Evolving Topological Learning Techniques for Vertical Domains

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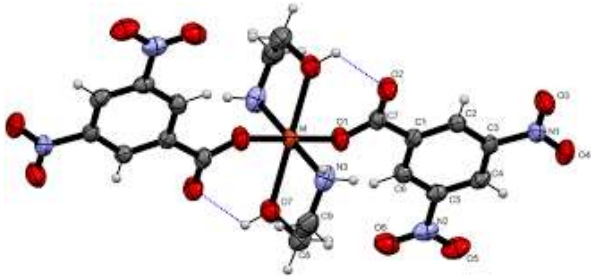
Outline

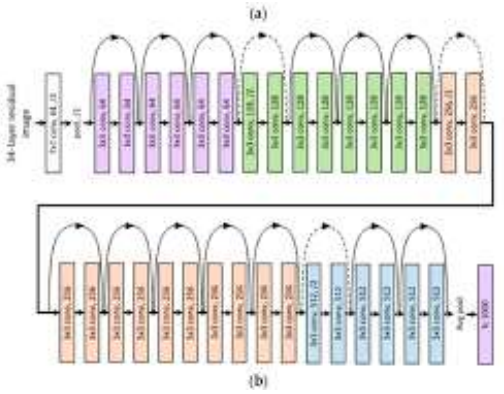
- Problem
- Algorithm
- Application
- Perspective

What is topology in data science?

Social networks

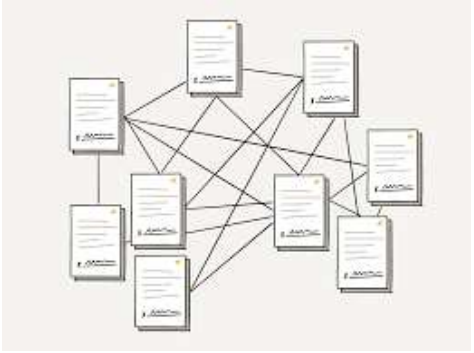


Molecule structure

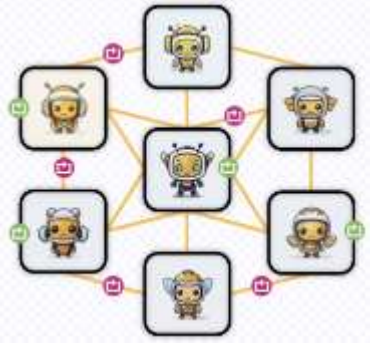


ML model architecture

Underground networks



Citation networks



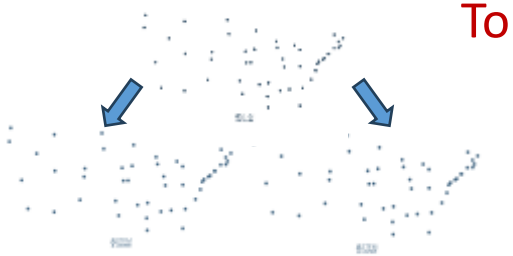
Intelligent agent system

Topology is everywhere in real-world problems!

Useful, especially in Vertical Domain

Topological learning is a approach that focus on construction, adaptation, optimization and analysis of topological structures so as to better handle specific machine learning problems.

Topological learning strategies **V.S.** Vertical domains

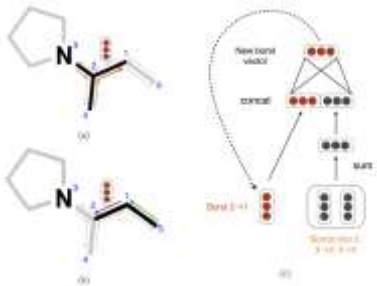


Combinatorial optimization: learn from topology structures in physical space

Small Data & Strong Knowledge

Financial Risk、Intelligence Analysis

Specialized Knowledge | Strict Norms

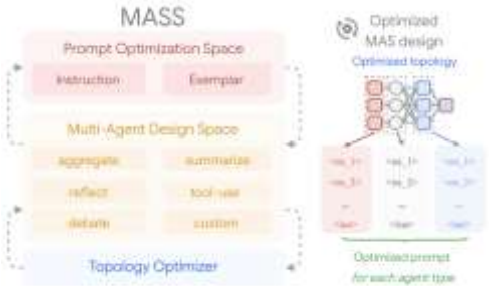


Molecular property prediction: learn from topology structures of molecules

Efficiency & Cost

Biomedicine & Healthcare

Expensive Labels | Few Samples



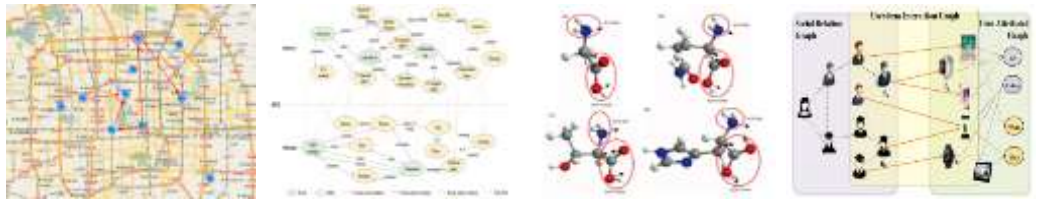
Multi-agent collaboration: learn topology among intelligent agents for better agent collaboration

Accumulation & Knowledge Transfer

Legal Judgments、Clinical Diagnosis

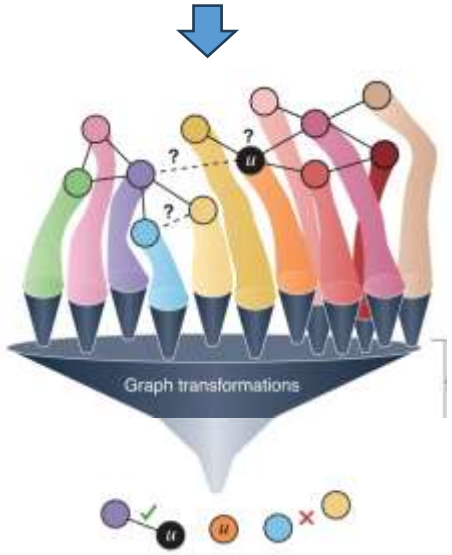
Clear Causality | Traceable Pathways

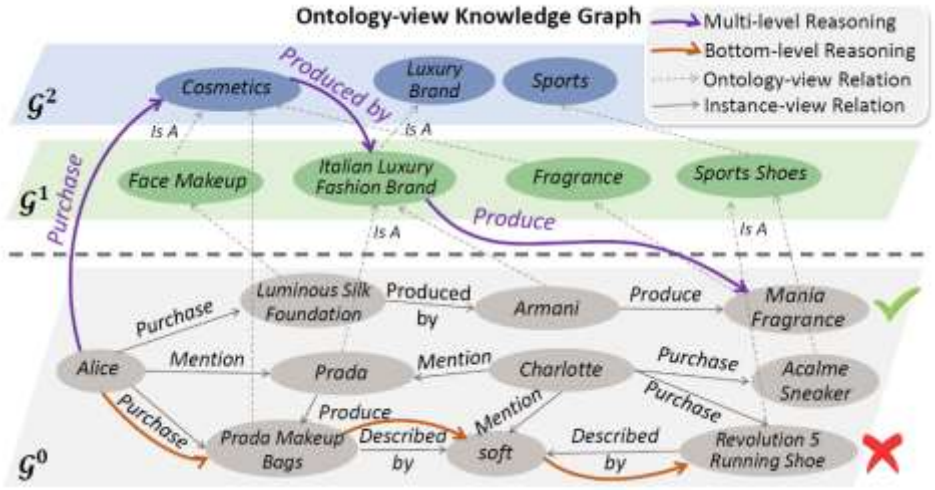
The strength of topological learning

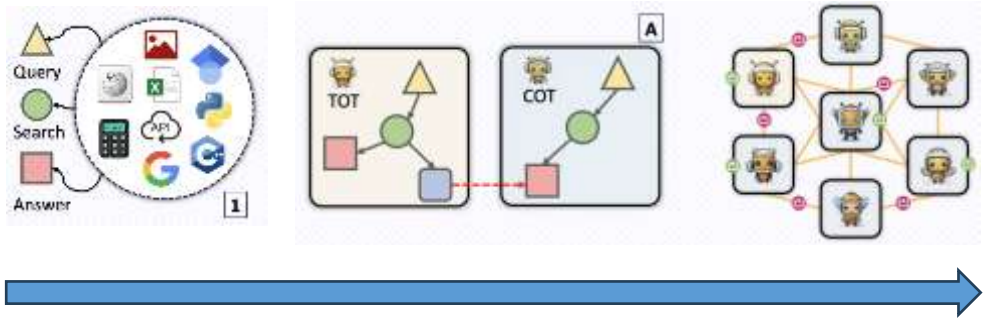


Various topological data

Topological analysis





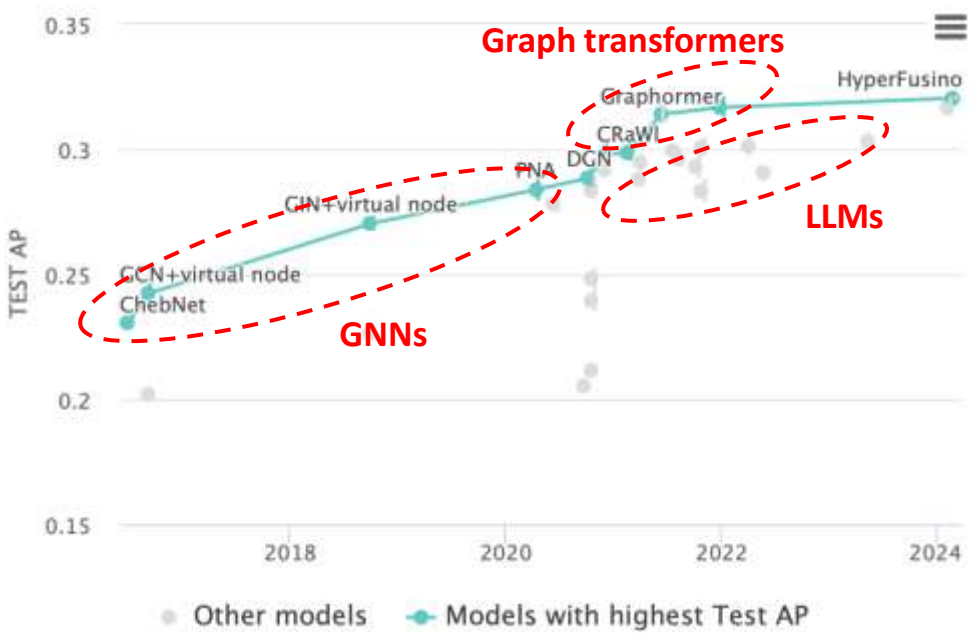


Better understanding and analysis on topological data in vertical domain.

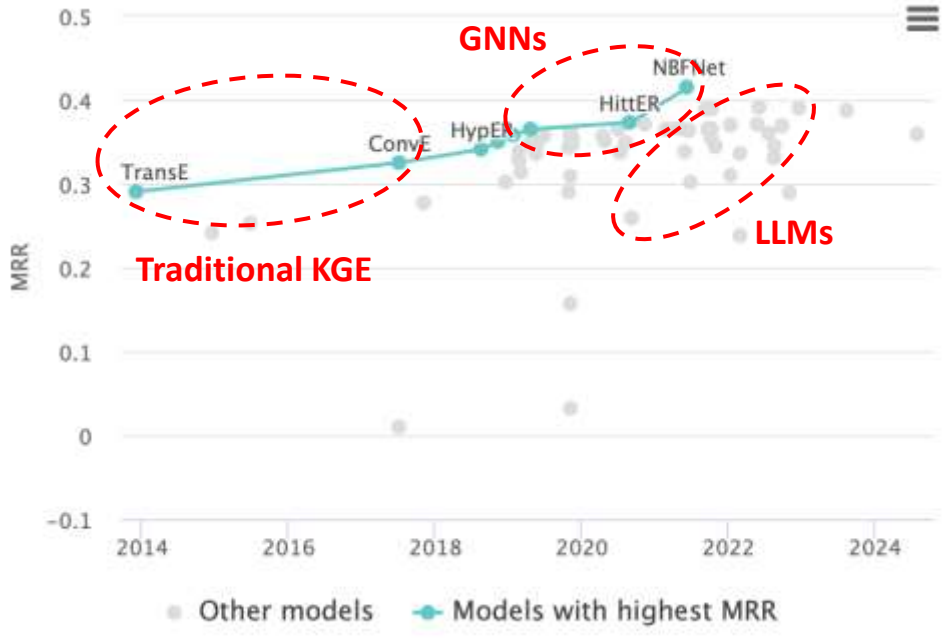
Provide solution with better transparency and reliability.

Technological trends

Molecular property prediction



Knowledge graph completion



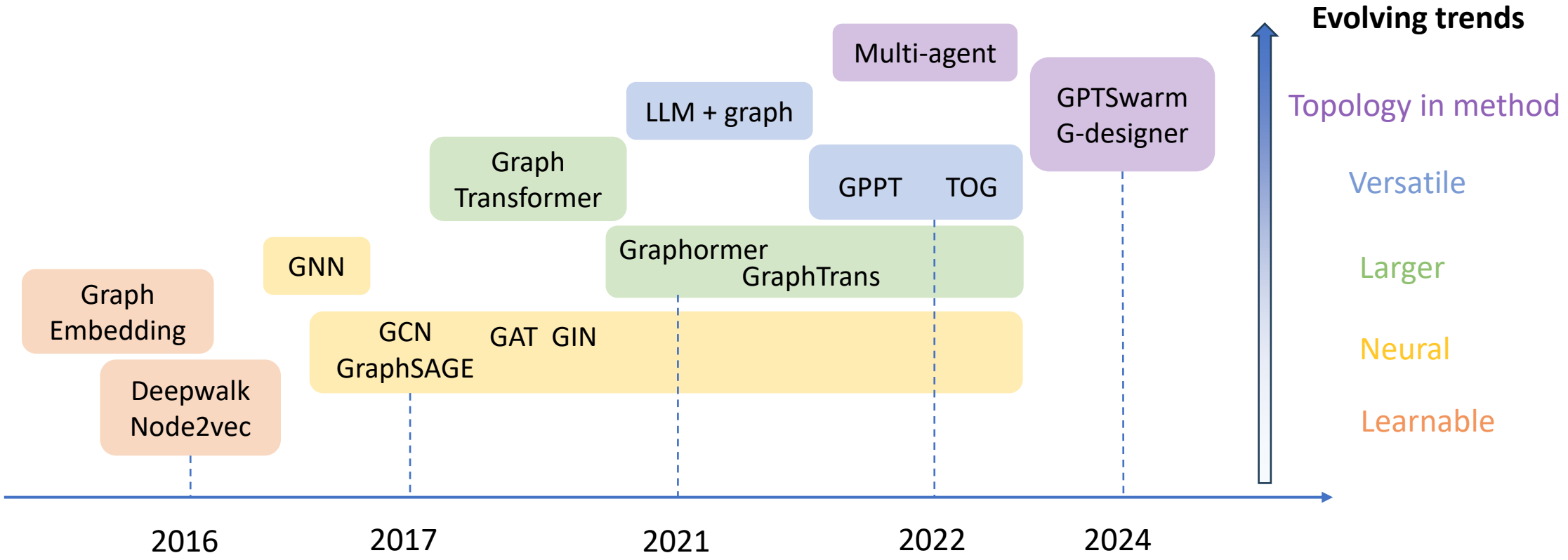
Topological learning develops fast

- Graph embedding — GNNs — Graph transformers
- LLMs are also used in topological learning problems recently

Timeline

The way we utilize topological structure is evolving

- From learnable embeddings to neural architectures
- From neural modeling to versatile integrations



Outline

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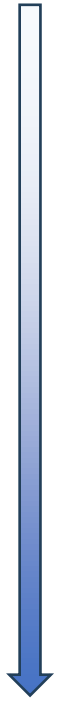
Our Works

- In recent years, we propose evolving topological learning algorithms

Evolving route



Method type	Name	Topology usage
KG embedding	AutoBLM	topological structure only in data
GNN	RedGNN	topological structure in graph model
LLM + GNN	DualR	use topological structure in graph model to enhance LLMs
Multi agent system	AIEvo	design topological structure among intelligent LLM agents

AutoBLM for automatic scoring design

Y. Zhang, Q. Yao, J.T. Kwok. Bilinear Scoring Function Search for Knowledge Graph Learning. IEEE TPAMI. 2023

Evolving route

Method type	Name
KG embedding	AutoBLM
GNN	RedGNN
LLM + GNN	DualR
Multi agent system	AIEvo

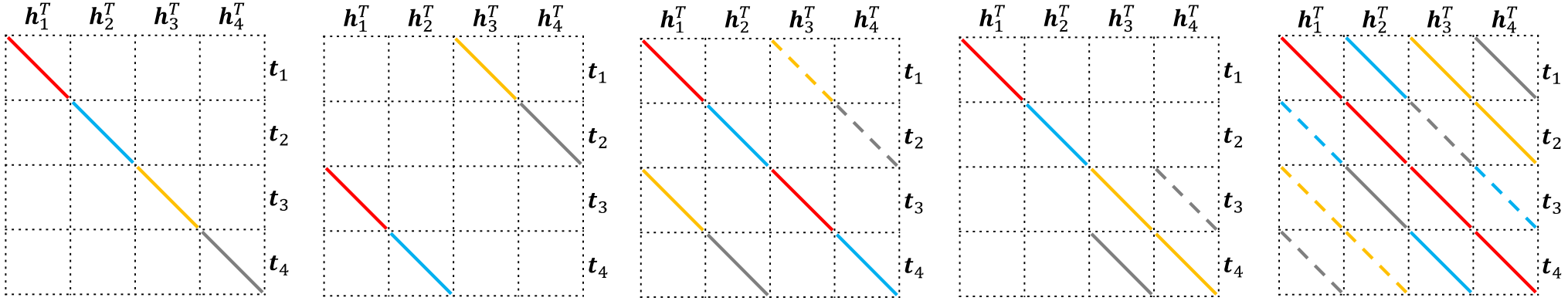
Contribution:

- **Concept**: An automated bilinear scoring function design framework that searches the best KG embedding method based on data patterns.
- **Technique**: Unified BLM search space with evolutionary algorithms, enhanced by filters/predictors exploiting data-inherent topological patterns.
- **Results**: Outperforms SOTA BLMs on KG tasks, proving that data-dependent approach leads to better performance.

