

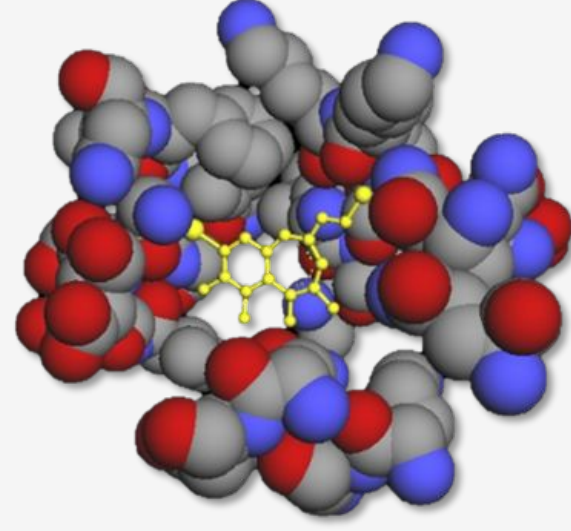
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Poly-pharmacology

- Drugs are organic small molecules that bind to bio-molecular targets to activate/inhibit their functions.
- Drug affect multiple targets, causing:
 - Adverse side-effects
 - Unexpected therapeutic effect



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Drug Repurposing



Sildenafil was originally developed for pulmonary arterial hypertension

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Probabilistic Soft Logic (PSL)

- PSL: Declarative language based on first-order logic to express collective probabilistic inference problems.
- General Rules:

$$\omega : P(A, B) \wedge Q(B, C) \rightarrow R(A, C)$$

- Predicates have soft truth values between [0,1]

- Rule Satisfaction: $r_{body} \rightarrow r_{head}$

$$I(r_{body}) \leq I(r_{head})$$

- Distance from satisfaction:

$$\delta_r = \max\{0, I(r_{body}) - I(r_{head})\}$$

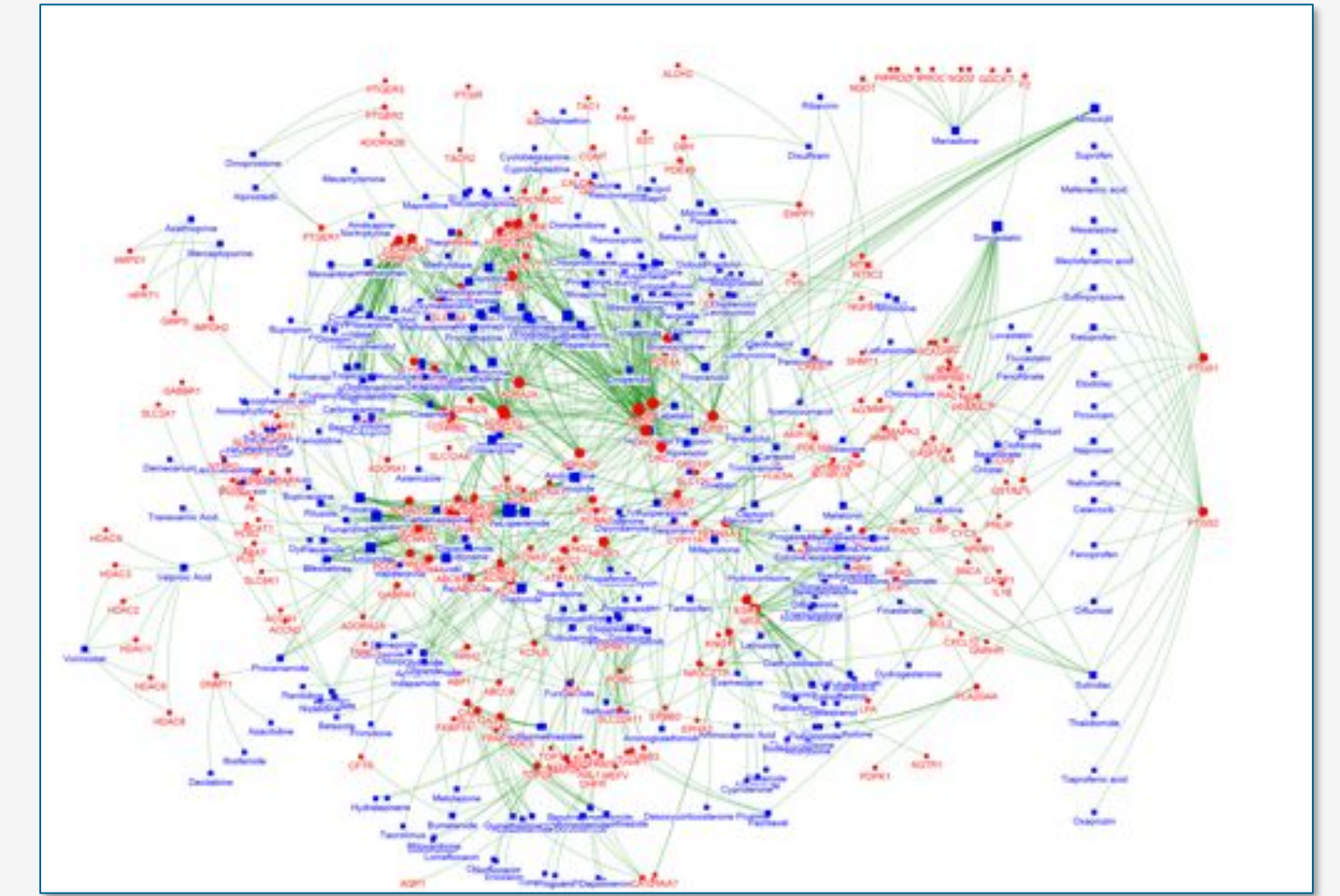
- Most probable explanation (MPE) by optimizing:

