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Context-Aware Hierarchical Fusion for Drug Relational Learning

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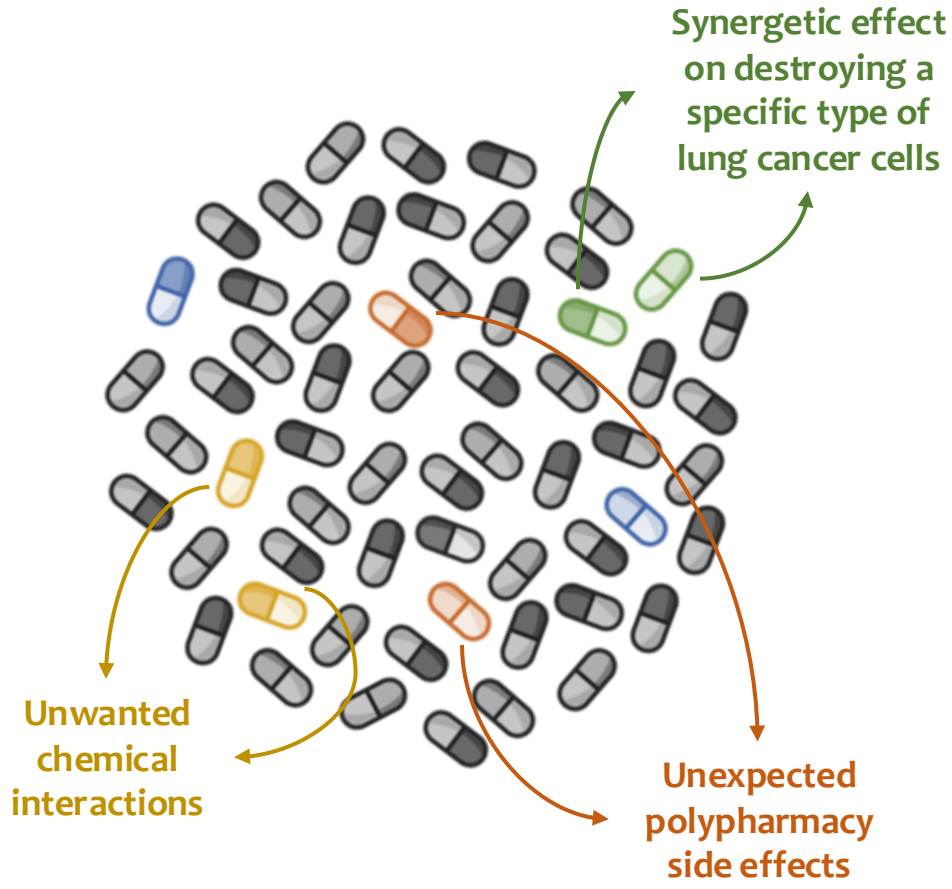
Outline

- **Background**
- Motivation
- Method
- Experiments
- Summary

Background | Drug Relational Learning

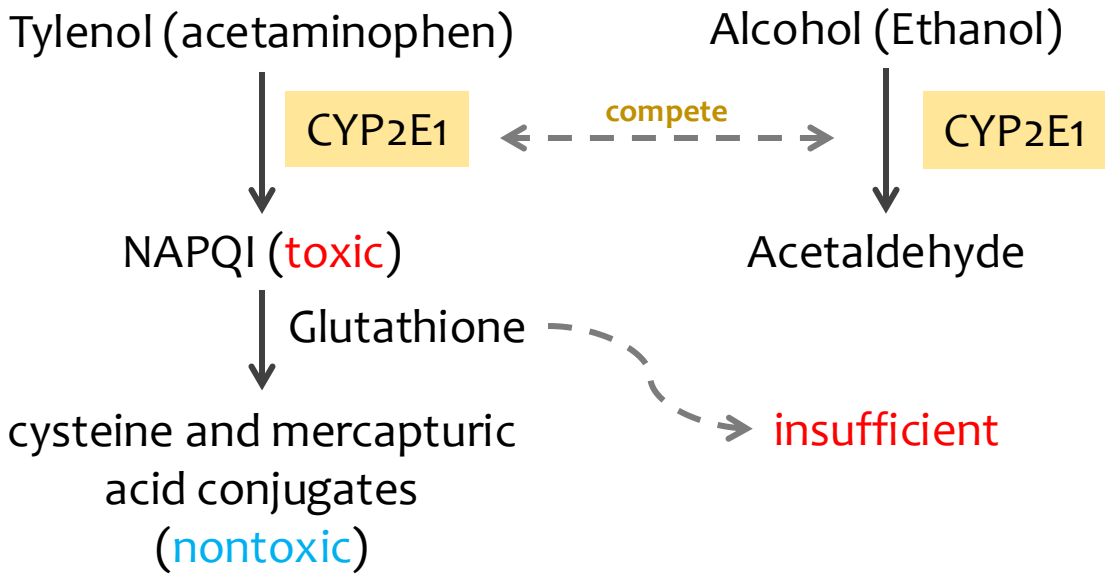
- Co-administration of drugs is a common practice in treating diseases.
- Chemical and physical reactions between drugs can alter the intended functionality of drugs.
- Complex biochemical mechanisms within the human body could further lead to adverse drug reactions.
- Discovering all possible drug combinations using traditional laboratory-based methods is challenging.