Scoring function should be data-dependent

- Limitation of existing works:
  - Manually designed bilinear scoring functions (e.g., DistMult, ComplEx) fail to generalize across various knowledge graphs due to their fixed topological inductive biases.

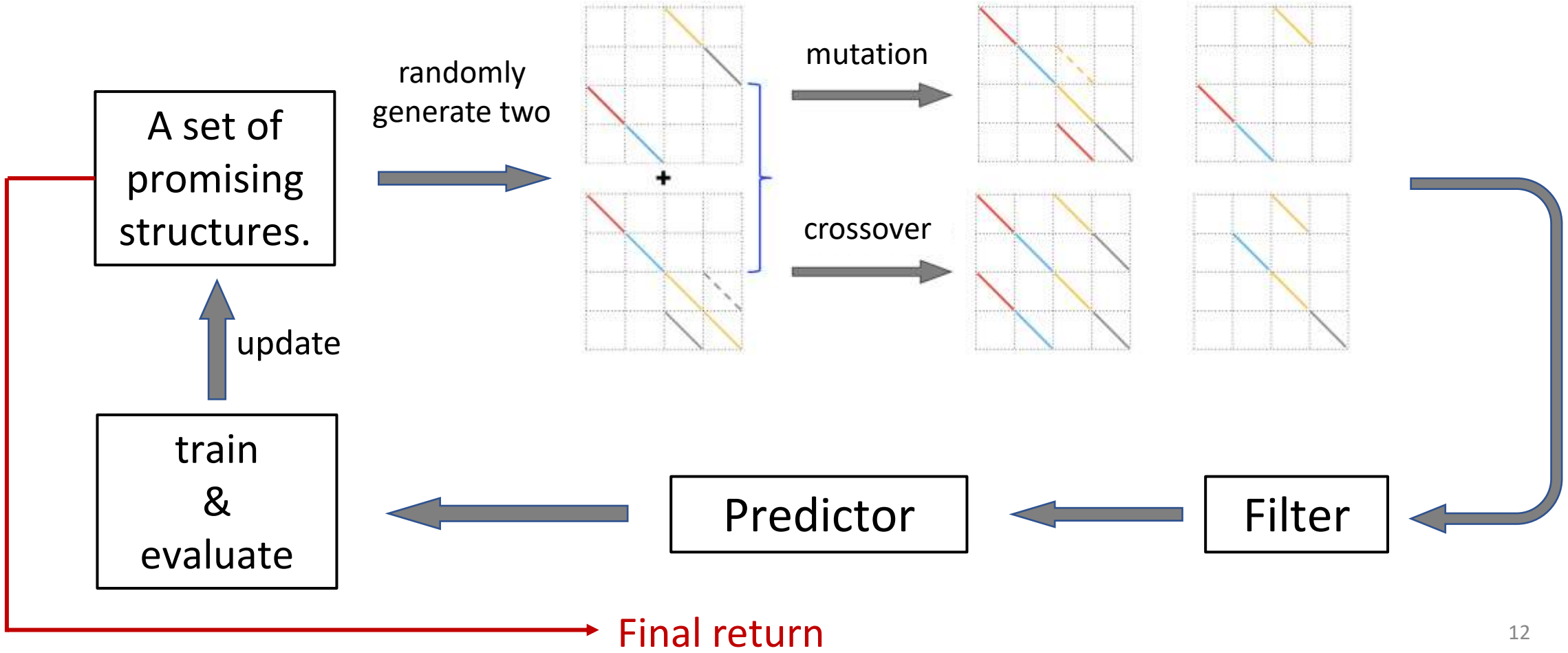
- Idea: KG embedding methods follow unified bilinear function form. Utilize AutoML to automatically search for the best scoring function to fit data patterns.



(a) DistMult. (b) SimplE. (c) ComplEx. (d) Analogy. (e) QuatE.

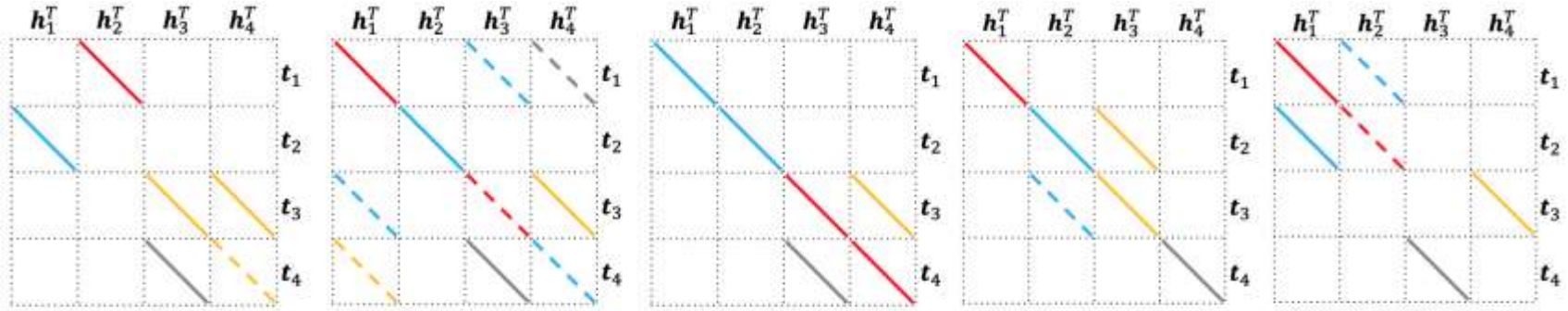
Evolutionary search with predictor

Search a unified discrete matrix space encoding topological interactions (e.g., symmetry/antisymmetry) via evolutionary operators, accelerated by a filter to reduce the size of search space and a predictor to reduce the cost of training.



Data-dependent approach leads to better performance

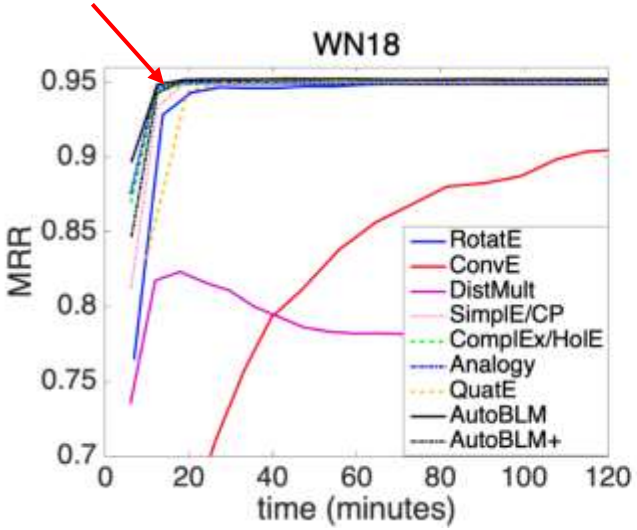
		WN18			FB15 k			WN18RR			FB15k237			YAGO3-10		
model		MRR	H@1	H@10	MRR	H@1	H@10	MRR	H@1	H@10	MRR	H@1	H@10	MRR	H@1	H@10
(TDM)	TransH	0.521	—	94.5	0.452	—	76.6	0.186	—	45.1	0.233	—	40.1	—	—	—
	RotatE	0.949	94.4	95.9	0.797	74.6	88.4	0.476	42.8	57.1	0.338	24.1	53.3	0.488	39.6	66.3
	PairE	—	—	—	0.811	76.5	89.6	—	—	—	0.351	25.6	54.4	—	—	—
(NNM)	ConvE	0.942	93.5	95.5	0.745	67.0	87.3	0.46	39.	48.	0.316	23.9	49.1	0.52	45.	66.
	RSN	0.94	92.2	95.3	—	—	—	—	—	—	0.28	20.2	45.3	—	—	—
	Interstellar	—	—	—	—	—	—	0.48	44.0	54.8	0.32	23.3	50.8	0.51	42.4	66.4
	CompGCN	—	—	—	—	—	—	0.479	44.3	54.6	0.355	26.4	53.5	—	—	—
(BLM)	TuckER	**0.953**	**94.9**	95.8	0.795	74.1	89.2	0.470	44.3	52.6	0.358	26.6	54.4	—	—	—
	DistMult	0.821	71.7	95.2	0.775	71.4	87.2	0.443	40.4	50.7	0.352	25.9	54.6	0.552	47.1	68.9
	SimplE/CP	0.950	94.5	95.9	0.826	79.4	90.1	0.462	42.4	55.1	0.350	26.0	54.4	0.565	49.1	71.0
	HolE/ComplEx	0.951	94.5	95.7	0.831	79.6	90.5	0.471	43.0	55.1	0.345	25.3	54.1	0.563	49.0	70.7
	Analogy	0.950	94.6	95.7	0.816	78.0	89.8	0.467	42.9	55.4	0.348	25.6	54.7	0.557	48.5	70.4
	QuatE	0.950	94.5	95.9	0.782	71.1	90.0	0.488	43.8	**58.2**	0.348	24.8	55.0	0.556	47.4	70.4
AutoBLM		0.952	94.7	**96.1**	0.853	82.1	91.0	0.490	45.1	56.7	0.360	26.7	55.2	0.571	50.1	**71.5**
AutoBLM+		0.952	94.7	**96.1**	**0.861**	**83.2**	**91.3**	**0.492**	**45.2**	56.7	**0.364**	**27.0**	**55.3**	**0.577**	**50.2**	**71.5**

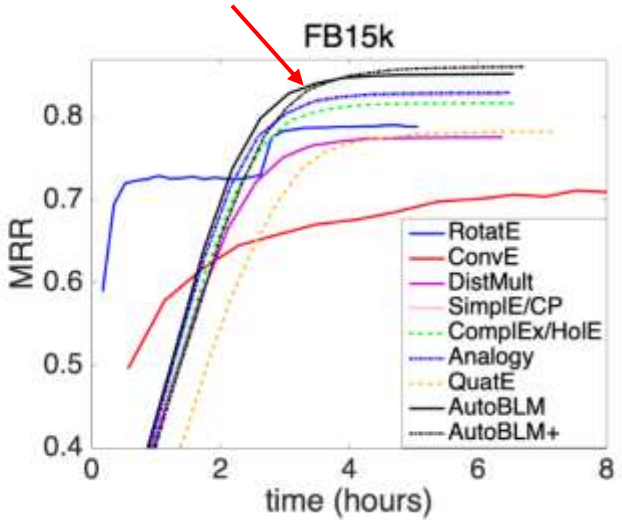


(a) WN18. (b) FB15k. (c) WN18RR. (d) FB15k237. (e) YAGO3-10.

- BLMs are better than the other models.
- There is no absolute winner among the BLMs.
- Compared with human-designed ones, the SFs searched by AutoBLM always lead the performance.

Outstanding performance on vertical domain tasks





- On entity relation prediction task for knowledge base, AutoBLM achieve better performance and comparable time as other human designed bilinear models

dataset	MUTAG
GCN	68.83
R-GCN	74.12
CompGCN	85.3*
AutoBLM	85.00
AutoBLM+	**85.88**

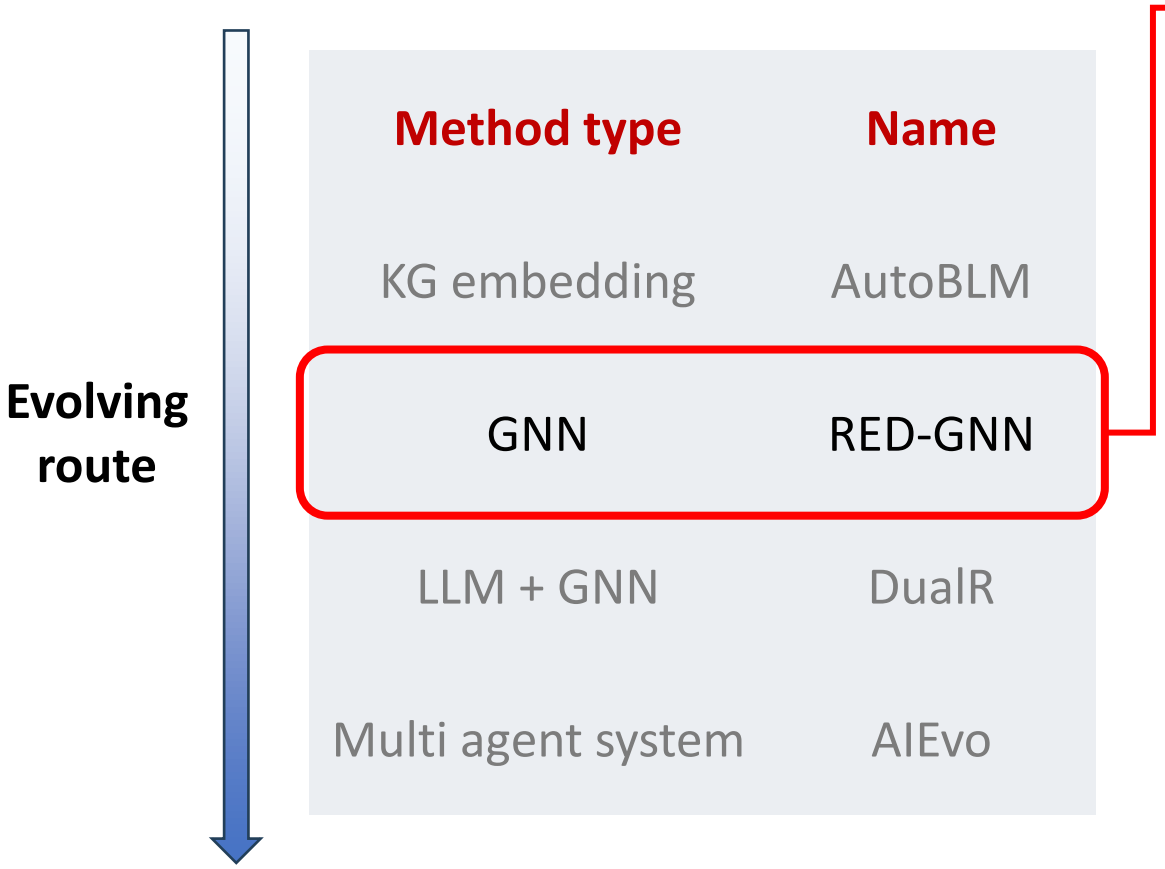
Molecule relation prediction

dataset	BGS
GCN	73.79
R-GCN	82.97
CompGCN	84.14
AutoBLM	84.83
AutoBLM+	**86.17**

Geological material prediction

RED-GNN for effective knowledge graph reasoning

Y. Zhang, Q. Yao. Knowledge graph reasoning with relational digraph. WWW. 2022



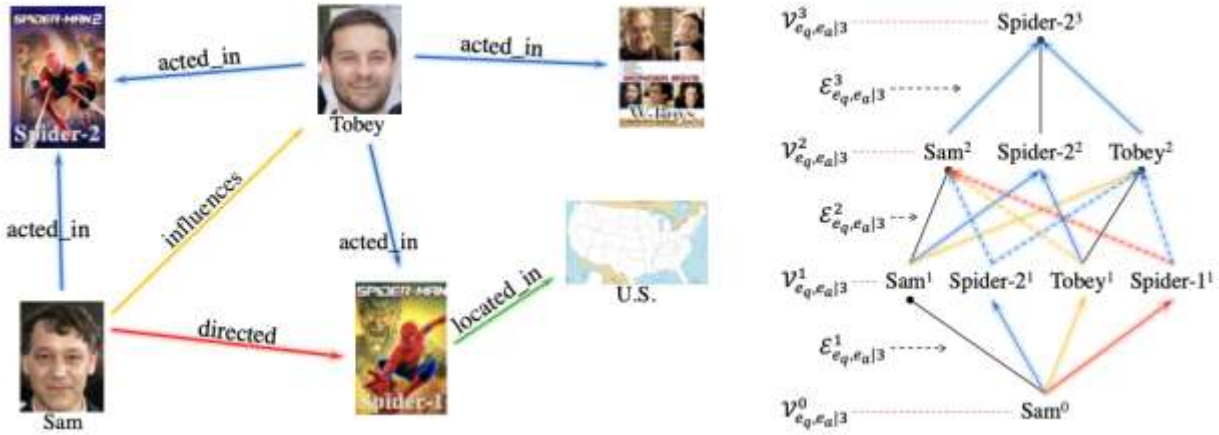
Contribution:

