ± 0.006**
	AUROC	0.925 ± 0.002	0.960 ± 0.001	0.913 ± 0.002	0.793 ± 0.001	0.913 ± 0.002	0.916 ± 0.001	**0.963 ± 0.001**
	AUPRC	0.337 ± 0.002	**0.640 ± 0.005**	0.423 ± 0.004	0.005 ± 0.000	0.423 ± 0.004	0.625 ± 0.004	**0.640 ± 0.004**
LRSSL	F1-score	0.422 ± 0.015	0.450 ± 0.015	0.403 ± 0.017	0.286 ± 0.008	0.412 ± 0.020	0.451 ± 0.015	**0.456 ± 0.017**
	Precision	0.389 ± 0.012	0.410 ± 0.017	0.352 ± 0.017	0.251 ± 0.007	0.366 ± 0.018	0.402 ± 0.015	**0.426 ± 0.017**
	Recall	0.462 ± 0.009	0.497 ± 0.010	0.472 ± 0.007	0.332 ± 0.002	0.472 ± 0.009	**0.515 ± 0.010**	0.497 ± 0.007
	AUROC	0.928 ± 0.002	0.957 ± 0.001	0.895 ± 0.001	0.768 ± 0.001	0.849 ± 0.003	0.948 ± 0.002	**0.959 ± 0.001**
	AUPRC	0.359 ± 0.002	0.417 ± 0.005	0.271 ± 0.002	0.004 ± 0.000	0.428 ± 0.004	0.417 ± 0.003	**0.432 ± 0.002**
Average	F1-score	0.422	0.530	0.457	0.372	0.479	0.506	**0.537**
	Precision	0.389	0.610	0.493	0.458	0.554	0.624	**0.647**
	Recall	0.462	**0.482**	0.446	0.330	0.448	0.451	0.479
	AUROC	0.921	0.954	0.900	0.779	0.881	0.936	**0.955**
	AUPRC	0.333	0.533	0.348	0.005	0.400	0.527	**0.545**
1st Count		0	4	0	0	0	2	**15**

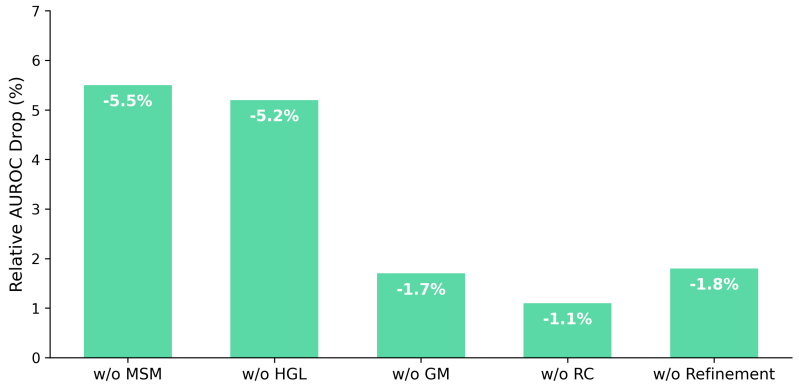
Finding: Panacea achieves **the highest score** in all 15 dataset-metric combinations