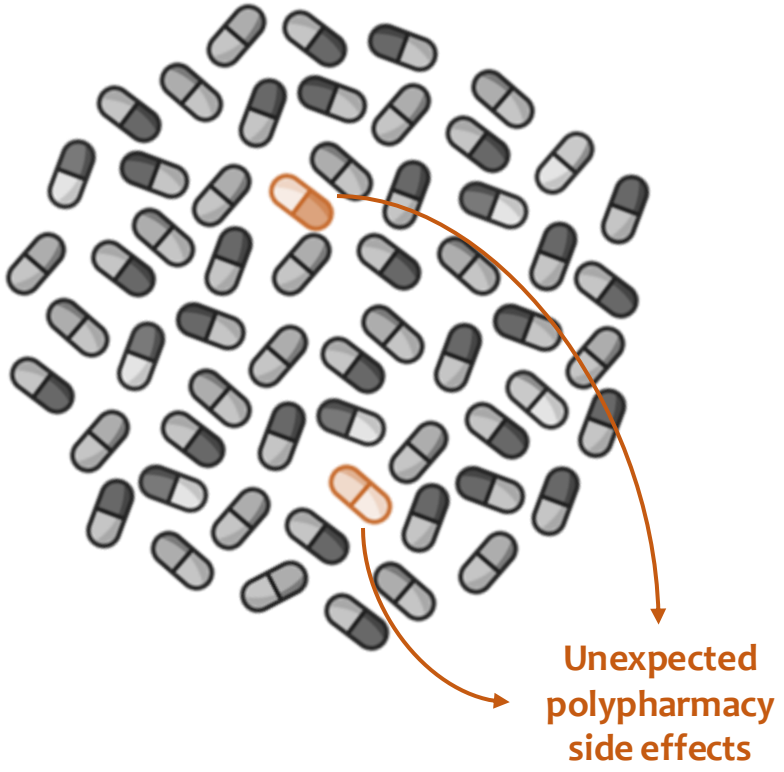


Background | Drug Relational Learning

1. Drug-drug interactions are context-dependent

- E.g. The concomitant intake of Tylenol and alcohol can lead to liver damage due to competition for the same metabolic enzyme.





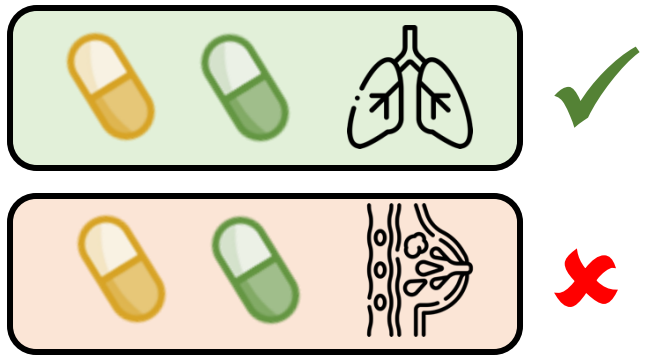
Background | Drug Relational Learning

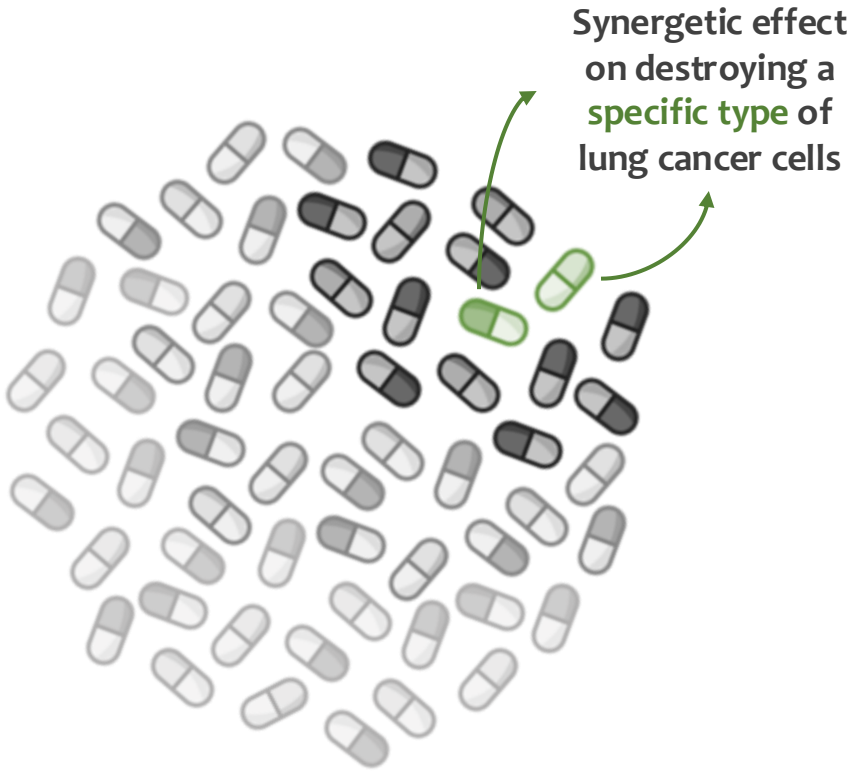
2. Drug relationships can change with context

- E.g. Cabazitaxal and zoledronic acid exhibit **synergy** in lung cancer cell lines but act **antagonistically** in breast cancer treatment.