- **Concept**: an effective GNN methods to capture complex graph pattern and interpretable reasoning path in knowledge reasoning problems
- **Technique**: propose r-digraph to bridge path and subgraph, and design RED-GNN to recursively encode r-digraph through query dependent attention weights
- **Results**: RED-GNN shows significant gains over the state-of-the-art reasoning methods in knowledge graph reasoning tasks. It also achieve high efficiency and interpretable results

Trade-off for informative reasoning and cost

- Limitation of existing works:
  - Path-based reasoning is interpretable and transferable, but cannot capture complex patterns in graphs
  - Subgraph-based reasoning can explicitly extract complex graph structures, but usually have high computational cost

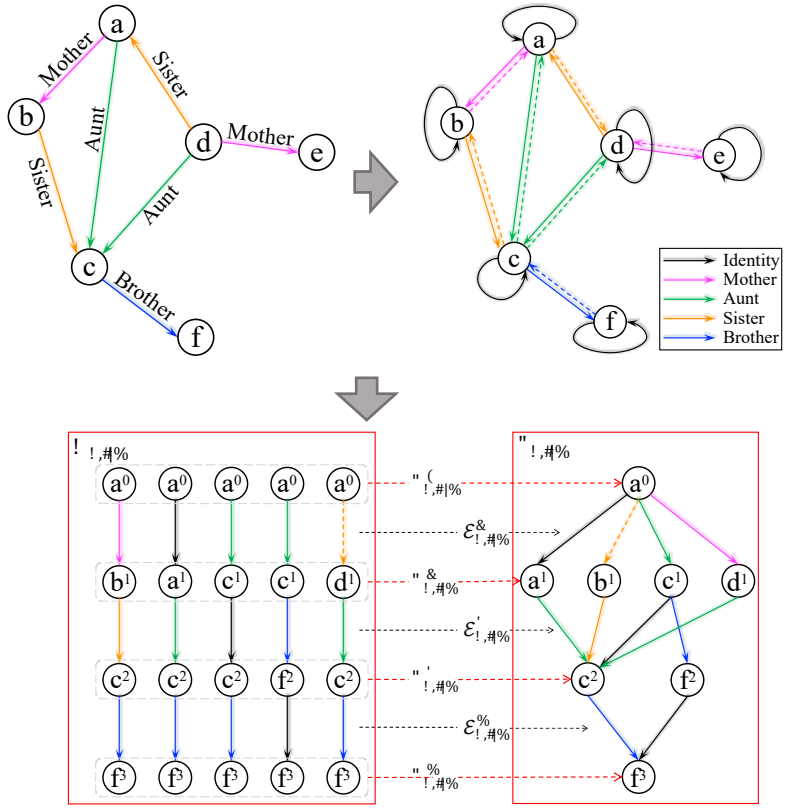
- Idea
  - Introduce a novel relational structure to bridge path and subgraph, and propose an effective GNN method to encode that relational structure



Knowledge graph and extracted r-digraph

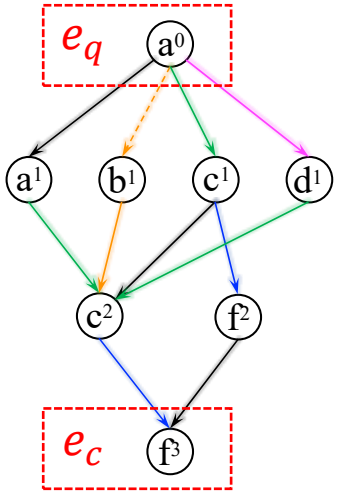
Relational digraph and encoder

- Relational digraph



- Path has more regular form than subgraph.
- The order in path can provide explanation.

- GNN for r-digraph encoding
  - Extract the neighborhoods of both e_q and e_c;
  - Intersect the neighbors to construct the subgraph;
  - Run the message passing



initialize $\boldsymbol{h}^0_{e_q}(e_q, r_q, e_c) = \mathbf{0}$;
for $\ell = 1, 2, \ldots, L$ **do**
  message passing for entities $e \in \mathcal{V}^{\ell}_{e_q, e_c|L}$ with (4);
end for

$$\boldsymbol{h}^{\ell}_{e}(e_q, r_q, e_c) = \delta\Big(\sum_{(e_s, r, e) \in \mathcal{E}^{\ell}_{e_q, e_c|L}} \varphi\big(\boldsymbol{h}^{\ell-1}_{e_s}(e_q, r_q, e_c), \boldsymbol{h}^{\ell}_{r}\big)\Big), \quad (4)$$

$$\varphi\big(\boldsymbol{h}^{\ell-1}_{e_s}(e_q, r_q, e_c), \boldsymbol{h}^{\ell}_{r}\big) = \alpha^{\ell}_{e_s, r|r_q} \boldsymbol{W}^{\ell}\big(\boldsymbol{h}^{\ell-1}_{e_s}(e_q, r_q, e_c) + \boldsymbol{h}^{\ell}_{r}\big)$$

- Scoring with graph-level representation

$$s(e_q, r_q, e_c) = \boldsymbol{w}^{\top} h^{L}_{e_c}(e_q, r_q, e_c)$$

- Loss function

$$\mathcal{L} = \sum_{(e_q, r_q, e_a) \in \mathcal{Q}_{\mathrm{tra}}} \Big(-\log s(e_q, r_q, e_a) - \sum_{e' \in \mathcal{N}} \frac{1}{|\mathcal{N}|} \log\big(1 - s(e_q, r_q, e')\big)\Big)$$

positive

negative

RED-GNN is effective and efficient

- Transductive reasoning

Transductive reasoning. Best performance is indicated by the bold face numbers, and the second best is underlined. Hit@1 and Hit@10 are formed as percentage values. '-' means unavailable results and results for methods with '*' are copied from the original papers.

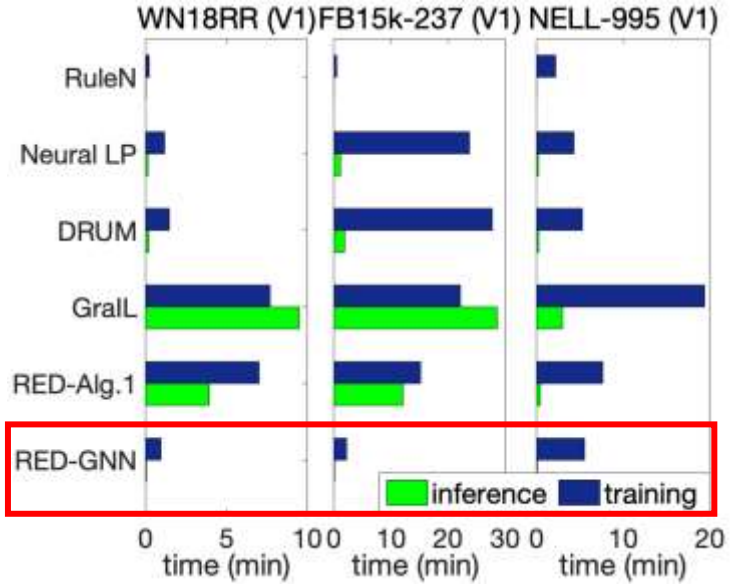
type	models	Family			UMLS			WN18RR			FB15k-237			NELL-995		
		MRR	Hit@1	Hit@10	MRR	Hit@1	Hit@10	MRR	Hit@1	Hit@10	MRR	Hit@1	Hit@10	MRR	Hit@1	Hit@10
triplet	RotatE	.921	86.6	98.8	.925	86.3	99.3	.477	42.8	57.1	.337	24.1	53.3	.508	44.8	60.8
	ConvE	.912	83.7	98.2	.937	92.2	96.7	.427	39.2	49.8	.325	23.7	50.1	.511	44.6	61.9
	SimplE	.941	89.6	99.1	.944	90.5	99.3	.480	44.0	55.1	.350	25.6	53.8	.533	46.6	64.3
path	MINERVA	.885	82.5	96.1	.825	72.8	96.8	.448	41.3	51.3	.293	21.7	45.6	.513	41.3	63.7
	Neural LP	.924	87.1	99.4	.745	62.7	91.8	.435	37.1	56.6	.252	18.9	37.5	.403	34.6	49.1
	DRUM	.934	88.1	99.6	.813	67.4	97.6	.486	42.5	58.6	.343	25.5	51.6	.423	37.1	51.0
	RNNLogic*	–	–	–	.842	77.2	96.5	.483	44.6	55.8	.344	25.2	53.0	–	–	–
subgraph	CompGCN	.933	88.3	99.1	.927	86.7	**99.4**	.479	44.3	54.6	.355	26.4	53.5	.412	33.5	55.3
	DPMPN	.981	97.4	98.1	.930	89.9	98.2	.482	44.4	55.8	.369	28.6	53.0	.513	45.2	61.5
	NBFNet	.989	**98.8**	98.9	.813	73.7	95.2	.551	49.7	66.6	.415	32.1	**59.9**	.294	24.3	38.0
	RED-GNN	**.992**	**98.8**	**99.7**	**.964**	**94.6**	99.0	**.564**	**50.2**	**67.8**	**.418**	**32.9**	59.0	**.543**	**47.6**	**65.1**

- Inductive reasoning

Inductive reasoning. The best performance is indicated by the bold face numbers, and the second best is underlined.

		WN18RR				FB15k-237				NELL-995			
		V1	V2	V3	V4	V1	V2	V3	V4	V1	V2	V3	V4
MRR	RuleN	0.668	0.645	0.368	0.624	0.363	0.433	0.439	0.418	0.615	0.385	0.381	0.333
	Neural LP	0.649	0.635	0.361	0.617	0.325	0.389	0.400	0.396	0.610	0.361	0.367	0.261
	DRUM	0.666	0.646	0.380	0.627	0.333	0.395	0.402	0.410	**0.628**	0.365	0.375	0.273
	GraIL	0.627	0.625	0.323	0.553	0.279	0.276	0.251	0.227	0.481	0.297	0.322	0.262
	NBFNet	0.684	0.652	0.425	0.604	0.307	0.369	0.331	0.305	0.534	0.410	0.425	0.237
	RED-GNN	**0.707**	**0.686**	**0.437**	**0.634**	**0.369**	**0.462**	**0.450**	**0.428**	0.623	**0.419**	**0.436**	**0.363**

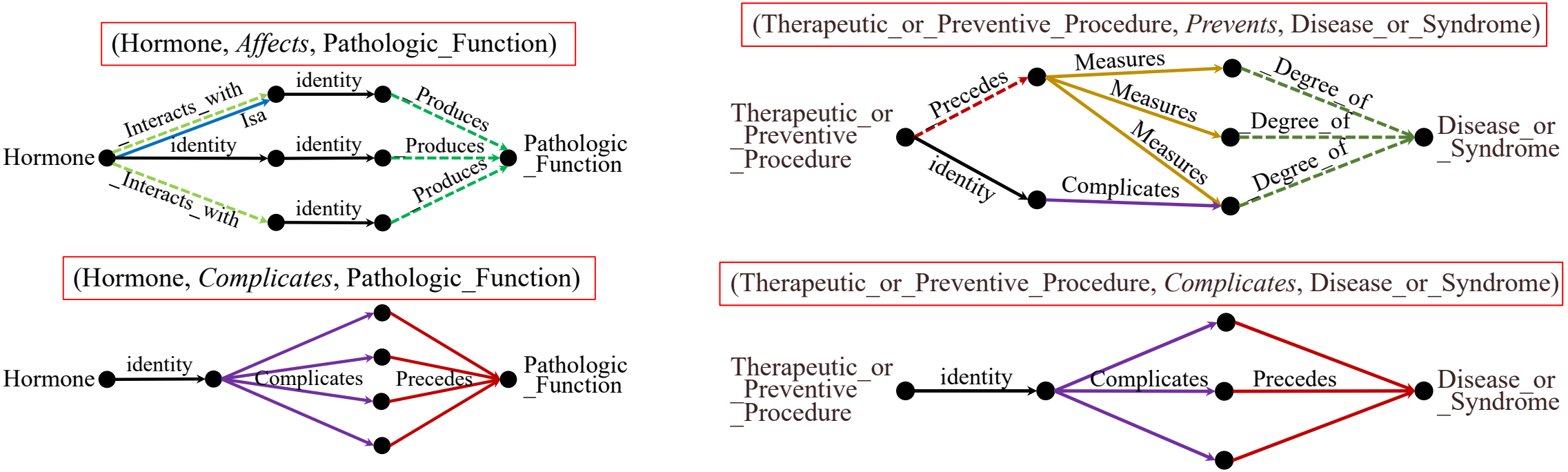
- RED-GNN consistently achieve good performance



- RED-GNN is efficient compared with subgraph-based reasoning methods

RED-GNN provide interpretable results

- Different query relations for the same query and answer entities



- Learned structures are query dependent and meaningful

DualR for Collaborative Reasoning

G. Liu, Y. Zhang, Y. Li, Q. Yao. Dual Reasoning: A GNN-LLM Collaborative Framework for Knowledge Graph Question Answering. Conference on Parsimony and Learning(CPAL) 2025.

Evolving route

Method type	Name
KG embedding	AutoBLM
GNN	REDGNN
LLM + GNN	DualR
Multi agent system	AIEvo

Contribution:

- **Concept**: Following dual-process theory, we introduce a novel framework, Dual-Reasoning, which integrates an external "System 2" for deliberate, explicit reasoning on KGs, complementing the implicit reasoning of LLMs.
- **Technique**: LLM-GNN collaborative framework leveraging LLM-empowered GNN model and knowledge-enhanced multiple-choice prompt.
- **Results**: SOTA performance on KGQA task, retaining high efficiency and interpretability.

Analogy to Dual-Process Theory

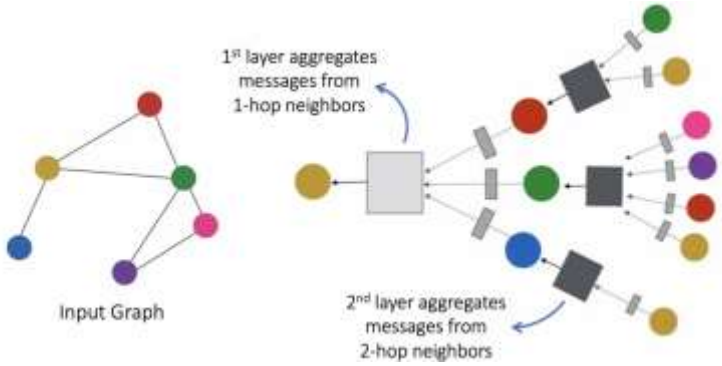
- Following dual-process theory, we propose Dual-Reasoning (DualR) framework, combines GNN-based structured, deliberate reasoning of "System 2" with LLM-based intuitive reasoning of "System 1".

System1

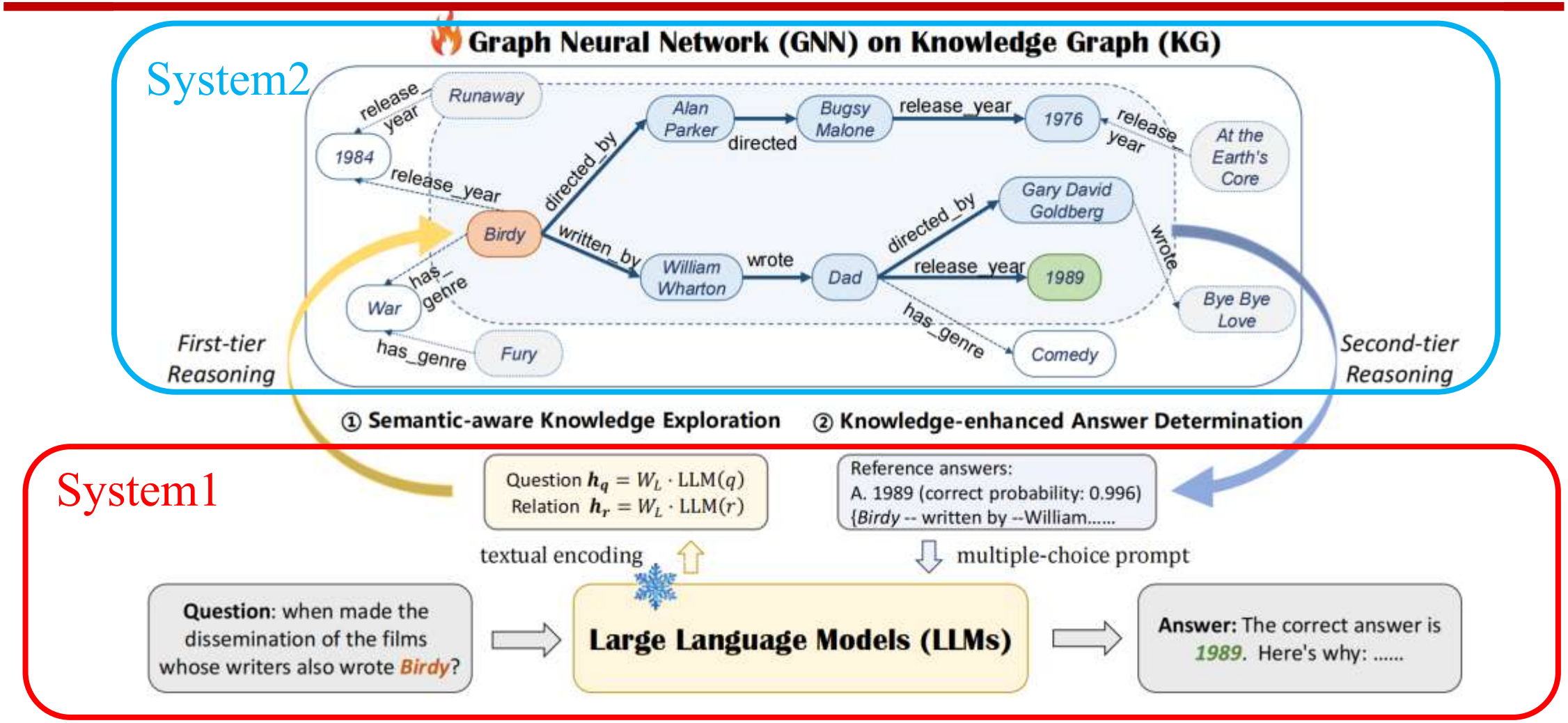
LLM
intuitive
associative
implicit reasoning
pretrained knowledge

System2

GNN on KG
logical
deliberate
explicit reasoning
up-to-date knowledge



Framework of Dual Reasoning



Dual Reasoning combines GNN-based structured, deliberate reasoning of “System 2” with LLM-based intuitive reasoning of “System 1”.

