# Drug-Target Interaction Prediction for Drug Repurposing with Probabilistic Similarity Logic

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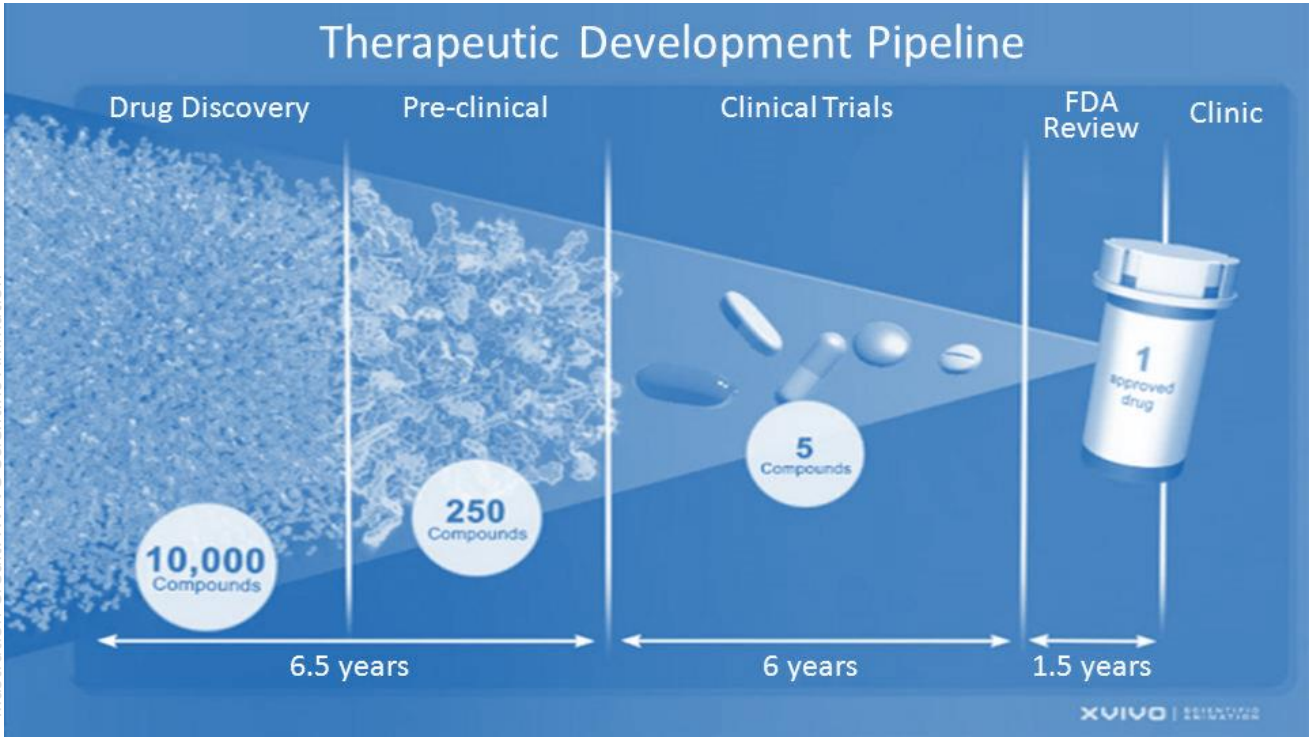
# Outline

- Drug Repurposing
- Drug-Target Interaction Network
- Probabilistic Similarity Logic (PSL)
- Drug-Target Interaction Prediction with PSL
- Experimental Results

# New Drug Development

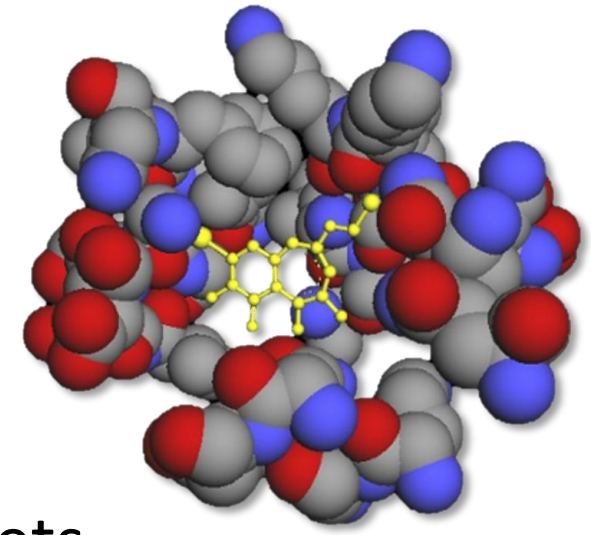



- Time Consuming: New drugs take a decade to reach market.
- Costly: Development cost reaches 2 billion US dollars.