Complex mechanisms affected by context changes:

- Tumor microenvironments.
- Antagonism in breast cancer.
- Drug transport and metabolism.

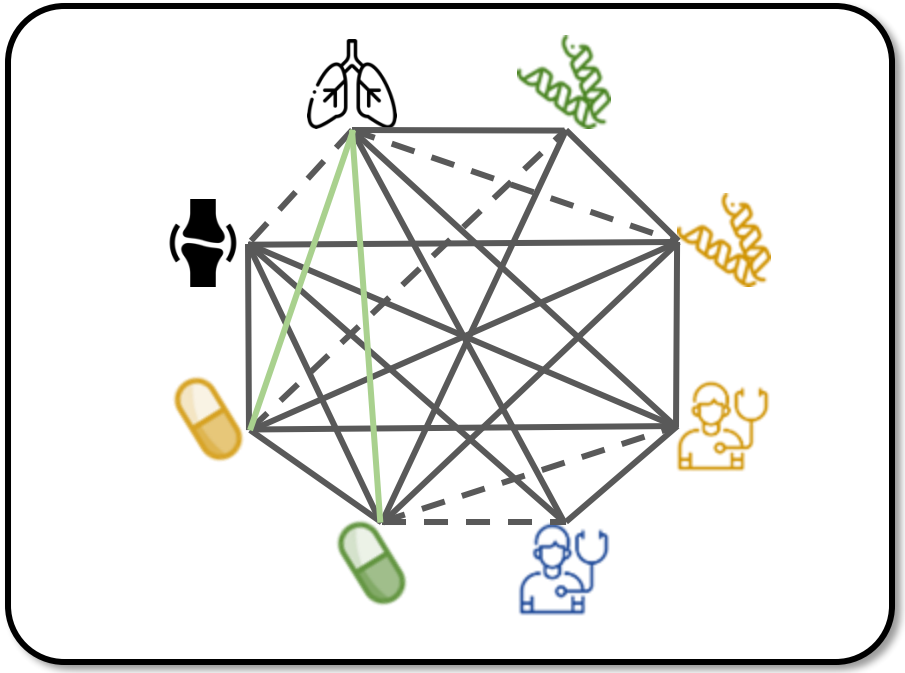




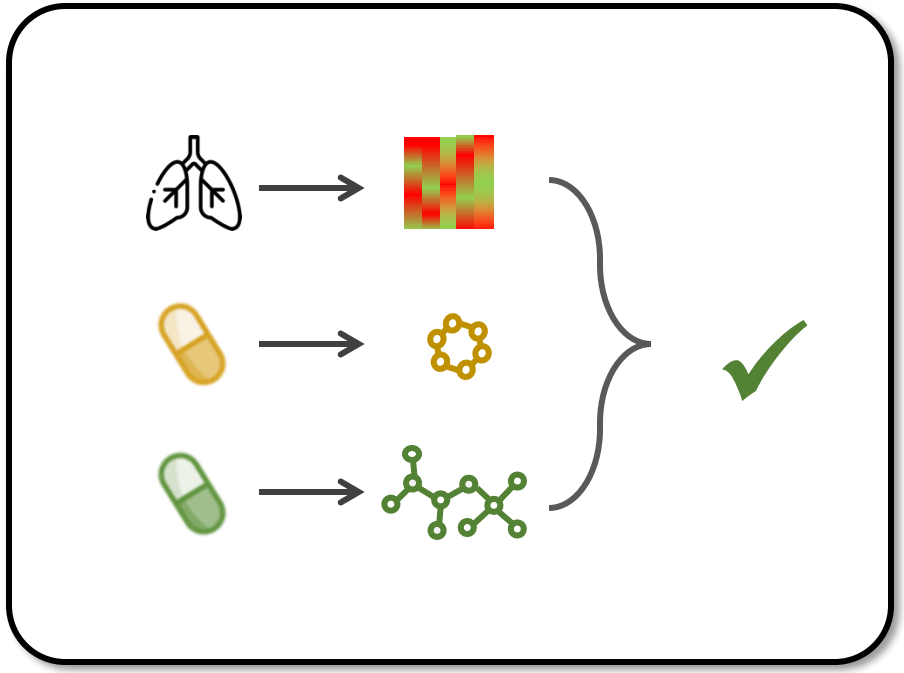
Background | Current Works

Current works on drug relational learning can be categorized into network-based and structure-based.

- *Network-based methods:*
  - Integrate multi-omics data to construct heterogeneous networks for inferring DDI.
- *Structure-based methods:*
  - Directly learn chemical properties and biological activities from molecular structure.