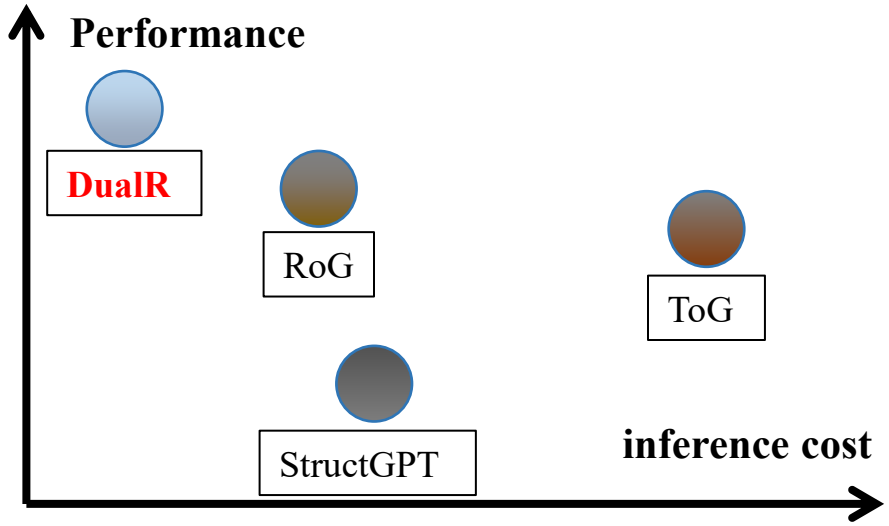
Performance and Efficiency

Dual Reasoning provides more accurate answer, outperforms all baselines on different datasets.

Type	Methods	WebQSP	CWQ	MetaQA-1
KG-based	KV-Mem	46.7	18.4	96.2
	GraftNet	66.4	36.8	97.0
	EmbedKGQA	66.6	-	97.5
	NSM	68.7	47.6	97.1
	SR+NSM	69.5	50.2	-
	UniKGQA	75.1	50.7	97.5
GPT-3-based	KB-Binder	74.4	-	92.9
	KAPING	73.9	55.4	-
Llama2-based	Llama2-13B	40.9	22.1	31.9
	RoG-Llama2-7B	74.2	56.4	-
	ToG-Llama2-70B	68.9	57.6	-
	DualR-Llama2-13B	**78.3**	**58.0**	**97.9**
ChatGPT-based	ChatGPT	61.2	38.8	61.9
	RoG-ChatGPT	81.5	52.7	-
	KD-CoT	68.6	55.7	-
	StructGPT	72.6	55.3	94.2
	ToG-ChatGPT	76.2	58.9	-
	DualR-ChatGPT	**82.8**	**62.0**	**98.1**
GPT-4-based	GPT-4	67.3	46.0	65.7
	ToG-GPT-4	82.6	69.5	-
	DualR-GPT-4	**87.6**	**73.6**	**98.3**

Dual Reasoning significantly reduces interactions with LLM, consuming less inference costs.

Methods	WebQSP time	WebQSP #interaction	CWQ time	CWQ #interaction
RoG	1.98	2	3.04	2
StructGPT	3.37	3	4.22	4
ToG	16.7	15	20.5	22
DualR	**1.29**	**1**	**1.99**	**1**



Case Study of Faithful Output

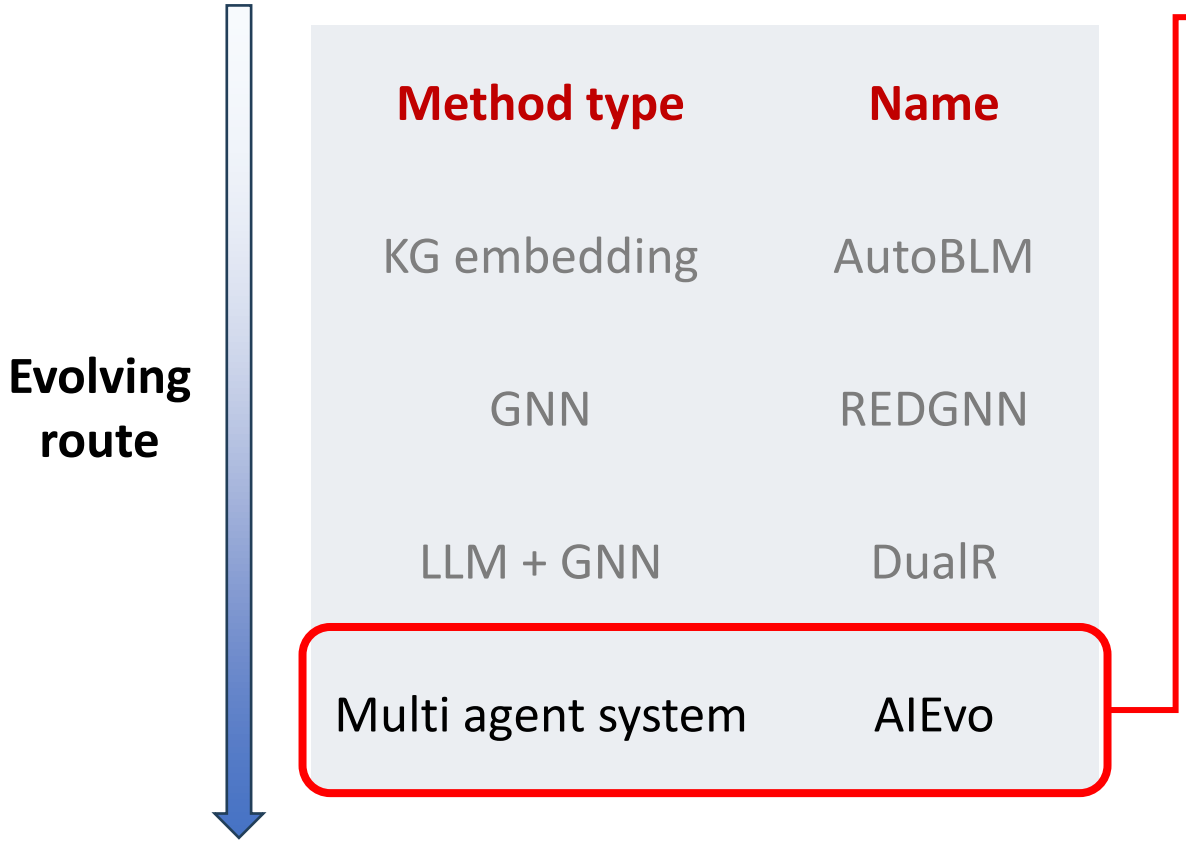
Question-Answer	What is the most current year the team who won the 2010 World Series has won another World Series? - 2014 World Series.
Output by Llama2-13B-CoT	The team that won the 2010 World Series, the San Francisco Giants, has not won another World Series since then. Therefore, the most current year they have won a World Series is 2010.
Input Question and Reference Answers	Question: What is the most current year the team who won the 2010 World Series has won another World Series? Reference answers: A. 2010 World Series (correct probability: 0.487) {relevant facts: (San Francisco Giants, time.participant.event, 2010 World Series), (San Francisco Giants, sports.sports_team.championships, 2010 World Series)} B. 2014 World Series (correct probability: 0.26) {relevant facts: (San Francisco Giants, sports.sports_team.championships, 2010 World Series), (San Francisco Giants, sports.sports_team.championships, 2014 World Series)} C. 2012 World Series (correct probability: 0.253) {relevant facts: (San Francisco Giants, time.participant.event, 2010 World Series), (San Francisco Giants, sports.sports_team.championships, 2012 World Series)}
Output by DualR-Llama2-13B	Based on the information provided, the most current year the team who won the 2010 World Series has won another World Series is: B. 2014 World Series. The relevant facts provided in the reference answer indicates that San Francisco Giants won 2010 World Series and 2014 World Series. Therefore, the answer is B. 2014 World Series.

CoT(without dual reasoning), suffers from hallucination and lack of knowledge, resulting in wrong answers. ❌

Dual Reasoning generates the correct answers, achieving accurate and faithful results. ✅

AIEvo for Multi-Agent Collaboration

G. Liu, H. Lin, H. Zeng, Q. Yao. Learning from SOP enables Autonomous Collaboration among LLM Multi-Agents. (ongoing).



Contribution:

- **Concept**: We propose AIEvo, an adaptive autonomous SOP-driven multi-agent framework that integrates RAG and process supervision.
- **Technique**: We introduce a structured SOP repository for adaptive SOP generation, and design a process supervision mechanism to ensure for robust SOP execution.
- **Results**: SOTA performance on agent benchmarks, retaining high task adaptability and robustness.

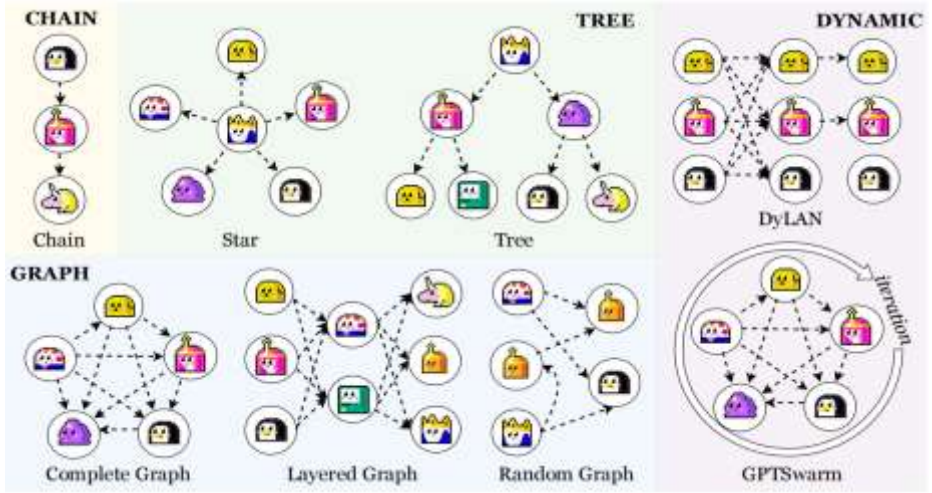
Limitations of Existing Works

◆ Limitations of existing multi-agent systems:

- **Rigid collaboration workflow:**
  - Lack of dynamic adaptability to different tasks
  - Cause agent redundancy and low efficiency
- **Blind execution process:**
  - Lack of supervision over the collaboration process
  - Lack of optimization for intermediate agents

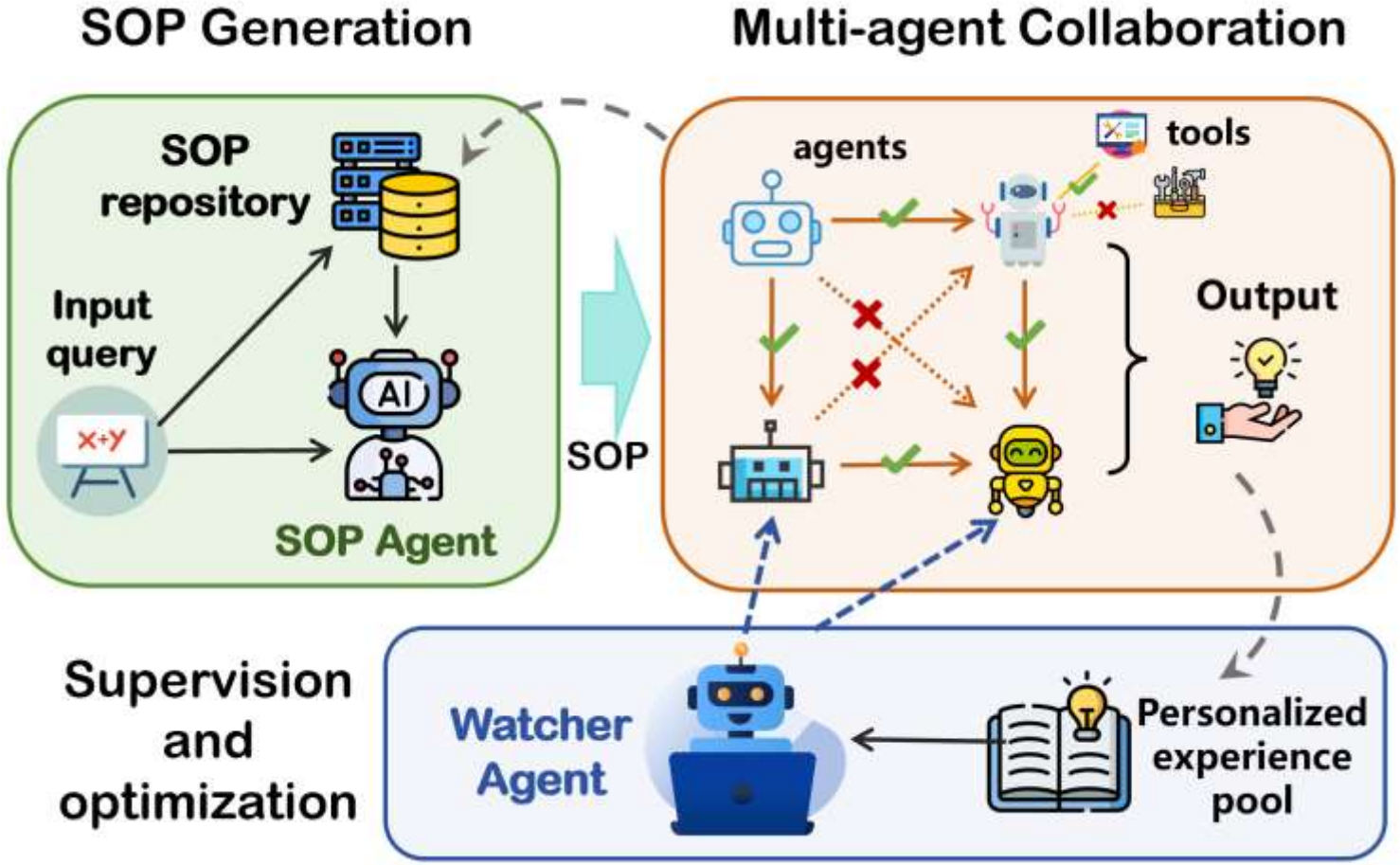
SOP in Multi-Agent System

- Standard Operating Procedure (SOP) :
  - ✓ a set of detailed and standardized instructions derived from practical experience.
  - ✓ serve as a guideline for designing multi-agent workflows.
  - ✓ SOP defines the entire collaborative architecture: the set of specialized agent roles (with specific instructions and tools) and communication topology/workflow.
- Idea:
  - ✓ leverage LLM to build an SOP repository to enable knowledge reuse.
  - ✓ autonomous SOP generation via Retrieval-augmented



Proposed Method

- We propose AIEvo, an autonomous SOP-driven multi-agent framework that integrates RAG for adaptive SOP generation, and process supervision for robust SOP execution.



- ✓ SOP Agent as Controller: customize agent roles and communication topology
- ✓ Watcher Agent as Supervisor: optimize the agent and workflow

Experiment Results

Table 2: Performance comparison on TravelPlanner using Qwen3-235B.

Method	Delivery Rate	Commonsense		Hard Constraint		Final
		Micro	Macro	Micro	Macro	
Sole-Planning						
Base	**100.0**	75.8	13.3	55.2	48.9	6.7
MetaGPT	98.3	82.5	22.2	60.5	50.5	13.3
EvoAgent	95.6	69.2	13.9	59.5	47.8	8.3
AgentVerse	**100.0**	79.2	11.1	59.0	53.3	6.7
AIEvo	98.9	**92.9**	**68.3**	**68.3**	**65.6**	**61.7**
Two-Stage						
ReAct	89.4	60.4	7.2	24.0	16.6	5.6
MetaGPT	95.6	65.3	14.4	19.8	16.1	8.9
AgentVerse	**100.0**	66.7	4.8	15.2	10.6	2.2
AgentSquare	98.3	81.2	33.3	20.5	15.6	13.3
AIEvo	95.6	**85.3**	**47.8**	**49.5**	**44.4**	**39.4**

Table 3: Performance comparison on GAIA using Qwen3-235B.