Results

RQ2: Ablation Study





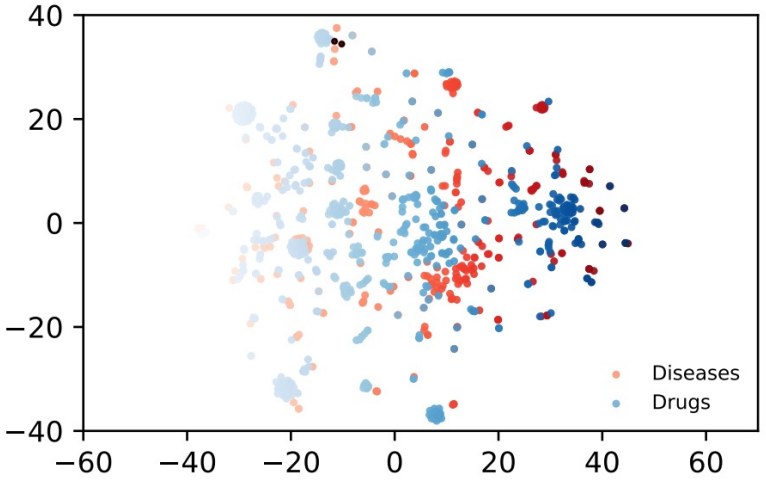


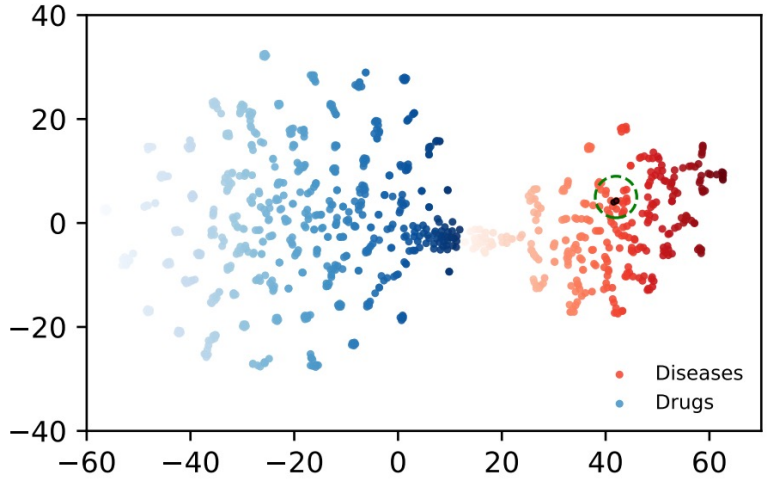
- **w/o HGL** → moderate overall drop (up to **-6.4% AUPRC**)
- **w/o MSM/ Refinement** → large impact (**~11%↓ F1**), proving multimodal priors are useful
- **w/o RC** → severe precision degradation on sparse datasets (**-18.3% F1**)

Finding: All modules contribute to performance. **MSM** and **RC** are most critical, reducing **AUROC** by up to **5.5%** and **F1** by **18.3%** when removed

Results

RQ3: Multimodal Representation Analysis





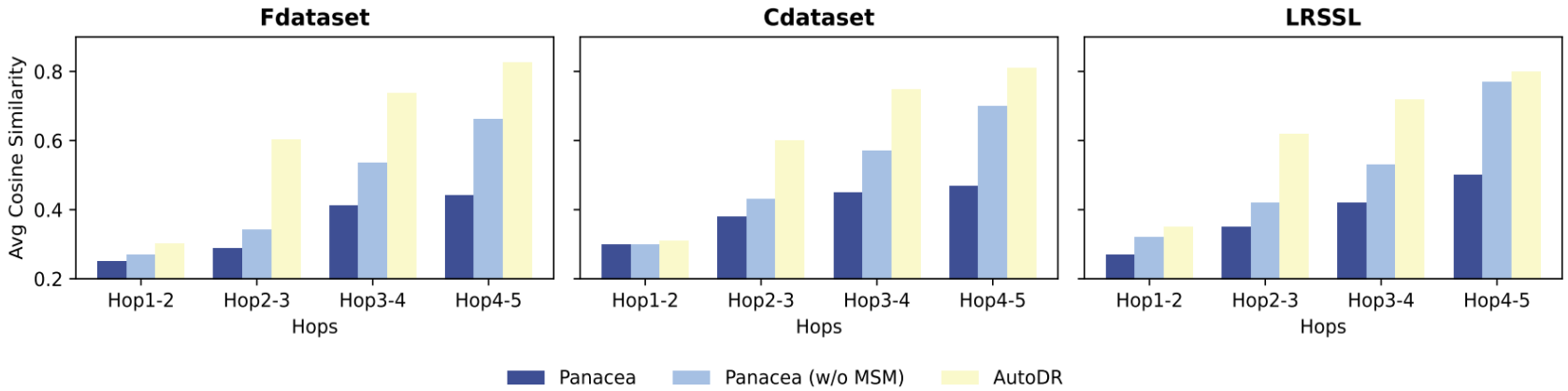
- Left: before hierarchical graph learning → **scattered & mixed embeddings**
- Right: after hierarchical graph learning → **clearer clustering and semantic separation**

Finding: Panacea transforms heterogenous multimodal inputs into **well-structured and semantically meaningful embeddings**, enabling more accurate drug-disease association modeling