Network-based Methods



Structure-based Methods

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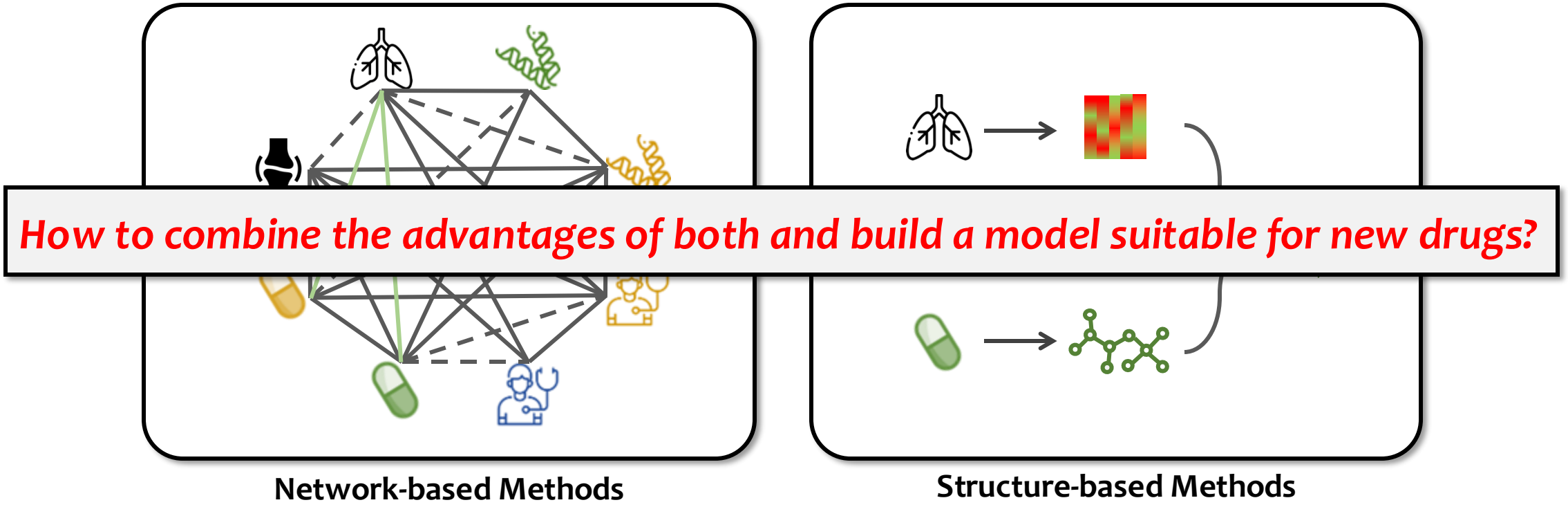
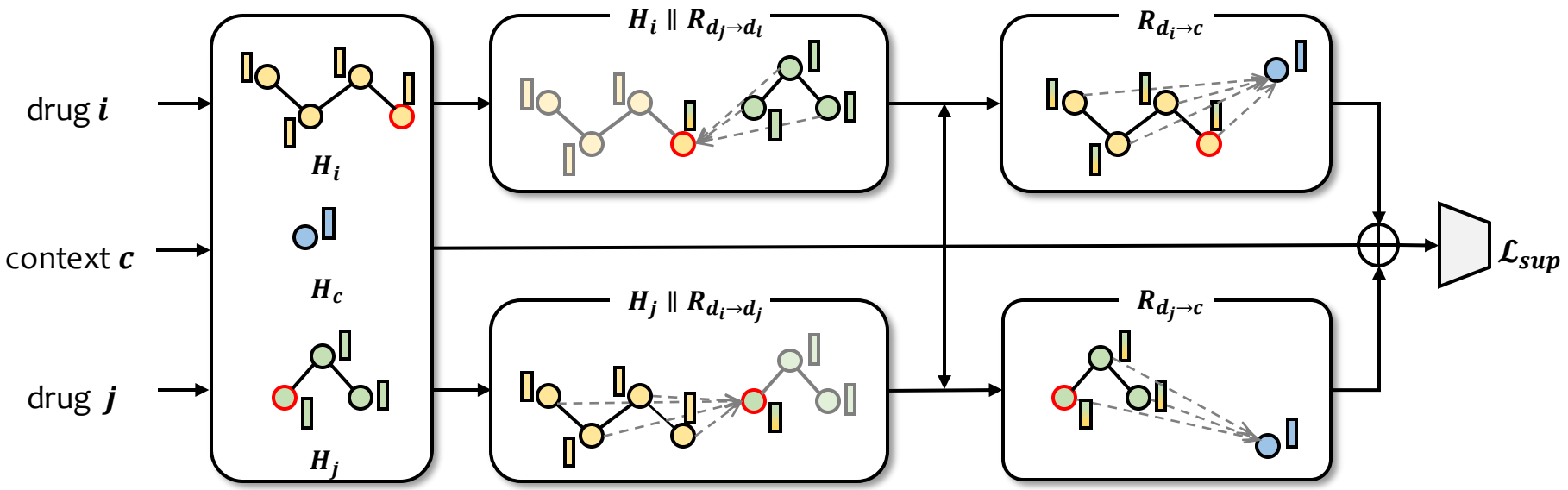


Method

Hierarchical Information Fusion

Context-aware drug-drug relational learning:

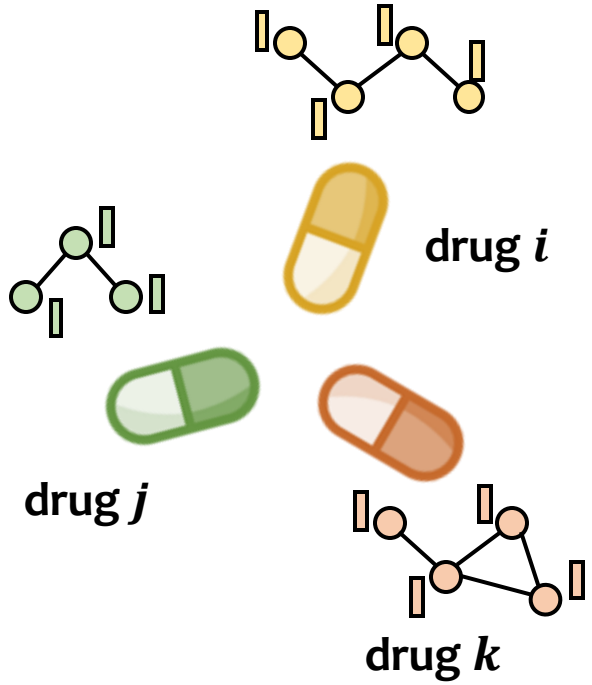
- Information fusion between **drugs**.
- Information fusion between **drug-context**.
- **Drug** feature encoder learns context-aware relation knowledge.
- Infer unknown relationship.

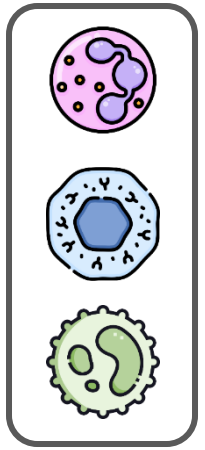


Method

Problem Definition

- Consider a set of annotated **drug-drug-context triplet tuples** (d_i, d_j, c, y), where $d_i, d_j \in D$, $c \in C$, and y is the target variable belonging to Y.
  - $D = \{d_1, d_2, ..., d_n\}$ represent a collection of n drugs, and $C = \{c_1, c_2, ..., c_m\}$ denote a set of m contexts.
- Here, y is a scalar value, ranging from negative to positive infinity in regression tasks, and taking binary values (0 or 1) in classification tasks.





→ ***relation*** (*e.g. whether two drugs i, j exhibit synergy in a specific cell line c*)

Method

Context-Aware Hierarchical Fusion

1. Drug Encoder and Context Encoder

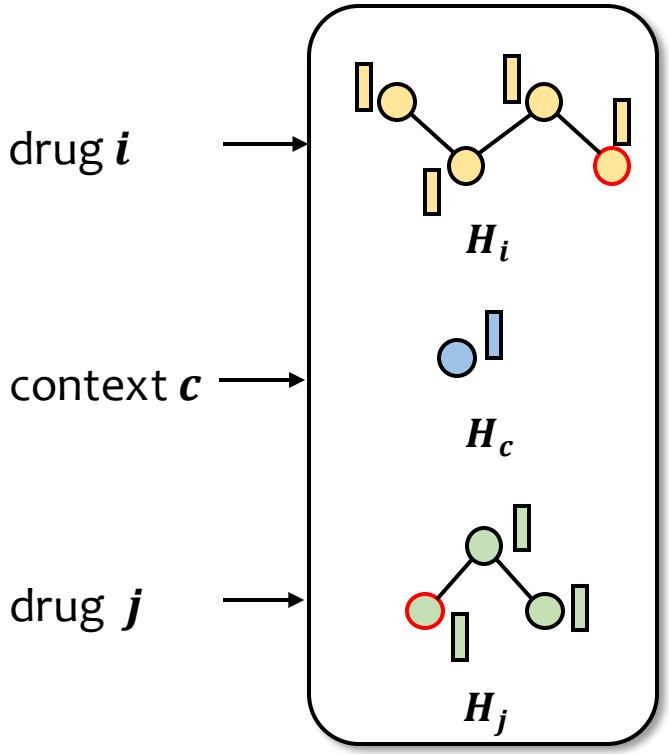
We employ:

- Graph Isomorphism Network (GIN) as graph encoder.

$$h_v^k = \text{MLP}\left(h_v^{k-1} + \sum_{u \in N(v)} h_u^{k-1}\right)$$

- Multi-Layer Perceptron (MLP) as context encoder.