Method	Level 1	Level 2	Level 3	Avg.
Base	29.3	11.3	0.0	16.4
ReAct	32.9	28.3	6.3	26.8
MetaGPT	34.1	32.1	6.3	29.1
AgentVerse	30.5	19.8	0.0	20.9
GPTSwarm	36.6	32.1	6.3	30.0
AgentSquare	41.5	37.7	9.4	35.0
AIEvo	**46.3**	**41.5**	**15.6**	**39.5**

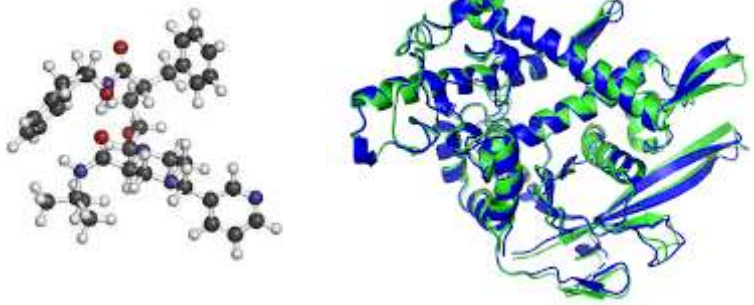
- AIEvo substantially outperforms all baselines on multi-agent multi-tool task.
- Customizing query-dependent workflows can effectively boost performance.

Outline

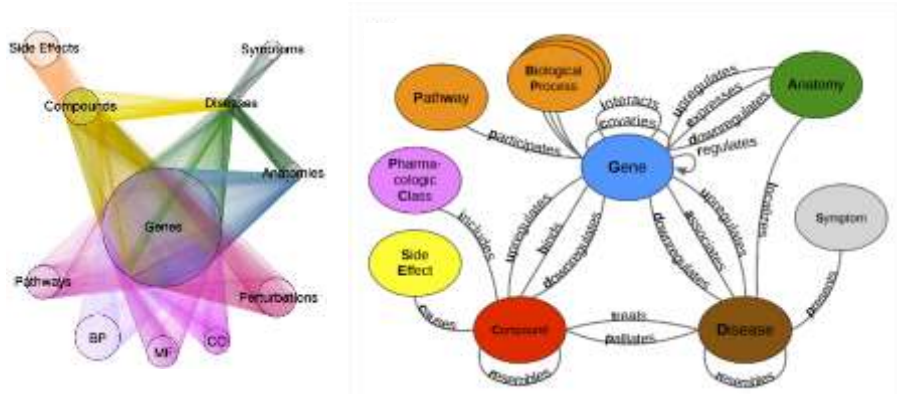
- Problem
- Algorithm
- Application
- Perspective

Typical Vertical Domain: Drug Related Applications

- In drug-related vertical domain tasks, there are various topological structures that are worth studying



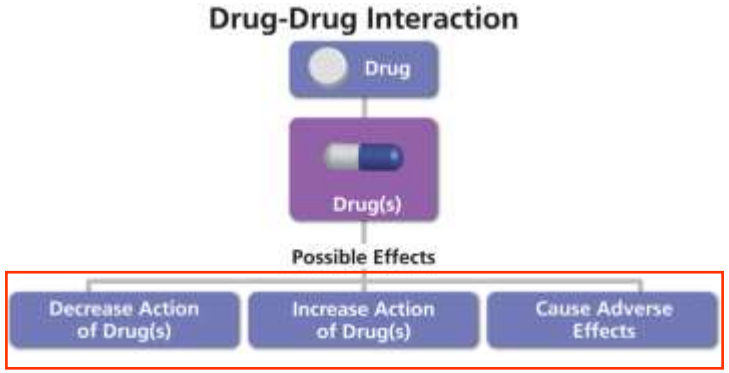
Molecule structure



Biomedical networks

- Typical tasks
  - Drug-drug interaction prediction
  - Drug-target interaction prediction
  - …
  - Molecular property prediction
  - Drug molecule generation

Application: drug-drug interaction prediction



Clinical drug combinations are common

Adverse reaction

S. No.	Drugs Interaction Combination	Frequency	Outcome
1	Ceftriaxone + Calcium Gluconate	6	Precipitation of ceftriaxone-calcium salt
2	Furosemide + Amikacin	5	Potentiate the risk of oto- and nephrotoxicity
3	Atracurium + Amikacin	3	Severe and/or prolonged respiratory depression
4	Omeprazole + Clopidogril	2	Decreased effectiveness of Clopidogril
5	Aspirin + Clopidogril	2	Increased platelet inhibition effect

Five major drug interaction combinations and their outcomes

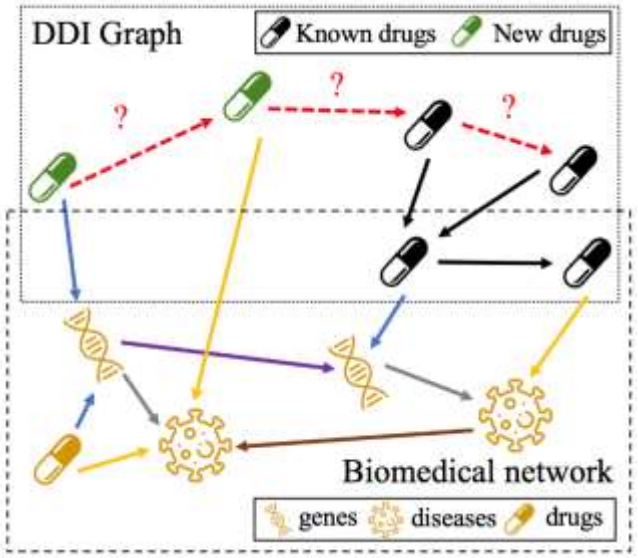
- 6.7% of hospitalized patients have a serious adverse drug reaction with a fatality rate of 0.32%.

  --U.S. Food and Drug Administration

- Identifying DDI by laboratory studies is extremely costly and time-consuming
  - Computational methods are proposed to speed up DDI discovery

Why DDI is topological learning problem?

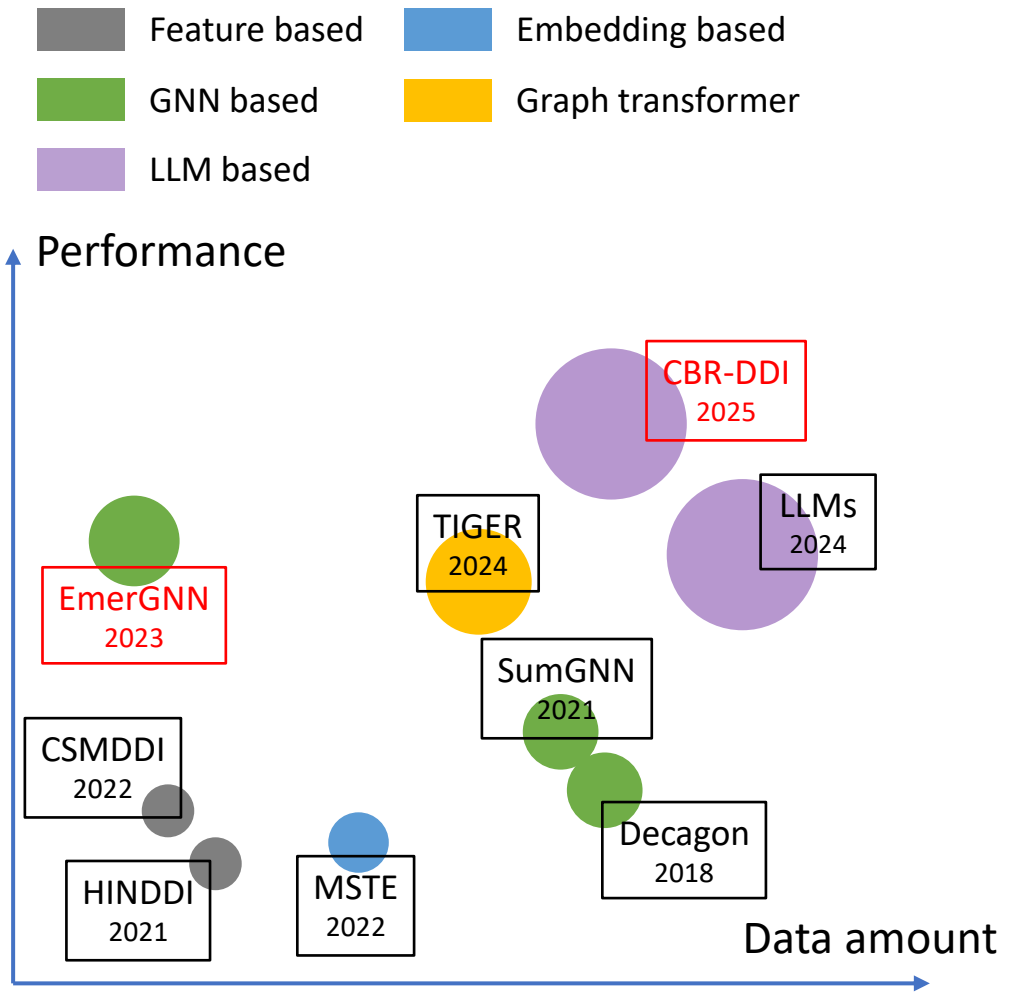
- Drug-drug interaction prediction problem setting:
- Input:
  - DDI graph with query drug pairs
  - Other relevant information, e.g. drug molecular structure, biomedical networks
- Output:
  - Interaction type between two drugs. (Drug A, ? , Drug B)



- DDI prediction is topological learning problem
  - DDI data can be naturally represented by graph
  - Relevant information, including drug molecular structure and biomedical networks can be well utilized through topological learning methods

Technique trend for DDI prediction

- DDI prediction methods are also evolving
  - Similar to evolutionary trajectory of topological learning
- Characteristic of DDI prediction (compare with topological learning)
  - Data sparsity
  - Requirement for interpretability
  - Distribution change



Here circle size represent model parameter number.

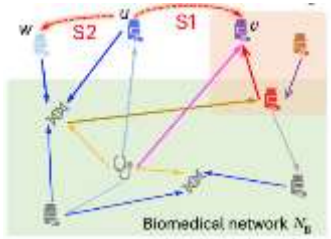
Methods marked in red are our works

Our Works

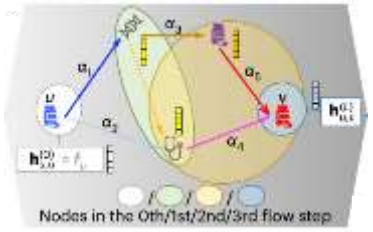
EmerGNN

A path-aware GNN leveraging topological structure within biomedical networks to handle data sparsity

Augmented network

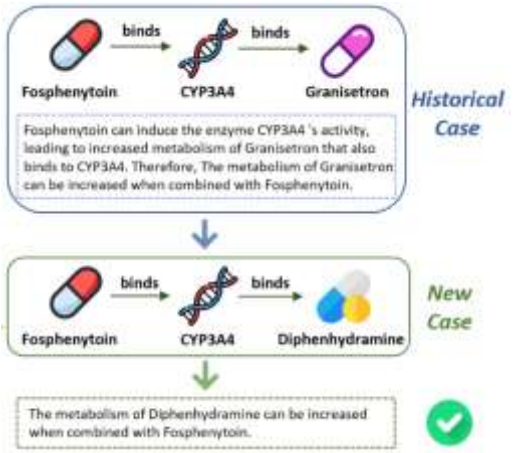


GNN structure



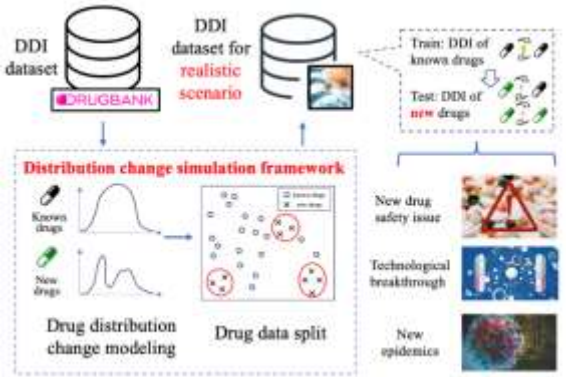
CBR-DDI

LLM-based DDI prediction by utilizing pharmacological knowledge from historical cases



DDI-Ben

DDI prediction benchmark focusing on the problem of distribution changes in realistic scenarios



EmerGNN for solving data-scarcity

Contribution:

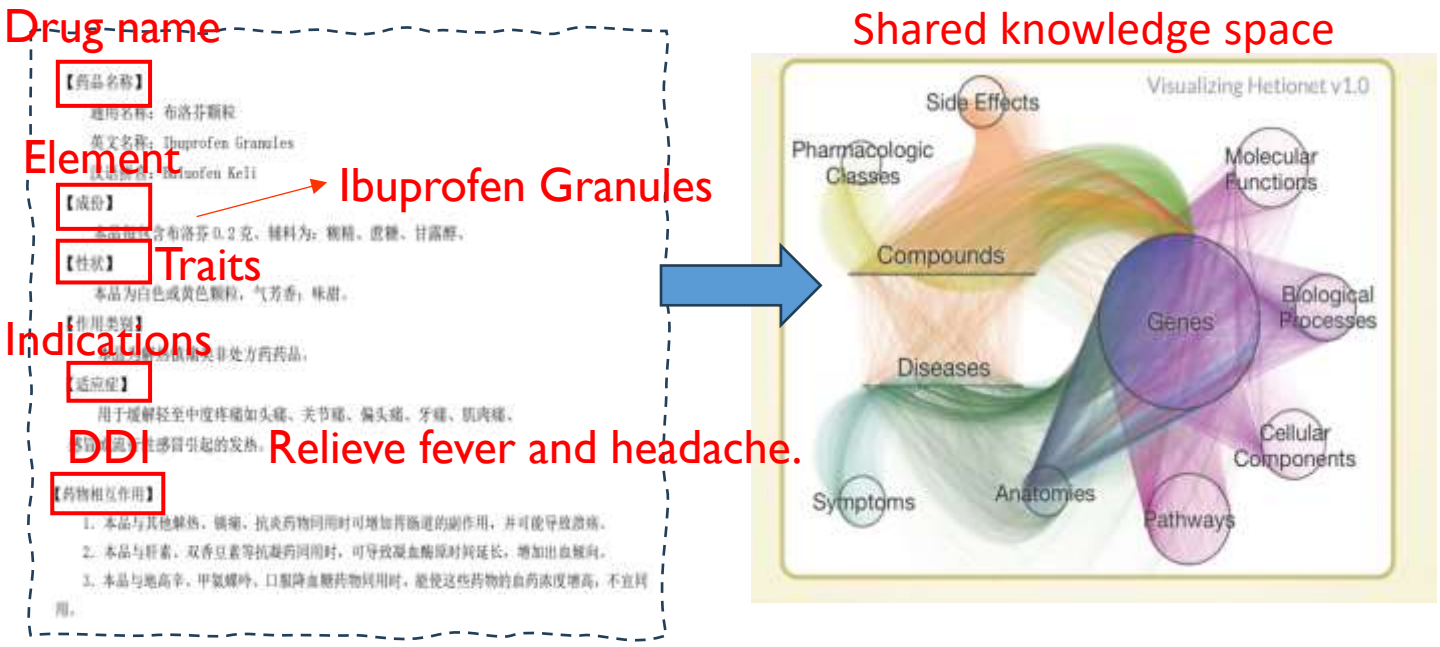
- **Concept**: A path-aware GNN under extreme data sparsity (emerging drugs) by leveraging topological connectivity within biomedical knowledge graphs.
- **Technique**: Weakly-supervised relational attention over dynamically extracted path subgraphs, and bi-directional propagation of structural information.
- **Results**: SOTA on S1/S2 DDI tasks with higher accuracy and interpretable biomedical insights, demonstrating effective knowledge transfer via KG pathways.

Y. Zhang, Q. Yao, L. Yue, X. Wu, Z. Zhang, Z. Lin, Y. Zheng. Emerging Drug Interaction Prediction Enabled by Flow-based Graph Neural Network with Biomedical Network. Nat. Comput. Sci. 2023

Data sparsity is a serious problem

- Limitation of existing methods
  - Existing deep learning methods do not perform well, as they require large amounts of data to train their over-parameterized models.