$$f(\mathcal{I}) = \frac{1}{\mathcal{Z}} \exp \left[- \sum_{r \in \mathcal{R}} \omega_r \delta_r(\mathcal{I}) \right]$$

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DataSet

- 315 Drugs and 250 Targets.
- 1,306 observed Interactions out of 78,750 possible.
- 3 target-target and 5 drug-drug similarities.
- We used 10-fold cross-validation for evaluation.



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Combining Similarities

Models with only one similarity vs.

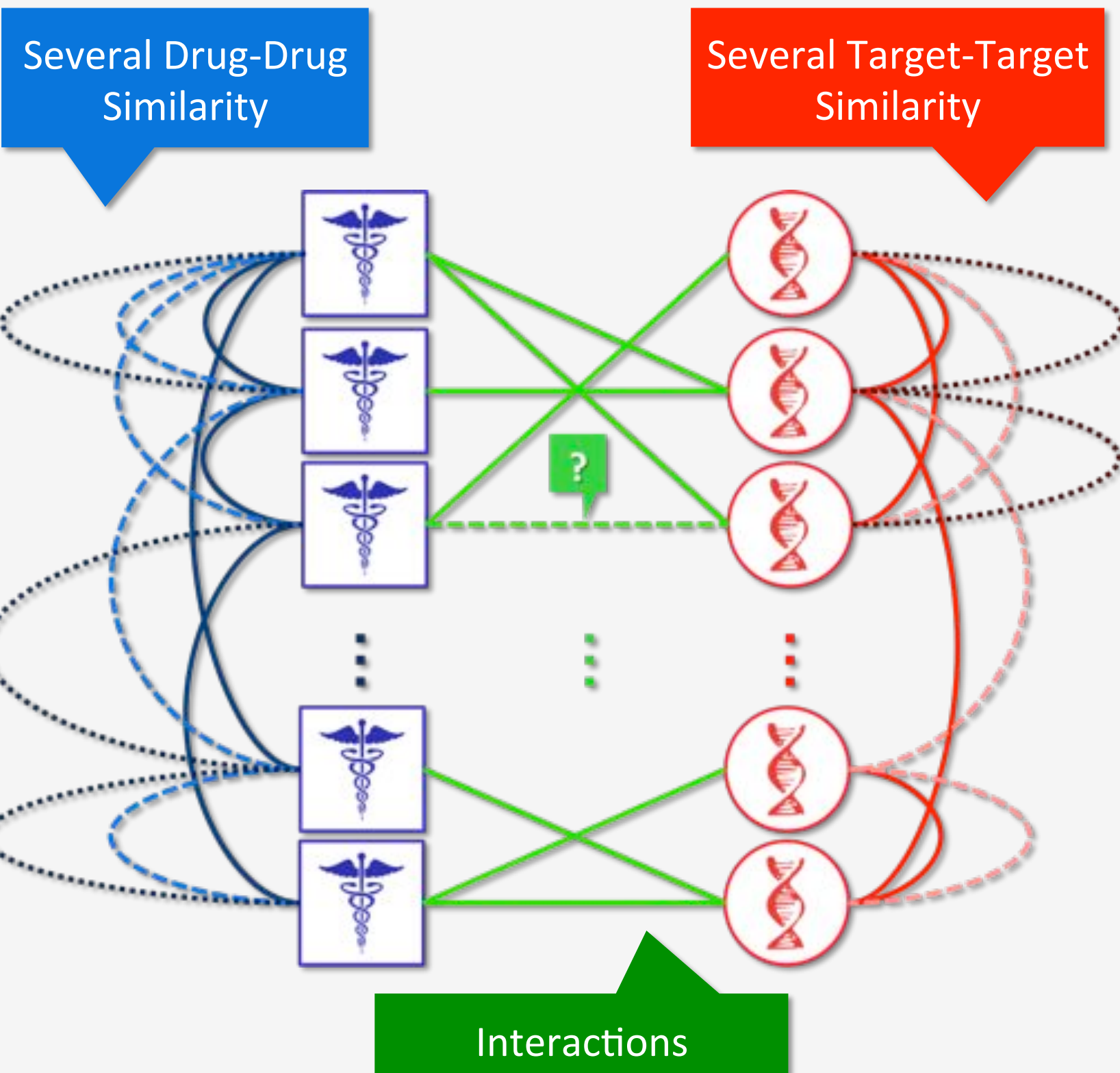
Model with all similarities

Similarities		AU-ROC	AU-PR	p@130
Drugs	Annotation-based	0.788 ± 0.022	0.122 ± 0.016	0.198 ± 0.019
	Chemical-based	0.755 ± 0.023	0.064 ± 0.015	0.155 ± 0.025
	Ligand-based	0.774 ± 0.025	0.069 ± 0.014	0.151 ± 0.027
	Expression-based	0.606 ± 0.024	0.005 ± 0.001	0.020 ± 0.009