$$h_c = \text{MLP}\left(x_c\right)$$



Method

Context-Aware Hierarchical Fusion

2. Drug-Drug Cross Fusion

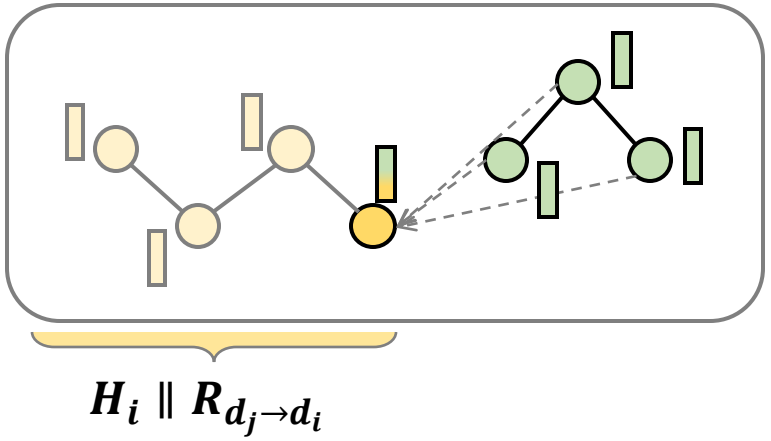
- we employ an atom-wise interaction map to calculate the directional relationship $R_{d_i \to d_j}$ between a pair of drugs i and j.

$$I_{ij} = \mathrm{sim}(H_i, H_j)$$

$$R_{d_i \to d_j} = I_{ij}^T \cdot H_j$$

- we update the representation of drug i as:

$$H_i' = \mathrm{concat}\left(H_i \parallel R_{d_i \to d_j}\right)$$



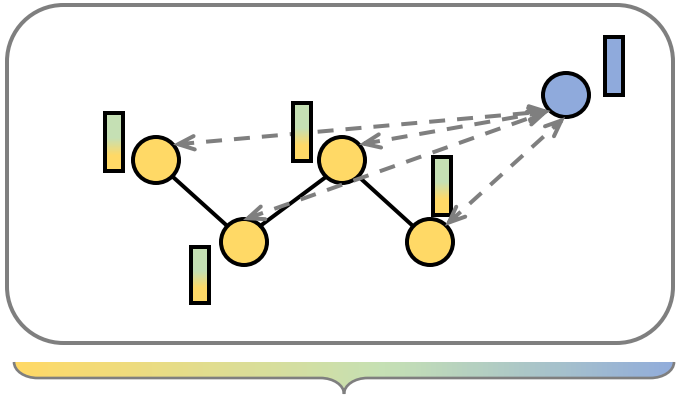
$\boldsymbol{H_i \parallel R_{d_j \to d_i}}$

3. Drug-Context Cross Fusion

- Similarly, we compute the relationships between drugs and context:

$$I_{ic} = \mathrm{sim}(H_i', H_c)$$

$$R_{d_i \to c} = I_{ic}^T \cdot H_i'$$



$\boldsymbol{R_{d_i \to c}}$

Method

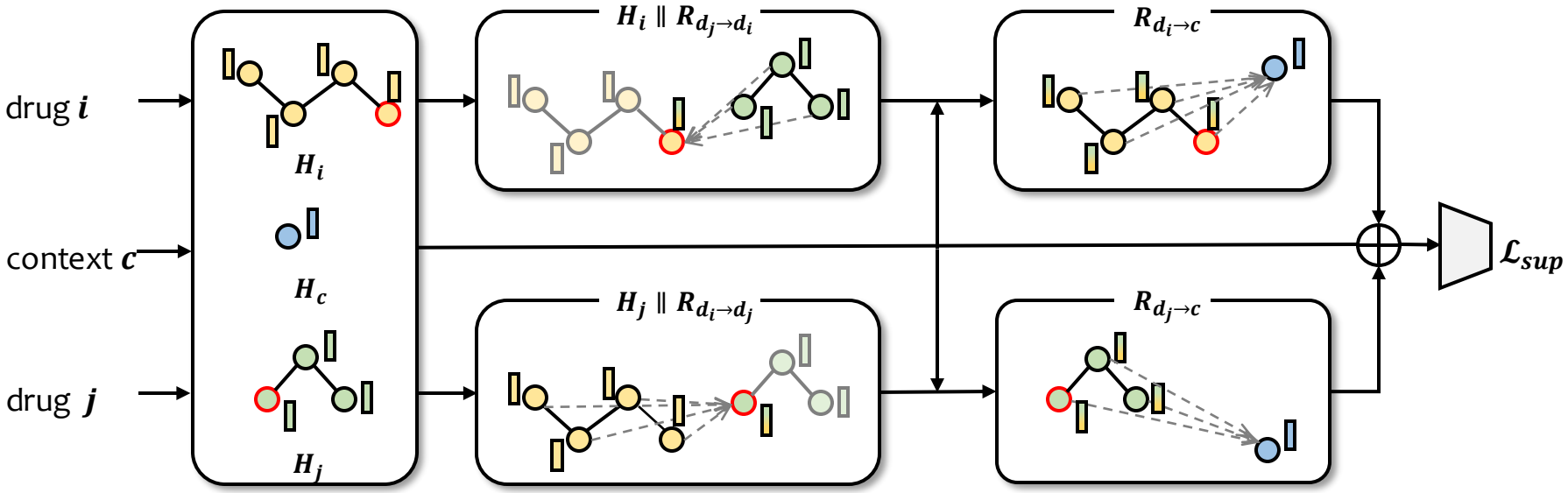
Context-Aware Hierarchical Fusion

4. Triplet Relation Predictor

- We feed the final hidden representation of the drug-drug-context triplet into MLP for relation prediction:

$$h_{d_i,d_j,c} = \text{concat}(H_c \parallel R_{d_i \to c} \parallel R_{d_j \to c})$$

$$\hat{y}_{d_i,d_j,c} = \text{MLP}(h_{d_i,d_j,c})$$



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Results

Benchmark Datasets

we consider the three most popular tasks in disease treatment:

- **Drug-Drug Synergy task:**
  - predicts whether a pair of drugs di, dj exhibit synergy in a specific cell line c.
- **Drug-Drug Polypharmacy Side Effect task:**
  - predicts whether a pair of drugs di, dj leads to a specific adverse event c.
- **Drug-Drug Interaction task:**
  - predicts whether a pair of drugs di, dj leads to a particular reaction c.