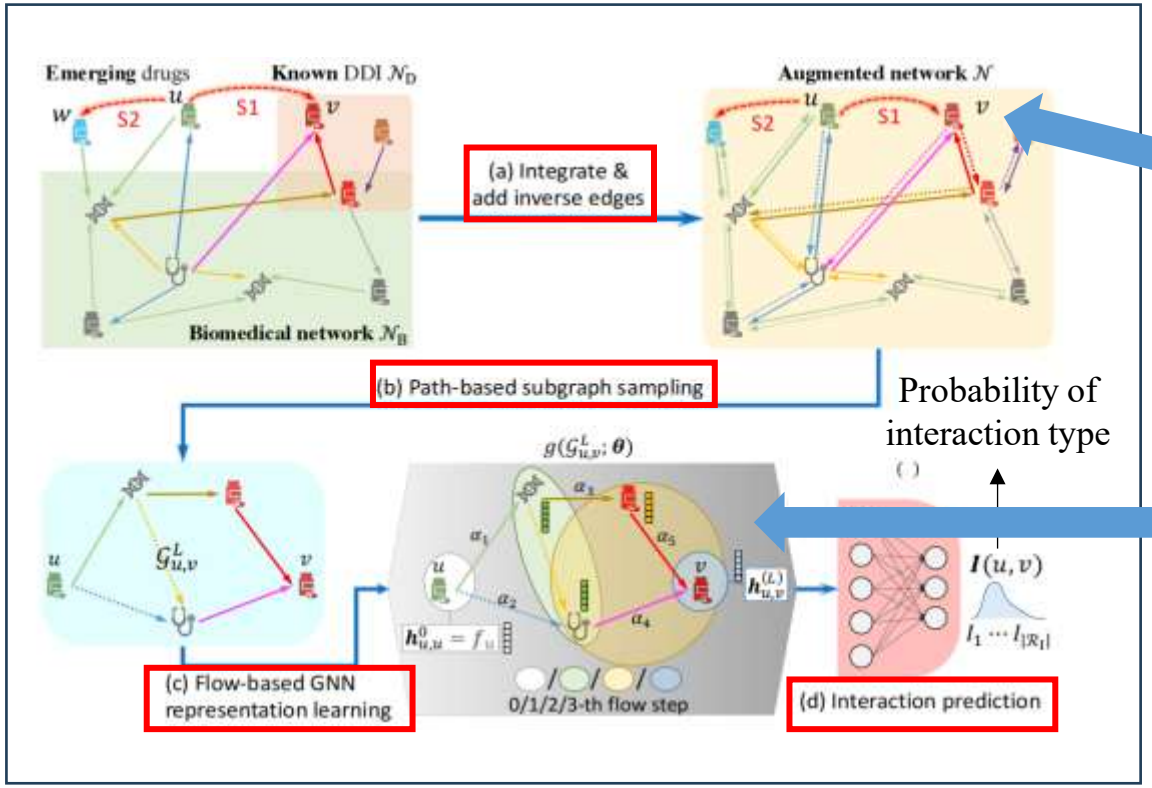
- Idea: design an effective and efficient method to extract the shared entities between emerging drugs and existing drugs, like the same targeted genes or diseases, through the structured graph relationships.



Weakly supervised learning from external KG

Key Concept:

- Construct a subgraph to extract knowledge related to emerging drugs
- Topological structures in model: set edge attention weights to highlight important paths and design GNN



u (emerging drugs) and v (existing drugs) share some of the same entities, such as genes, side effects, and compounds.

- Weighing the different types of relationships in a biomedical network.
- More weighted edges on the path help interpretability.

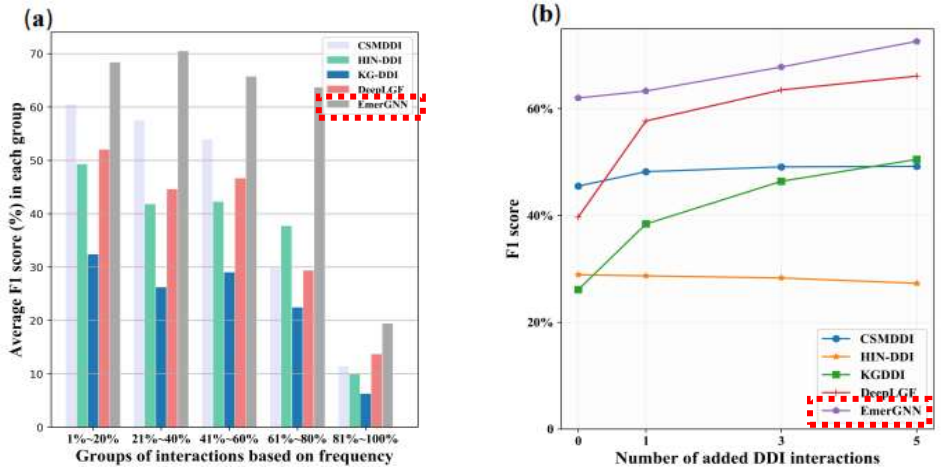
Effective knowledge transfer via KG pathways

Datasets		Drugbank			Twosides		
Type	Methods	F1-score	Accuracy	Kappa	PR-AUC	ROC-AUC	Accuracy
DF	CSMDDI	45.5(1.8)	62.6(2.8)	55.0(3.2)	73.2(2.6)	74.2(2.9)	69.9(2.2)
GF	HIN-DDI	37.3(2.9)	58.9(1.4)	47.6(1.8)	81.9(0.6)	83.8(0.9)	79.3(1.1)
Emb	KG-DDI	26.1(0.9)	46.7(1.9)	35.2(2.5)	79.1(0.9)	77.7(1.0)	60.2(2.2)
GNN	DeepLGF	39.7(2.3)	60.7(2.4)	51.0(2.6)	81.4(2.1)	82.2(2.6)	72.8(2.8)
GF	TIGER	47.0(3.0)	60.5(2.8)	52.3(3.2)	86.0(0.5)	85.6(0.5)	77.9(1.0)
LLM	TextDDI	58.7(1.2)	66.3(0.3)	59.2(0.4)	86.5(0.6)	87.2(0.6)	79.0(0.2)
GNN	EmerGNN	62.0(2.0)	68.6(3.7)	62.4(4.3)	90.6(0.7)	91.5(1.0)	84.6(0.7)

Index:

- F1 Score (Macro) (Main)
- Accuracy
- Cohen's Kappa coefficient(Cohen, 1960)

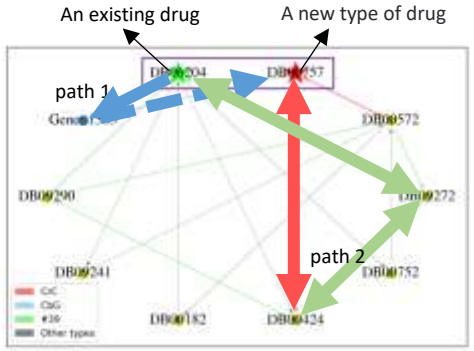
Overall, EmerGNN significantly outperforms all comparison methods with a small P-value.

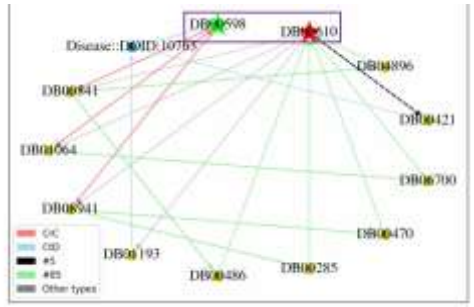


(a) EmerGNN outperforms baseline on all occurrence frequencies.

(b) Complementing emerging drug interactions: EmerGNN improves performance by adding more interactions and remains the best of all methods compared.

Enhancement on interpretability





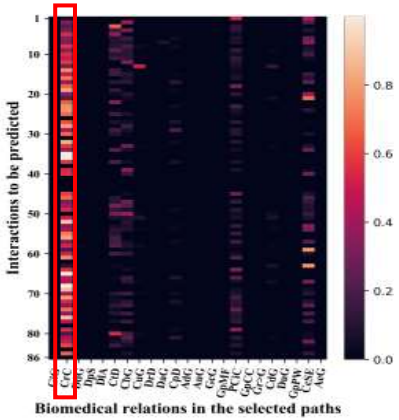
Target: Tapentadol (DB06204) may reduce the analgesic activity of Dolacidol (DB00757)

Path1: Tapentadol CYP2D6(P450) Dorasichon

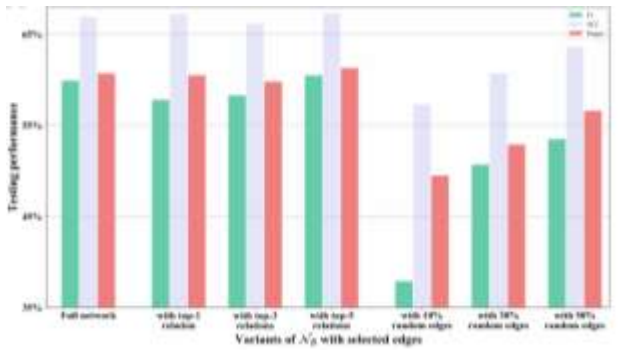
Path declaration: Tapantadol binds to the P450 enzyme CYP2D6 (Gene: :1565), which is critical for the metabolism of many drugs, such as Dolacidone (Estabrook, 2003). In addition, the binding of drugs to plasma proteins is reversible, and changes in the ratio of bound to unbound drugs can lead to drug-drug interactions.

Target: Tapentadol (DB06204) may decrease the analgesic activity of Dolasetron (DB00757).
Path1 (0.6666): Tapentadol $\xrightarrow{\text{binds}}$ CYP2D6 (P450) $\xrightarrow{\text{binds\_inv}}$ Dolasetron
Explanation: Tapentadol can binds the P450 enzyme CYP2D6 (Gene::1565), which is vital for the metabolism of many drugs like Dolasetron (Estabrook, 2003). In addition, Binding of drug to plasma proteins is reversible, and changes in the ratio of bound to unbound drug may lead to drug-drug interactions (Kneip et. al. 2008).
Path2 (0.8977): Dolasetron $\xrightarrow{\text{resembles}}$ Hyoscyamine $\xrightarrow{\text{\#39:↑ constipating}}$ Eluxadoline $\xrightarrow{\text{\#39\_inv}}$ Tapentadol
Explanation: Dolasetron is similar to drug Hyoscyamine (DB00424). Hyoscyamine and Tapentadol can get some connection since they will both increase the constipating activity of Eluxadoline (DB09272). As suggested by Liu and Wittbrodt (2022), reversing opioid-induced constipation often causes the unwanted side effect of analgesia reversal.

EmerGNN can find important pathways for emerging drug interactions



Correlation between i_{pred} and the biomedical relationship r



Use only Full network/First 1 Relationship (CrC)/First 3 relationships /... /10% random edge /30% random edge /...

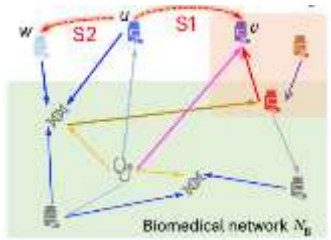
EmerGNN can select important and relevant relationships in the biomedical network

Our Works

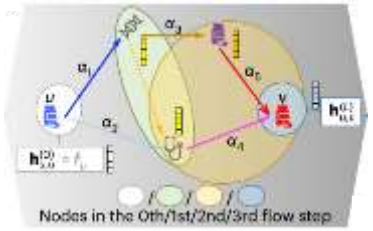
EmerGNN

A path-aware GNN leveraging topological structure within biomedical networks to handle data sparsity

Augmented network

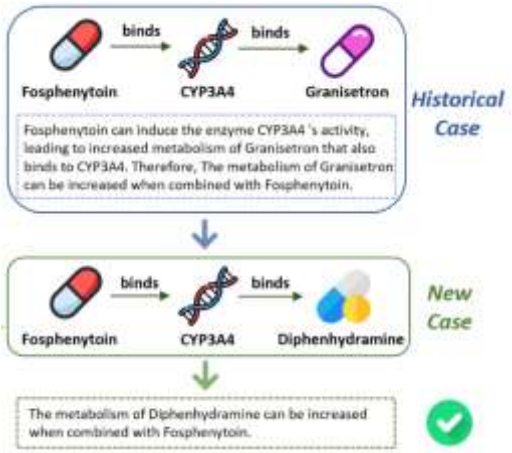


GNN structure



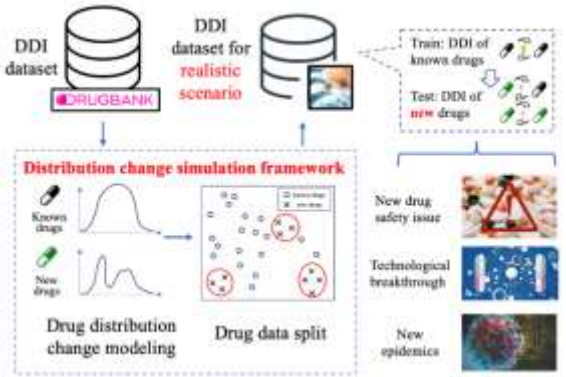
CBR-DDI

LLM-based DDI prediction by utilizing pharmacological knowledge from historical cases



DDI-Ben

DDI prediction benchmark focusing on the problem of distribution changes in realistic scenarios



CBRDDI for distilling knowledge

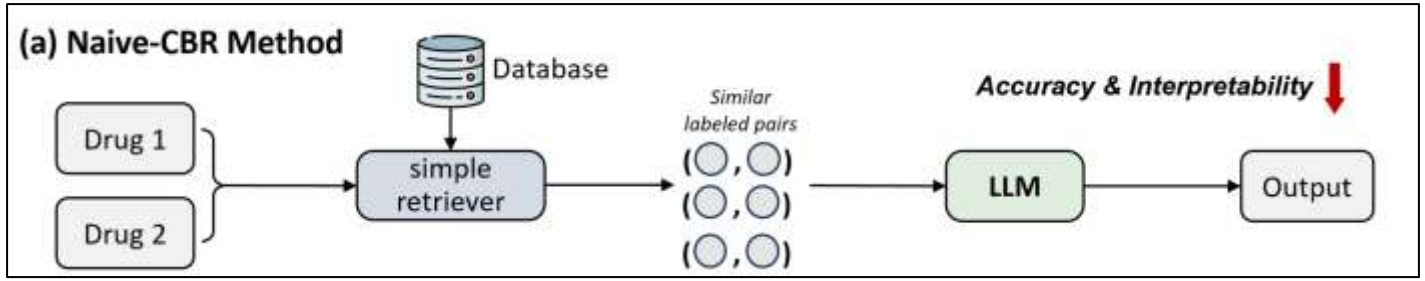
Contribution:

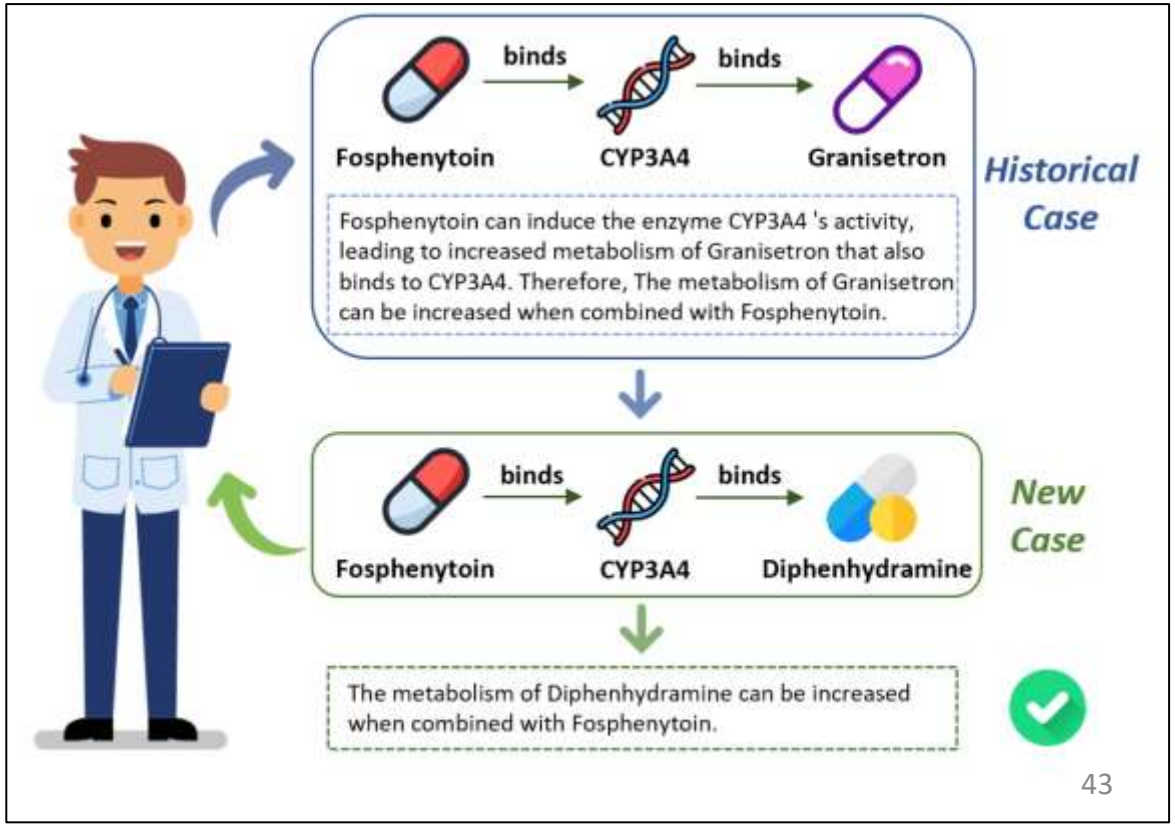
- **Concept**: Inspired by clinical case-based reasoning, CBR-DDI enhances LLM-based DDI prediction by integrating topological graph structures to distill pharmacological patterns from historical cases.
- **Technique**: LLM-GNN collaborative framework leveraging graph topological structures, hybrid retrieval, dual-layer knowledge prompting, and representative sampling for effective case reuse.
- **Results**: State-of-the-art DDI prediction performance with significant accuracy gains, retaining high interpretability and flexibility.