	Side-effect-based	0.726 ± 0.015	0.068 ± 0.015	0.151 ± 0.032
Target	PPI-network-based	0.851 ± 0.021	0.167 ± 0.046	0.225 ± 0.045
	GO-based	0.678 ± 0.029	0.025 ± 0.006	0.080 ± 0.022
	Sequence-based	0.826 ± 0.027	0.129 ± 0.034	0.213 ± 0.045
All Similarities Combined		0.931 ± 0.018	0.190 ± 0.032	0.249 ± 0.041

Combining multiple similarities significantly improves performance.

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Drug-Target Interaction Network



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Drug-Target Interaction Predicates

$Interacts(D, T)$

$SimilarDrug_{\alpha}(D_1, D_2)$

α indicates different drug-drug similarities including: annotation-based, chemical-based, ligand-based, expression-based, side-effect-based

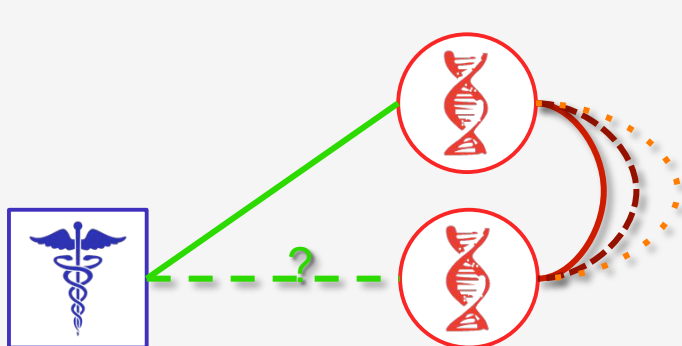
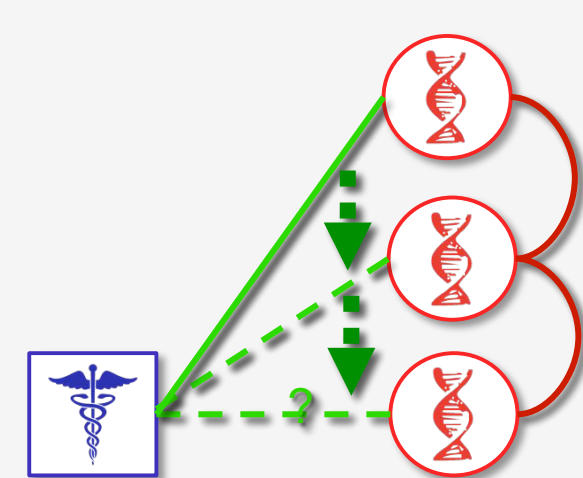
$SimilarTarget_{\beta}(T_1, T_2)$