Task		Dataset	$\#D^1$	$\#D^2$	$\#C$	$\#DrugPair$	$\#Triplet$	Source
classification	Drug-Drug Synergy	DrugComb	4,117	895	288	74,378	659,333	chemicalx
		DrugCombDB	1,547	485	112	41,573	191,391	
	Drug-Drug Polypharmacy Side Effect	TWOSIDES	644	644	10	225,070	499,582	
	Drug-Drug Interaction	DrugbankDDI	1,706	1,706	86	365,056	383,496	
regression	Drug-Drug Synergy	OncoPolyPharmacology	37	37	39	583	23,052	TDC
		*DrugComb**	127	126	59	5,628	297,098	

Results

Performance

- Our models consistently outperform the baselines across all tasks, underscoring the effectiveness of our architecture in **learning complex drug relations across diverse tasks.**

	DrugComb			DrugCombDB			TwoSides			DrugBankDDI		
	AUROC ↑	AUPRC ↑	F1 ↑	AUROC ↑	AUPRC ↑	F1 ↑	AUROC ↑	AUPRC ↑	F1 ↑	AUROC ↑	AUPRC ↑	F1 ↑
GCN (w/)	66.1 (0.2)	72.3 (0.2)	70.5 (0.3)	76.3 (0.2)	60.7 (0.4)	47.3 (0.9)	92.6 (0.1)	90.8 (0.2)	86.1 (0.3)	97.1 (0.0)	96.0 (0.0)	92.5 (0.1)
GAT (w/)	66.2 (0.2)	72.4 (0.1)	70.7 (0.6)	76.1 (0.2)	60.5 (0.4)	47.1 (0.6)	92.4 (0.1)	90.6 (0.2)	85.6 (0.5)	97.0 (0.0)	95.8 (0.0)	92.5 (0.0)
DeepDrug	64.3 (0.1)	70.3 (0.2)	72.4 (0.1)	74.0 (0.1)	57.3 (0.1)	43.5 (1.0)	92.3 (0.4)	90.4 (0.2)	85.7 (0.2)	86.1 (0.3)	82.7 (0.3)	80.5 (0.2)
SSIDDI	66.3 (0.2)	72.6 (0.3)	70.4 (0.3)	77.9 (0.3)	62.4 (0.7)	52.8 (2.8)	91.7 (0.3)	89.8 (0.5)	83.8 (2.9)	85.5 (0.4)	82.2 (0.4)	79.0 (0.5)
CMRL	68.5 (0.2)	74.8 (0.1)	70.3 (0.0)	81.3 (0.1)	67.0 (0.3)	58.1 (0.8)	94.5 (0.0)	92.9 (0.2)	**91.7 (0.0)**	94.6 (0.2)	91.1 (0.0)	91.3 (0.6)
DeepSynergy (w/)	70.2 (0.3)	75.8 (0.3)	72.5 (0.2)	76.3 (0.5)	59.8 (0.8)	48.8 (1.2)	94.0 (0.1)	91.9 (0.1)	88.7 (0.1)	99.2 (0.1)	98.7 (0.1)	96.8 (0.1)
MatchMaker (w/)	66.2 (0.2)	72.5 (0.1)	71.2 (0.2)	78.6 (0.4)	63.7 (0.9)	50.8 (2.0)	91.2 (0.2)	89.2 (0.1)	84.9 (0.1)	98.7 (0.1)	98.1 (0.1)	95.9 (0.1)
DeepDDS (w/)	69.1 (0.2)	74.9 (0.2)	73.0 (0.3)	79.0 (0.6)	64.6 (1.0)	53.7 (1.3)	94.1 (0.0)	92.2 (0.0)	88.2 (0.2)	98.9 (0.0)	98.5 (0.1)	96.1 (0.1)
Ours	**81.8 (0.1)**	**85.7 (0.0)**	**77.8 (0.2)**	**86.0 (0.1)**	**74.8 (0.2)**	**66.4 (0.7)**	**95.6 (0.0)**	**93.4 (0.2)**	91.6 (0.1)	**99.8 (0.0)**	**99.6 (0.0)**	**99.0 (0.0)**