G. Liu, Y. Zhang, X. Liu, Q. Yao. Case-Based Reasoning Enhances the Predictive Power of LLMs in Drug-Drug Interaction. arXiv preprint arXiv 2025.

Historical knowledge should be valued

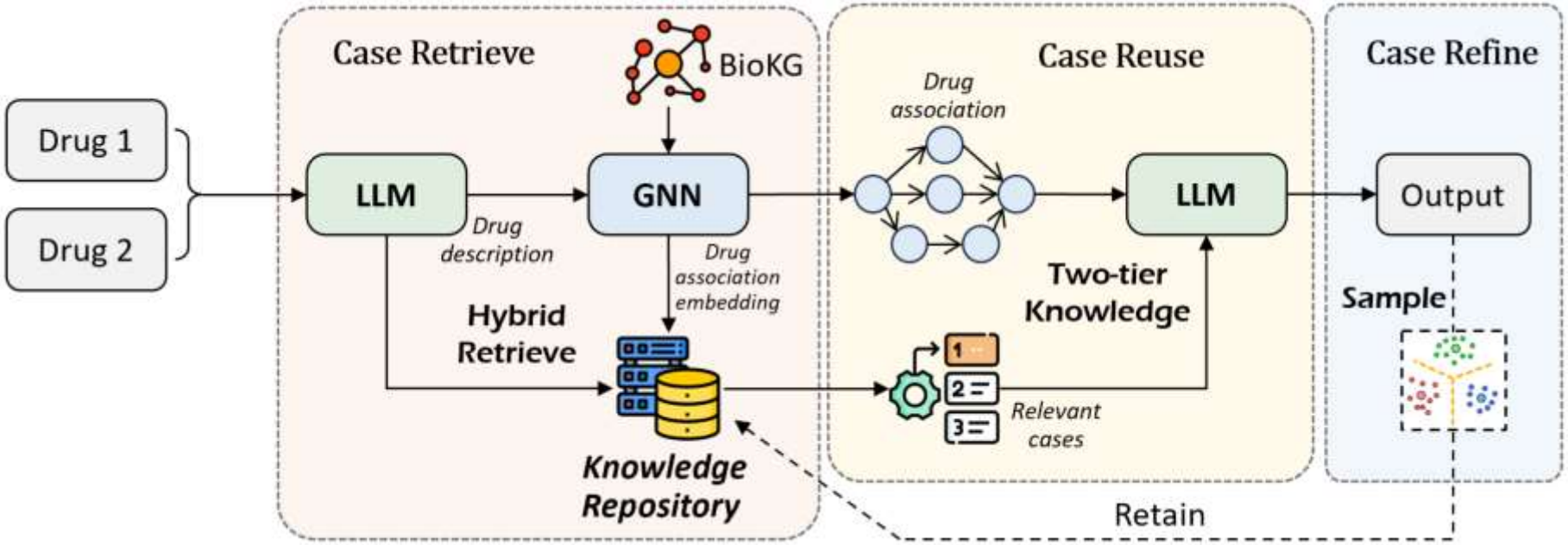
- Limitation of existing works:
  - Existing methods are fundamentally constrained by their inability to distill actionable pharmacological mechanisms from complex drug topological associations.
- Idea:
  - Transfer of known interaction mechanisms from the historical case to the new one.





Distill transferable knowledge from historical cases

- Extract DDI learning cases from GNN-based DDI prediction methods
- Utilizing LLMs to conduct case-based reasoning for DDI prediction
  - Case retrieve: based on drug pair input, retrieve relevant historical cases
  - Case reuse: using LLMs, obtain prediction results based on retrieved cases
  - Case refine: update the knowledge repository based on prediction results



Transferring distilled knowledge is promising

Type	Method	DrugBank				TWOSIDES				Δ_{avg}
		S1		S2		S1		S2		
		Acc	F1	Acc	F1	Recall	NDCG	Recall	NDCG	
Feature-based	MLP	57.77	42.53	39.85	20.15	12.70	14.88	3.60	5.95	6.42 ↑
Graph-based	ComplEx	4.02	1.74	4.32	1.77	2.30	3.61	1.62	1.81	32.06 ↑
	MSTE	54.66	40.57	32.88	4.93	5.12	7.37	2.78	3.12	11.02 ↑
	Decagon	32.41	28.56	22.47	6.12	4.48	6.36	2.38	3.61	19.54 ↑
	SumGNN	57.04	54.77	25.28	17.85	4.08	5.24	2.11	3.48	13.03 ↑
	EmerGNN	68.10	65.78	44.84	34.22	13.79	16.06	3.01	4.93	2.45 ↑
	TIGER	60.11	57.21	33.46	19.78	11.72	14.33	2.69	3.90	7.81 ↑
LM-based	TextDDI	66.75	66.53	44.23	32.79	9.88	13.24	4.16	6.04	3.35 ↑
Llama3.1-8B	Base	8.71	4.10	7.30	3.94	0.04	0.06	0.02	0.03	28.92 ↑
	Naive-CBR	47.88	42.38	15.02	8.70	3.60	4.47	0.27	0.50	16.24 ↑
	K-Paths	17.62	9.06	12.29	7.34	0.25	0.38	0.07	0.08	25.38 ↑
	CBR-DDI	**68.52**	**61.57**	**44.94**	**32.43**	**13.89**	**15.45**	**4.38**	**7.04**	-
Llama3.1-70B	Base	8.93	4.37	8.02	4.12	0.05	0.06	0.03	0.03	30.21 ↑
	Naive-CBR	48.09	50.62	21.22	13.04	4.54	5.46	0.68	0.84	15.84 ↑
	K-Paths	31.35	16.43	31.12	14.87	2.09	3.18	1.01	1.42	18.08 ↑
	CBR-DDI	**71.36**	**70.85**	**47.43**	**36.88**	**14.40**	**16.97**	**4.68**	**7.32**	-
DeepSeek-V3 -671B	Base	12.62	9.61	12.12	6.78	0.03	0.04	0.03	0.05	28.82 ↑
	Naive-CBR	55.20	47.24	22.26	15.46	3.18	4.22	0.32	0.47	14.78 ↑
	K-Paths	34.52	18.17	32.33	15.41	1.73	2.21	1.19	1.66	17.58 ↑
	CBR-DDI	**71.05**	**74.38**	**49.45**	**40.69**	**14.85**	**16.56**	**4.73**	**6.60**	-

- CBR-DDI substantially outperforms all baselines.
- CBRDDI can bring strong performance gains to various LLMs.
- Appropriate utilization of external knowledge can reduce the demand for LLM model size.

Trustworthy Case Analysis

<Query drug pair-Answer>

Rifabutin, Zopiclone — The metabolism of Zopiclone can be increased when combined with Rifabutin.

<Input Task Description>

You are a medical expert. Your task is to predict the interaction between a pair of drugs. There are some examples for your reference before the given question. You can refer to the interaction mechanisms in the provided examples. You should answer the given question based on the candidate answers, correct probability, related facts and your own knowledge. Please end your reply with 'The interaction is <your answer>'.

<Input Reference Cases>

Historical reference cases

Example: What is the interaction between *Fosphenytoin and Cytarabine*?

Related Facts:

(Fosphenytoin, binds, Gene::CYP2C19), (Glucosamine, binds, Gene::CYP2C19), (Glucosamine, resembles, Cytarabine);

(Fosphenytoin, binds, Gene::CYP3A4), (Cytarabine, binds, Gene::CYP3A4);

(Modafinil, resembles, Fosphenytoin), (The metabolism of Modafinil can be decreased when combined with Glucosamine), (Glucosamine, resembles, Cytarabine);

Answer: The given facts suggest that Fosphenytoin binds to CYP2C19 and CYP3A4, and Cytarabine also binds to CYP3A4. Since Glucosamine resembles Cytarabine, it is likely that Cytarabine also binds to CYP2C19. Fosphenytoin's binding to CYP2C19 can lead to increased metabolism of Cytarabine, therefore, The metabolism of Cytarabine can be increased when combined with Fosphenytoin.

<Input question, drug associations and candidate answers>

Question: What is the interaction between *Rifabutin and Zopiclone*?

Candidate Answers:

The serum concentration of Zopiclone can be decreased when it is combined with Rifabutin. (correct probability: 0.251)

The metabolism of Zopiclone can be increased when combined with Rifabutin. (correct probability: 0.233)

The risk or severity of adverse effects can be increased when Rifabutin is combined with Zopiclone. (correct probability: 0.211)

Drug association

Related Facts:

(Rifabutin, resembles, Rifapentine), (Rifapentine, binds, Gene::CYP2C9), (Zopiclone, binds, Gene::CYP2C9);

(Rifabutin, resembles, Rifapentine), (Rifapentine, binds, Gene::CYP3A4), (Zopiclone, binds, Gene::CYP3A4);

(Rifabutin, resembles, Rifapentine),(The metabolism of Eszopiclone can be increased when combined with Rifapentine),(Zopiclone, resembles, Eszopiclone);

<Output by CBR-DDI-Llama3.1-70B>

The given facts suggest that Rifabutin resembles Rifapentine and Rifampicin, which increase the metabolism of Eszopiclone, a drug that resembles Zopiclone. This implies that Rifabutin may have a similar effect on Zopiclone, increasing its metabolism. Additionally, Rifapentine binds to CYP2C9, and CYP3A4 enzymes, and Zopiclone also binds to these enzymes. This suggests that Rifabutin may induce these enzymes, leading to increased metabolism of Zopiclone. Considering these facts, the most likely interaction between Rifabutin and Zopiclone is that the metabolism of Zopiclone can be increased when combined with Rifabutin.

The interaction is: The metabolism of Zopiclone can be increased when combined with Rifabutin.

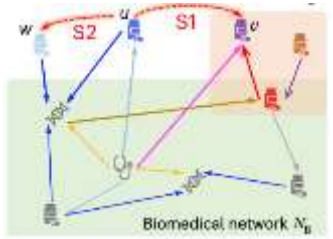
Faithful output

Our Works

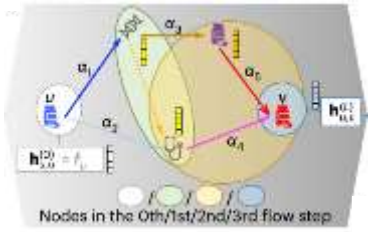
EmerGNN

A path-aware GNN leveraging topological structure within biomedical networks to handle data sparsity

Augmented network

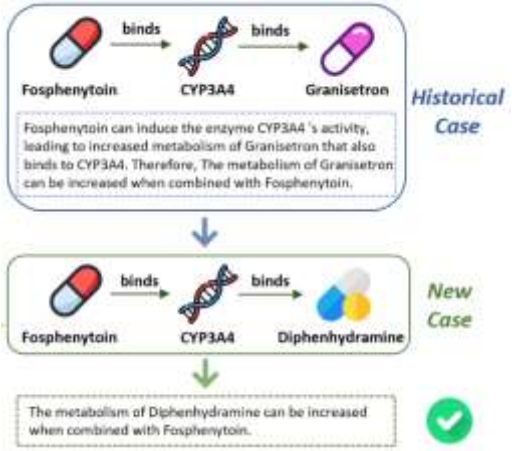


GNN structure



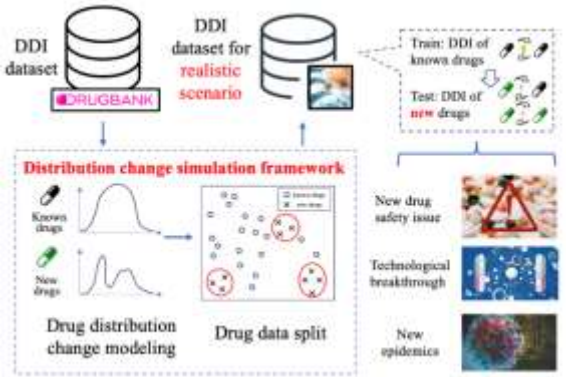
CBR-DDI

LLM-based DDI prediction by utilizing pharmacological knowledge from historical cases



DDI-Ben

DDI prediction benchmark focusing on the problem of distribution changes in realistic scenarios



DDI-Ben for the Problem of Distribution Change

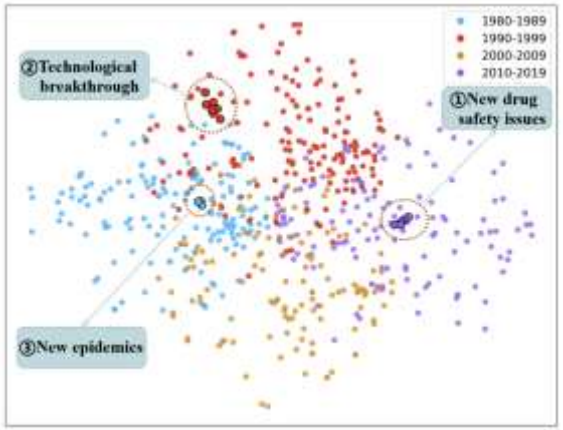
Contribution:

- **Concept**: A benchmarking framework for emerging DDI prediction under distribution changes to bridge the gap between existing DDI prediction methods and realistic scenarios.
- **Technique**: a distribution change simulation framework that leverages distribution changes between drug sets as a surrogate for real-world distribution changes of DDIs, which is compatible with various drug split strategies.
- **Results**: Most existing approaches suffer substantial performance degradation under distribution changes, verifying the importance to consider this phenomenon in method design.

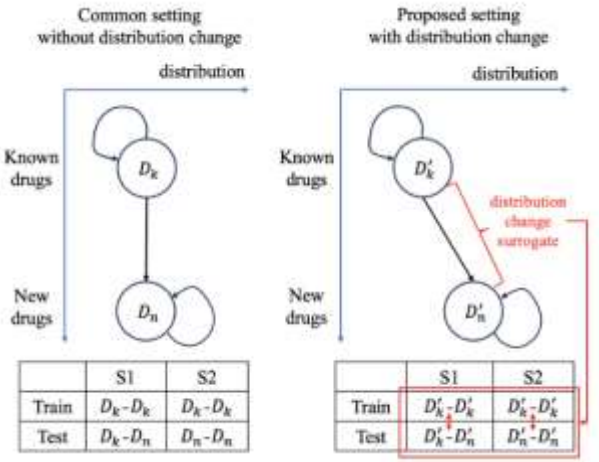
Z. Shen, M. Zhou, Y. Zhang, Q. Yao. Benchmarking drug-drug interaction prediction methods: a perspective of distribution changes. Bioinformatics 2025.

Distribution Change is Overlooked in Existing Evaluation

- Limitation of existing works:
  - Current DDI prediction methods neglect the distribution changes under realistic scenarios, making their performance in real-world emerging DDI prediction problems questionable.
- Idea
  - Design a distribution change simulation framework and use distribution change between known/new drug sets as a surrogate for distribution change of DDIs.