**Valley of death:**
**Most novel drug candidates never get approved!**

# Drugs

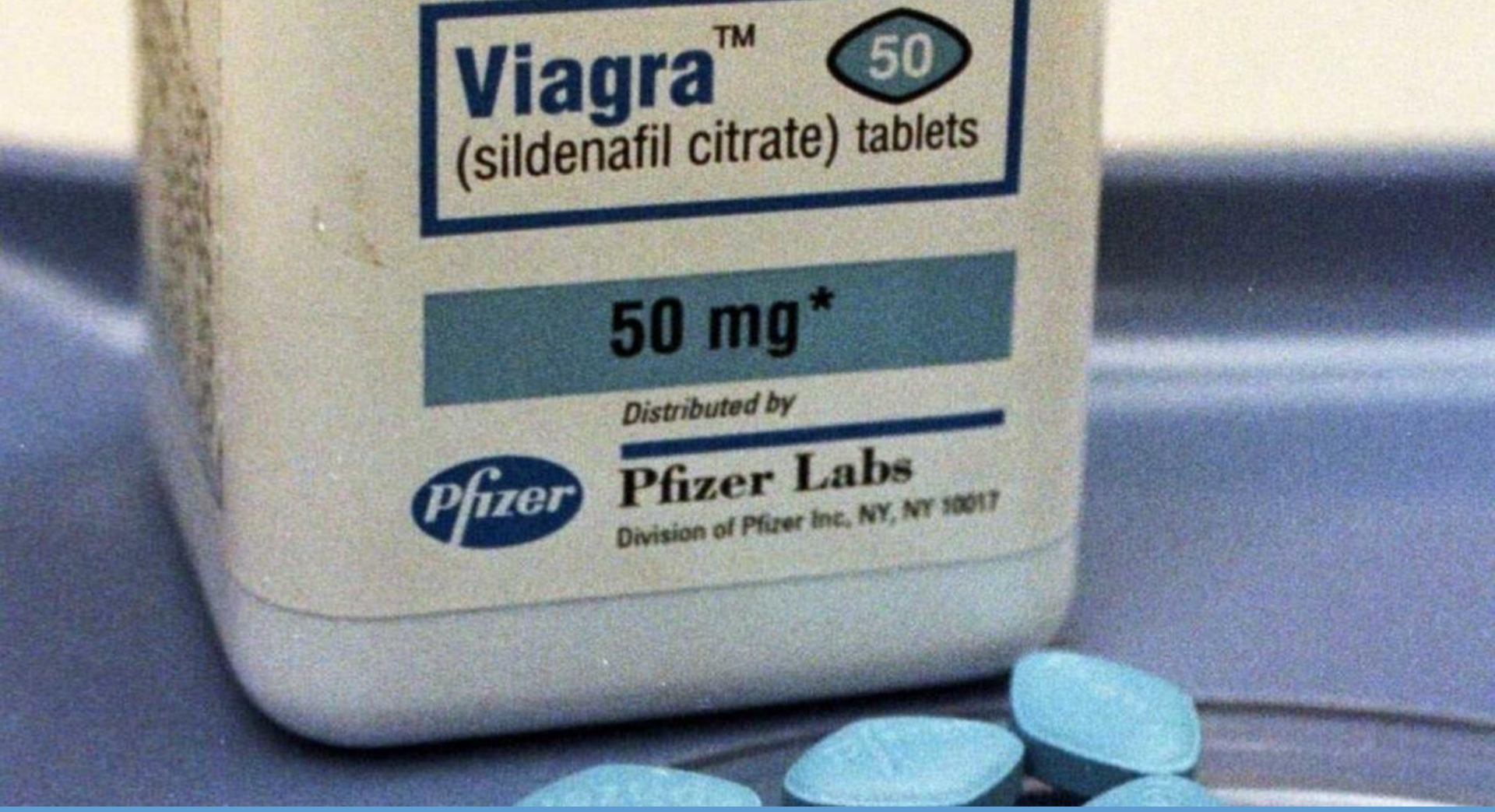
- Drugs:
  Organic small molecules that bind to bio-molecular targets to activate/inhibit their functions



- Drug often affect multiple targets.
- Poly-pharmacology is an area of growing interest