	ZIP			HSA			Bliss			Loewe		
	RMSE ↓	SCC ↑	PCC ↑	RMSE ↓	SCC ↑	PCC ↑	RMSE ↓	SCC ↑	PCC ↑	RMSE ↓	SCC ↑	PCC ↑
DeepDrug	5.35 (0.02)	0.38 (0.00)	0.34 (0.01)	5.88 (0.03)	0.31 (0.01)	0.32 (0.00)	6.02 (0.03)	0.26 (0.00)	0.29 (0.00)	17.18 (0.06)	0.06 (0.01)	0.11 (0.01)
SSIDDI	4.56 (0.02)	0.48 (0.00)	0.53 (0.00)	4.93 (0.02)	0.48 (0.00)	0.56 (0.01)	5.13 (0.03)	0.42 (0.01)	0.55 (0.00)	11.52 (0.03)	0.55 (0.00)	0.61 (0.00)
CMRL	4.26 (0.01)	0.49 (0.01)	0.54 (0.01)	4.59 (0.01)	0.50 (0.00)	0.58 (0.00)	4.78 (0.01)	0.45 (0.00)	0.57 (0.00)	11.23 (0.03)	0.57 (0.00)	0.63 (0.00)
DeepSynergy (w/)	4.02 (0.01)	0.61 (0.00)	0.66 (0.00)	4.38 (0.02)	0.57 (0.00)	0.68 (0.00)	4.55 (0.02)	0.52 (0.00)	0.67 (0.00)	10.63 (0.09)	0.61 (0.01)	0.69 (0.00)
MatchMaker (w/)	4.65 (0.02)	0.51 (0.00)	0.51 (0.00)	5.32 (0.03)	0.42 (0.00)	0.47 (0.01)	5.50 (0.03)	0.38 (0.01)	0.46 (0.01)	13.20 (0.31)	0.39 (0.04)	0.44 (0.06)
DeepDDS (w/)	4.56 (0.02)	0.51 (0.00)	0.54 (0.01)	5.17 (0.04)	0.45 (0.00)	0.53 (0.01)	5.40 (0.03)	0.40 (0.01)	0.51 (0.01)	12.01 (0.12)	0.50 (0.01)	0.58 (0.00)
Ours	**3.38 (0.03)**	**0.69 (0.00)**	**0.74 (0.00)**	**3.67 (0.06)**	**0.65 (0.01)**	**0.76 (0.01)**	**3.93 (0.03)**	**0.61 (0.01)**	**0.74 (0.00)**	**9.30 (0.08)**	**0.69 (0.00)**	**0.76 (0.00)**

Results

Ablation Study

One of the most noteworthy distinctions between our model and other baselines is that our model explicitly learns drug relations hierarchically through the drug-drug-context triplet.

- There is a significant drop when relations are not explicitly modeled.
- Without hierarchy, the model's performance drops by around 3.3% in AUROC.
  - suggesting that the hierarchical architecture effectively filters out features that are irrelevant to model prediction.
- Removing either side of the fusion results in a drop in performance.

RL	H	$d_i \rightarrow d_j \rightarrow c$	$d_j \rightarrow d_i \rightarrow c$	AUROC	AUPRC	F1
Implicit	-			76.4 (0.1)	60.7 (0.1)	48.8 (0.2)
Explicit	w/o	-		82.7 (0.2)	69.5 (0.4)	60.9 (0.4)
	w/	✓	-	84.5 (0.4)	72.6 (0.6)	64.7 (0.8)
	w/	-	✓	84.0 (0.3)	71.7 (0.8)	63.0 (1.4)
	w/	✓	✓	**86.0 (0.1)**	**74.8 (0.2)**	**66.4 (0.7)**

Results

Performance under cold-drug setting

To assess the generalization ability of our model in predicting relationships between unknown drug pairs, we adopted a cold-drug setting by partitioning a small subset of drugs from the original dataset.

- Our model outperformed other models by a significant margin on DrugBankDDI, and achieve comparable performance to the best baseline on DrugComb.
- In such a context-rich environment, the ability of models to learn contextual information is more critical for performance.

	DrugBankDDI		
	AUROC ↑	AUPRC ↑	F1 ↑
DeepDrug	67.2 (1.0)	66.6 (1.3)	55.4 (1.0)
SSIDDI	66.2 (0.8)	65.9 (1.3)	53.0 (4.5)
CMRL	94.0 (0.2)	90.3 (0.3)	90.0 (0.2)
DeepSynergy (w/)	90.8 (0.6)	90.6 (0.5)	73.1 (2.1)
MatchMaker (w/)	92.8 (0.1)	93.3 (0.6)	74.7 (2.5)
DeepDDS (w/)	93.4 (0.5)	94.1 (0.4)	85.3 (0.6)
HypergraphSynergy (w/)	91.8 (0.4)	92.6 (0.5)	85.7 (0.8)
Ours	**99.6 (0.0)**	**99.4 (0.1)**	**98.8 (0.1)**

Summary

Main challenges in Drug Relational Learning:

- extracting crucial features from **drugs conditioned on a given context.**
- modeling the problem of drug relational learning in a **simple yet robust manner.**

Our Main Contributions:

- we tackle the aforementioned challenges in drug relational learning through our proposed **context-aware hierarchical cross-fusion model**.
- Recognizing that **drugs act as causes and context as a result in co-administration,** our model constrains the drug relation learned with context by integrating drug-drug relations into drug-context relations.
- Our model exhibits **significantly superior performance** compared to baselines across various drug relation databases, encompassing both classification and regression tasks.

Thank you for listening!