β indicates different target-target similarities including: sequence-based, PPI-network-based, gene ontology-based

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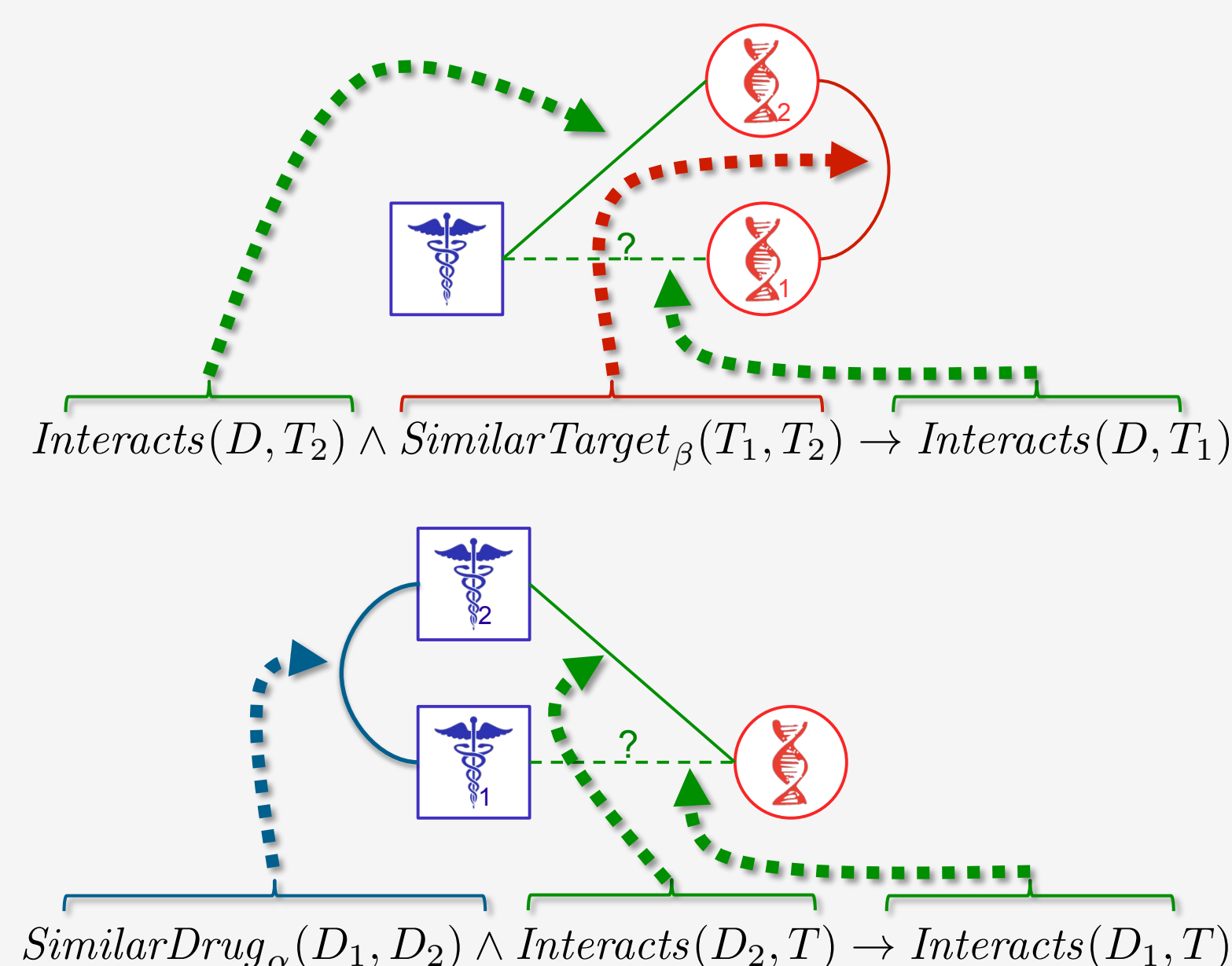
Studies

- Collective Inference:** The effect of jointly reasoning over interdependent interactions.
- Combining Similarities:** The effect of incorporating multi-relational heterogeneous information.