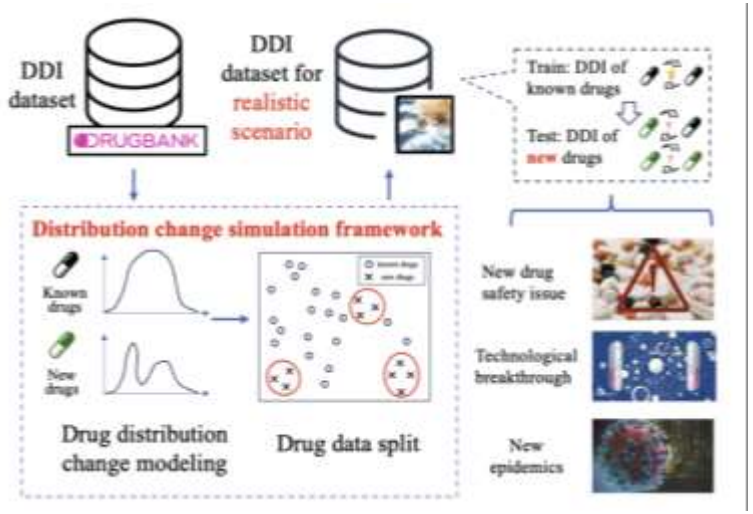
Drugs developed in different time periods follow different distributions



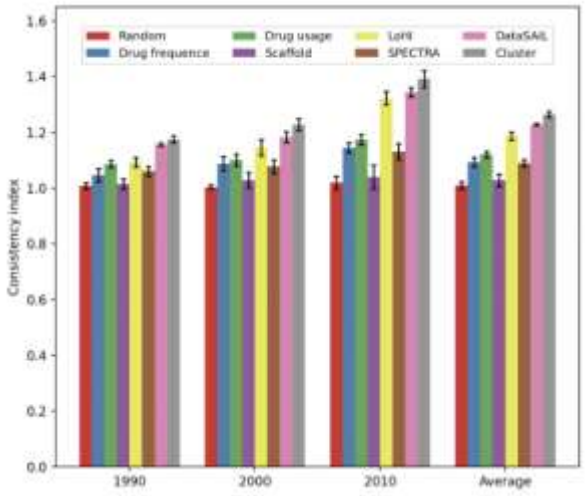
Without / with distribution changes for emerging DDI prediction

Use drug split strategy to simulate distribution change

- Use drug distribution change as surrogate
  - ✓Compatible with different drug split strategy
- Introduce a cluster-based drug split strategy to simulate real-world drug split
  - ✓Enable controllable distribution change in benchmarking evaluation
  - ✓Highly consistent with real-world data



Distribution change simulation framework



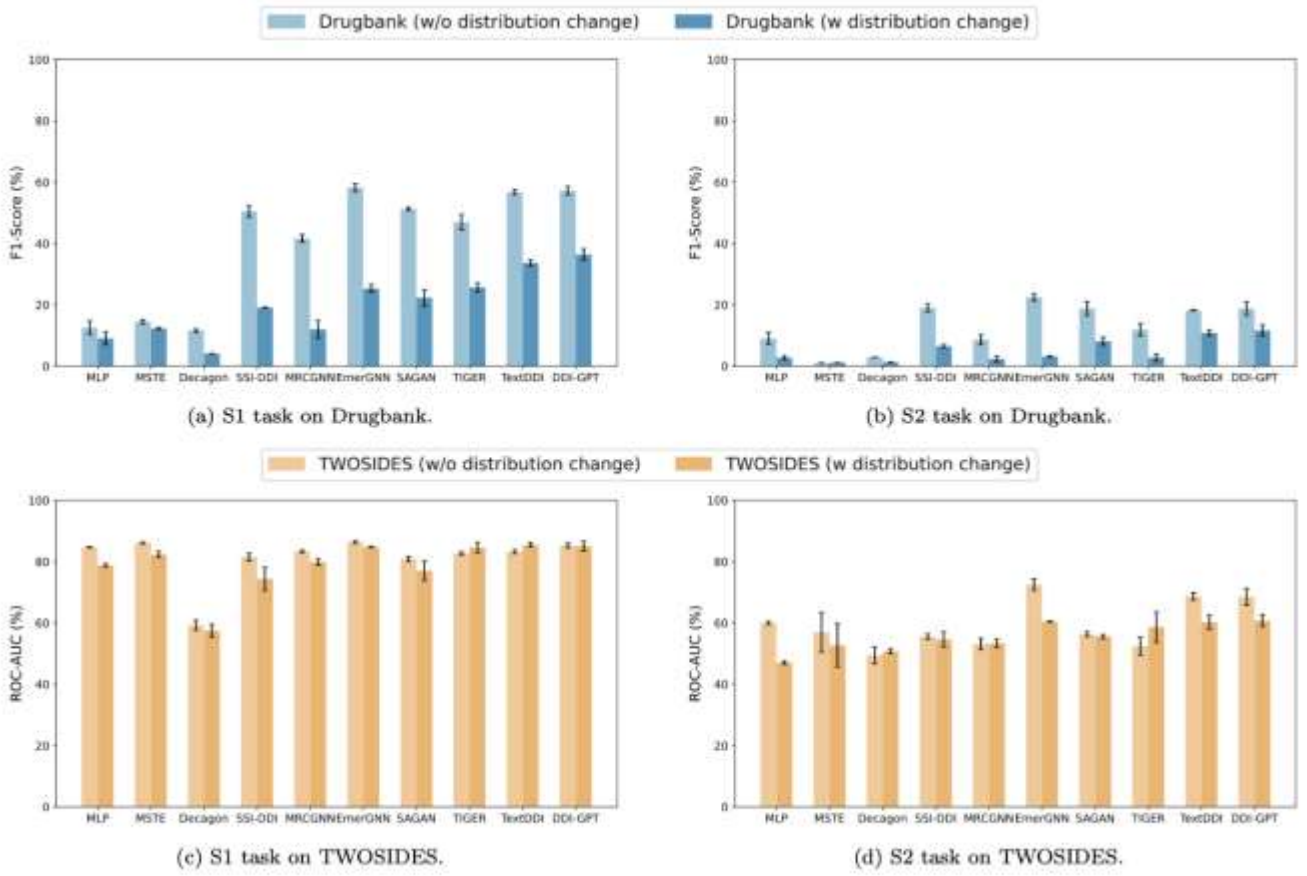
Consistency with real-world data

Split strategy	Random	Drug frequence	Drug usage	Scaffold	LoHi	SPECTRA	DataSAIL	Cluster
Preserve all data	✓	✓	✓	✓	×	×	✓	✓
Controllable distribution change	×	×	×	×	×	✓	×	✓
Consistency with approval time	Low	Low	Low	Low	Medium	Low	Medium	High

Comparison among different drug split strategy

Distribution change influences DDI prediction performance

- Existing computation methods cannot deal with distribution change well
  - In S1, S2 setting, there is a significant performance drop for existing computational DDI methods
- For comparison among evaluated methods
  - GNN based methods, Graph transformer based methods, LLM based methods perform relatively better

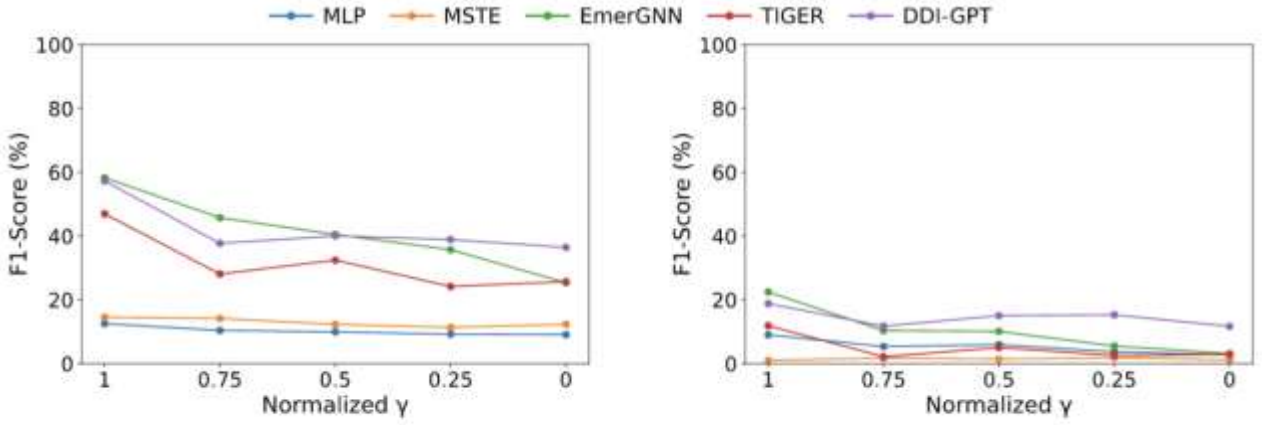


LLM-based methods can be potential solutions

- LLM-based method (DDI-GPT) achieves better performance on long tail DDI types
  - The performance gap is not significant on DDI types with high occurence frequency

Method	Distribution change	Major			Medium			Long-tail		
		#48	#46	#72	#29	#71	#57	#24	#1	#18
MLP	w/o	84.9	56.9	64.2	25.6	64.1	32.6	27.1	0.0	0.0
	w	73.9	52.3	**44.5**	0	17.5	13.2	15.1	0.0	0.0
MSTE	w/o	80.0	65.5	52.3	16.4	24.0	30.4	0.0	22.2	0.0
	w	74.9	**63.2**	37.9	2.9	10.9	0.3	9.9	17.1	0.0
EmerGNN	w/o	82.4	73.0	59.3	77.2	96.7	86.0	59.1	83.3	75.0
	w	65.3	59.1	40.8	61.8	24.1	56.7	35.1	55.7	35.0
TIGER	w/o	75.8	60.4	55.4	46.7	93.8	95.9	27.6	53.7	62.5
	w	73.5	42.5	37.9	32.3	56.1	**87.4**	5.6	48.5	13.3
DDI-GPT	w/o	82.5	69.5	50.7	80.7	92.4	89.2	54.4	66.7	65.0
	w	**76.1**	62.3	42.3	**67.7**	**72.4**	84.3	**58.3**	**61.4**	**53.3**

- LLM-based method (DDI-GPT) performs relatively better when distribution change is more significant



(a) S1 task on Drugbank.

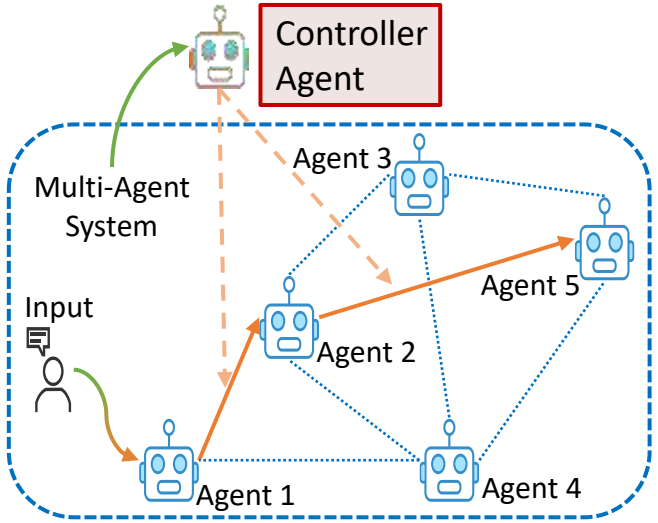
(b) S2 task on Drugbank.

Outline

- Problem
- Algorithm
- Application
- Perspective

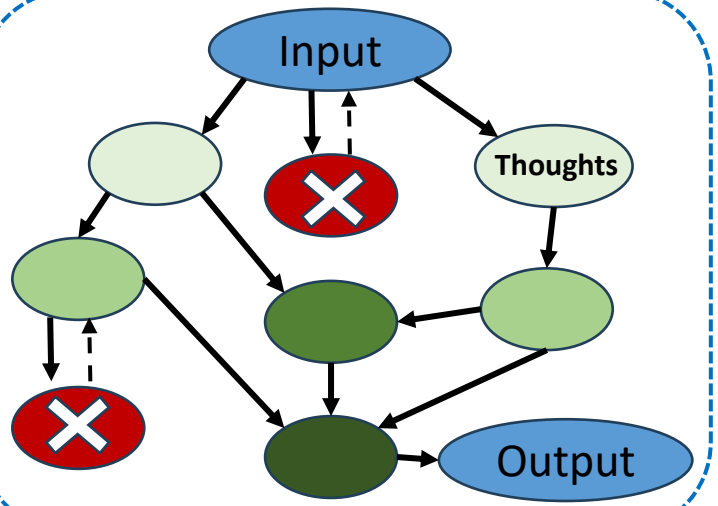
Frontiers in topological learning methods

- Learning topology in agent collaborations



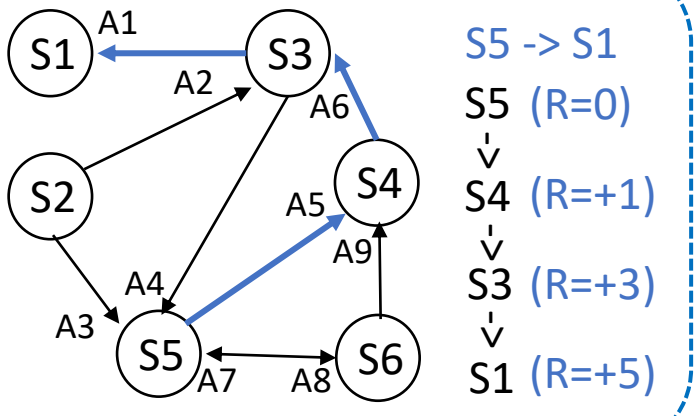
The workflow of agent can be seen as a dynamic graph.

- Learning topology in LLM reasoning (test-time scaling)



The search space of reasoning (CoT / Reflection) can be represented as a graph.

- Learning topology in progress rewards

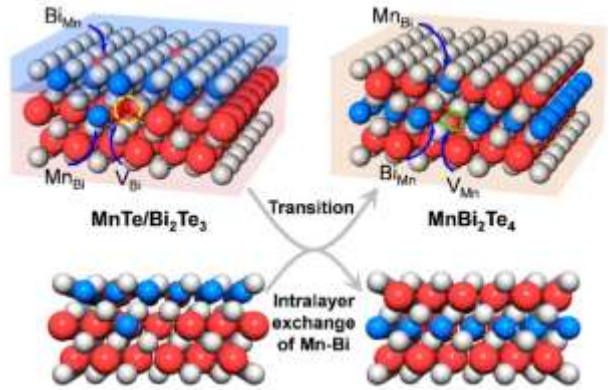


The execution of a task can be represented as a graph.

Promising vertical domains

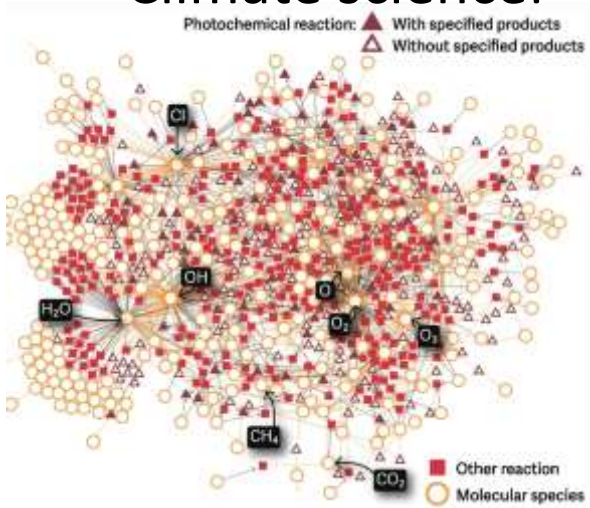
- There are still many promising direction for topological learning in vertical domains

- Material design:



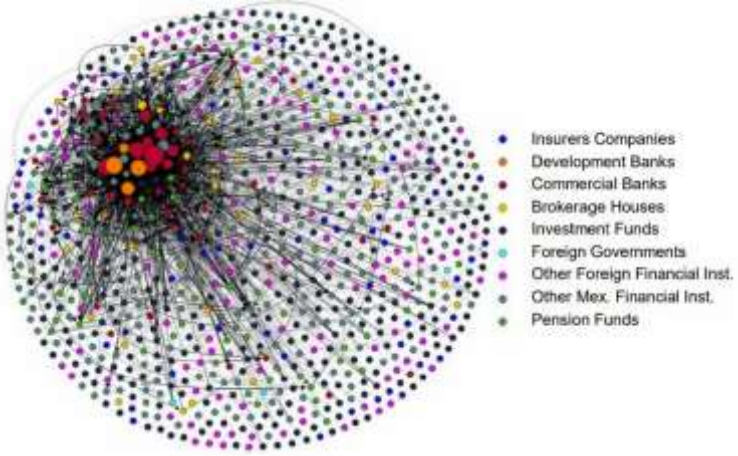
learn microscopic topology of materials, domain knowledge graph construction, multi-agent material discovery system

- Climate science:



topological clustering of climate fields, atmospheric system modeling

- Financial system:



topological anomaly detection, combinatorial optimization on financial graphs

- Welcome further exploration on this topic!

Recent works in our group

- Z. Shen, M. Zhou, Y. Zhang, Q. Yao. Benchmarking Computational Methods for Emerging Drug-Drug Interaction Prediction. Bioinformatics. 2025
- Q. Yao, Y. Zhang, Y. Wang, N. Yin, J. Kwok, Q. Yang. Beyond scaleup: Knowledge-aware parsimony learning from deep networks. AI Mag. 2025
- G. Liu, Y. Zhang, X. Liu, Q. Yao. Case-Based Reasoning Enhances the Predictive Power of LLMs in Drug-Drug Interaction. arXiv preprint arXiv 2025.
- S. Wu, Y. Wang, Y. Bian, Quanming Yao Learning to Learn with Contrastive Meta-Objective. NeurIPS 2025
- S. Wu, Y. Wang, Q. Yao. Why In-Context Learning Models are Good Few-Shot Learners? ICLR. 2025
- H. Yang, Q. Yao, J. Kwok. Curriculum-aware Training for Discriminating Molecular Property Prediction Models. ICLR. 2025
- Y. Chen, Q. Yao, J. Zhang, J. Cheng, Y. Bian. Hierarchical Graph Tokenization for Molecule-Language Alignment. ICML 2025
- Q. Yao, Z. Shen, Y. Wang, D. Dou. Property-Aware Relation Networks for Few-Shot Molecular Property Prediction. IEEE TPAMI. 2024
- Y. Wang, Z. Yang, Q. Yao. Accurate and Interpretable Drug-drug Interaction Prediction Enabled by Knowledge Subgraph Learning. Commun. Med. 2024
- H. Du, Q. Yao, J. Zhang, Y. Liu, Z. Wang. Customized Subgraph Selection and Encoding for Drug-drug Interaction Prediction. NeurIPS. 2024
- J. Zhang, L. Wei, Z. Xu, Q. Yao. Heuristic Learning with Graph Neural Networks: A Unified Framework for Link Prediction. KDD. 2024
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- Y. Zhang, Z. Zhou, Q. Yao, Y. Li. KGTuner: Efficient Hyper-parameter Search for Knowledge Graph Learning. ACL. 2022
- Y. Zhang, Q. Yao. Knowledge Graph Reasoning with Relational Digraph. WebConf. 2022
- H. Zhao, Q. Yao, W. Tu. Search to aggregate neighborhood for graph neural network. ICDE. 2021

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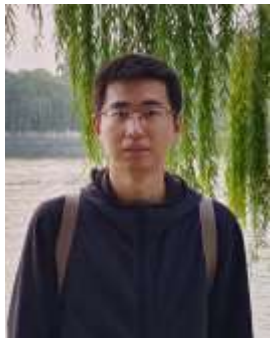

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Zhouming Yang
Master

Haotong Du
PhD (Visit)

Thanks.