Results

RQ4: Over-smoothing Mitigation Verification

Similarity ↑ ⟹ Over-smoothing ↑

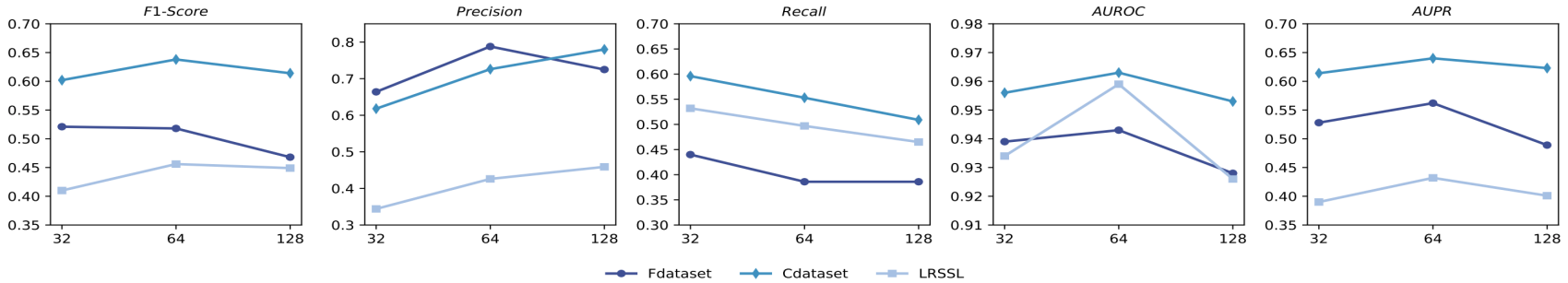


Average cosine similarity between node embeddings at adjacent hops (lower = less over-smoothing)

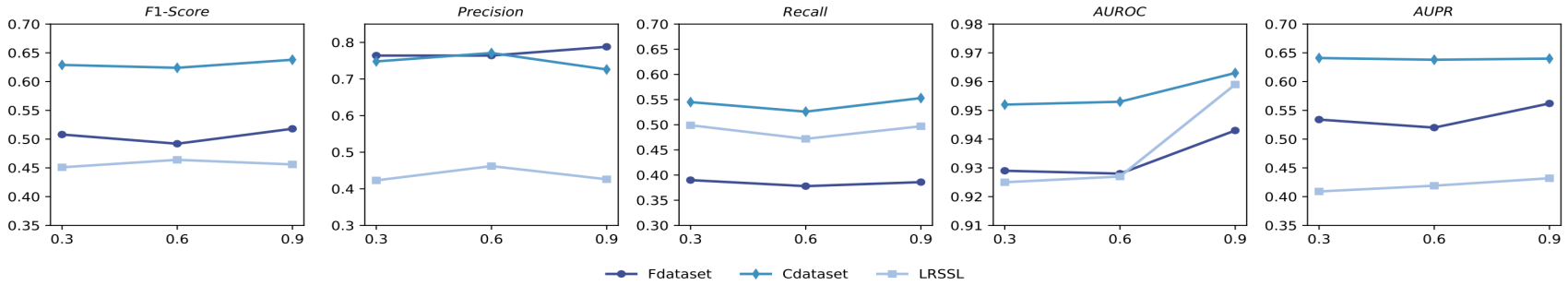
Finding: Panacea effectively **alleviates over-smoothing**, maintaining expressive node representations across deep layers

Results

RQ5: Hyperparameter Robustness Evaluation



(a) Embedding Size



(b) Adaptive Weight

Finding: Panacea remains stable across different **embedding sizes** and **adaptive weights**, demonstrating strong robustness to hyperparameter variations

Results

RQ6: Case Study

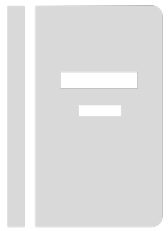
- **Goal**: Validate whether predicted drug-disease associations are clinically meaningful and supported by literature

- **Takeaway**: Predicted associations are **clinically relevant and literature-supported**, demonstrating the practical utility of Panacea in real-world drug repositioning

TABLE IV: Representative drug-disease predictions made by Panacea and supporting evidences from the literature.

Diseases	DrugBankIDs	Candidate Drugs	Evidences
BC	DB01229	Paclitaxel	[27]
AD	DB00747	Scopolamine	[28]
PD	DB00246	Ziprasidone	[29]
BC	DB00755	Tretinoin	[30]
PNE	DB00321	Amitriptyline	[31]

Outline



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Conclusion

- Panacea Framework: We propose Panacea, a *multimodal semantics-enhanced graph learning* framework for drug repositioning
- Multimodal Integration: Panacea integrates *biomedical graphs*, *drug molecular structures*, and *disease symptom descriptions*, aligned via modality-specific encoders and a learnable fusion layer
- Hierarchical Graph Learning: A *gated hierarchical GIN* with residual connections enhances representation capacity and mitigates over-smoothing
- Performance Gains: Panacea achieves state-of-the-art results across three benchmark datasets, with consistent improvements in *F1*, *AUROC*, and *AUPRC*, particularly under *high data sparsity*
- Future Work: We plan to explore *fine-grained semantic alignment* and extend Panacea to broader biomedical association prediction tasks

Thank You!

Q & A

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