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Triad-based Rules



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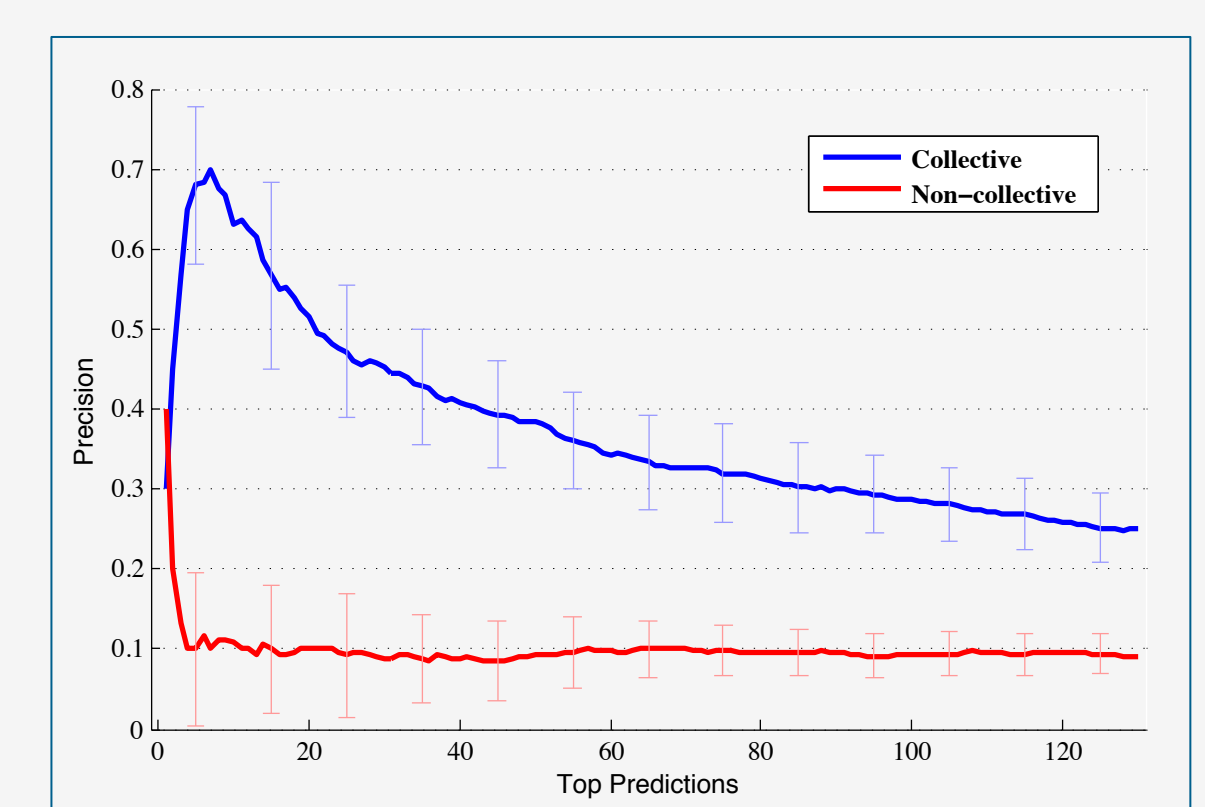
Collective Inference

Collective

$SimilarDrug_{\alpha}(D_1, D_2) \wedge Interacts(D_2, T) \rightarrow Interacts(D_1, T)$
 $SimilarTarget_{\beta}(T_1, T_2) \wedge Interacts(D, T_2) \rightarrow Interacts(D, T_1)$
 vs.

Non-Collective

$SimilarDrug_{\alpha}(D_1, D_2) \wedge ObservedInteracts(D_2, T) \rightarrow Interacts(D_1, T)$
 $SimilarTarget_{\beta}(T_1, T_2) \wedge ObservedInteracts(D, T_2) \rightarrow Interacts(D, T_1)$



Collective inference significantly outperforms non-collective prediction.

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