# Drug Repurposing

- Drug Affecting Multiple Targets:
  - Adverse side-effects
  - Unexpected therapeutic effect
- Drug Repurposing/Repositioning: Finding new uses for approved drugs.
- No need for tests required for a new therapeutic compound (Already approved)




**Sildenafil was originally developed for pulmonary arterial hypertension**

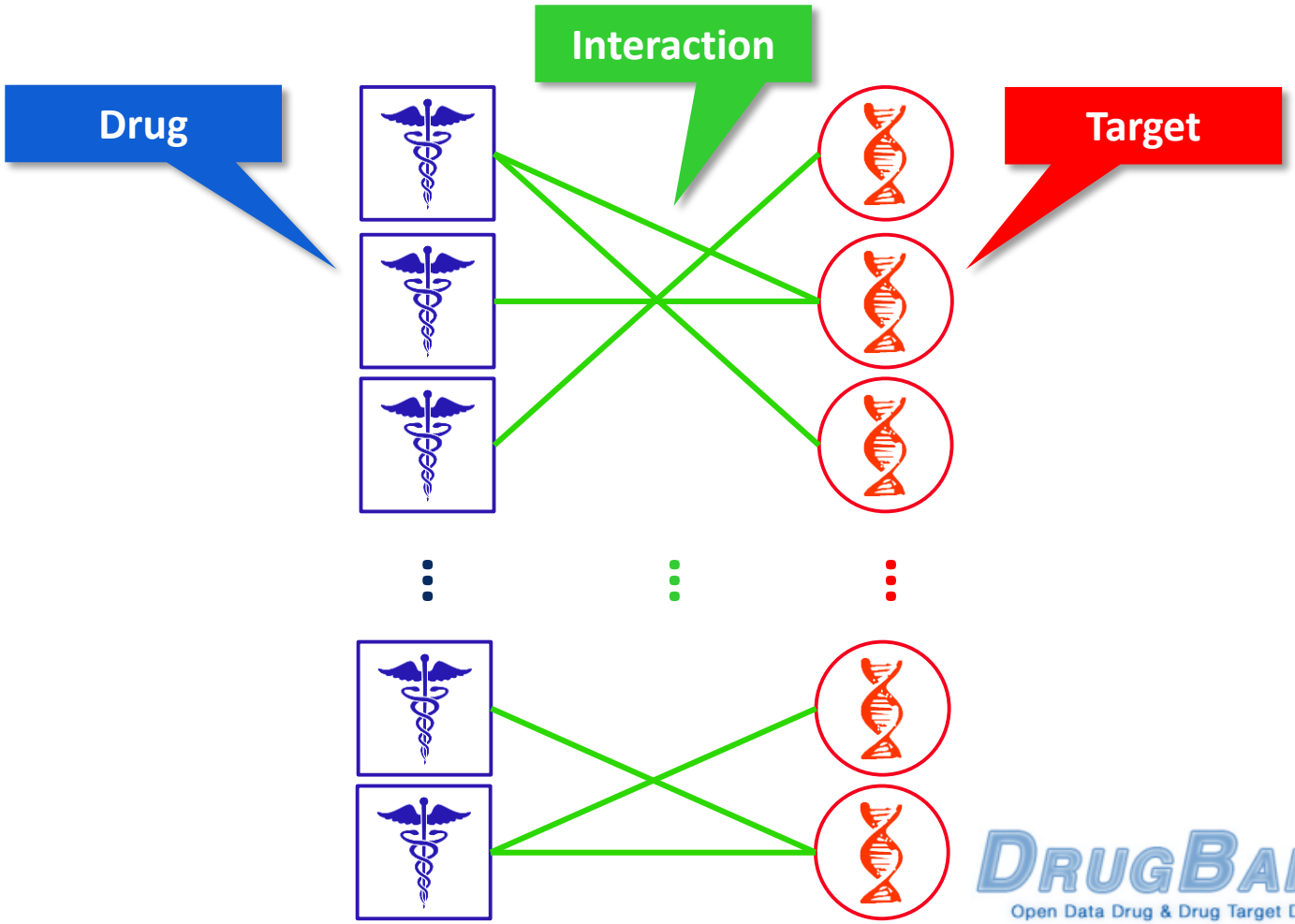
# Need for Systematic Search

- Most new treatment are discovered by chance during clinical trials.
- There is a need for a better systematic approach.
- Experimental identification of drug-target associations is labor intensive and costly

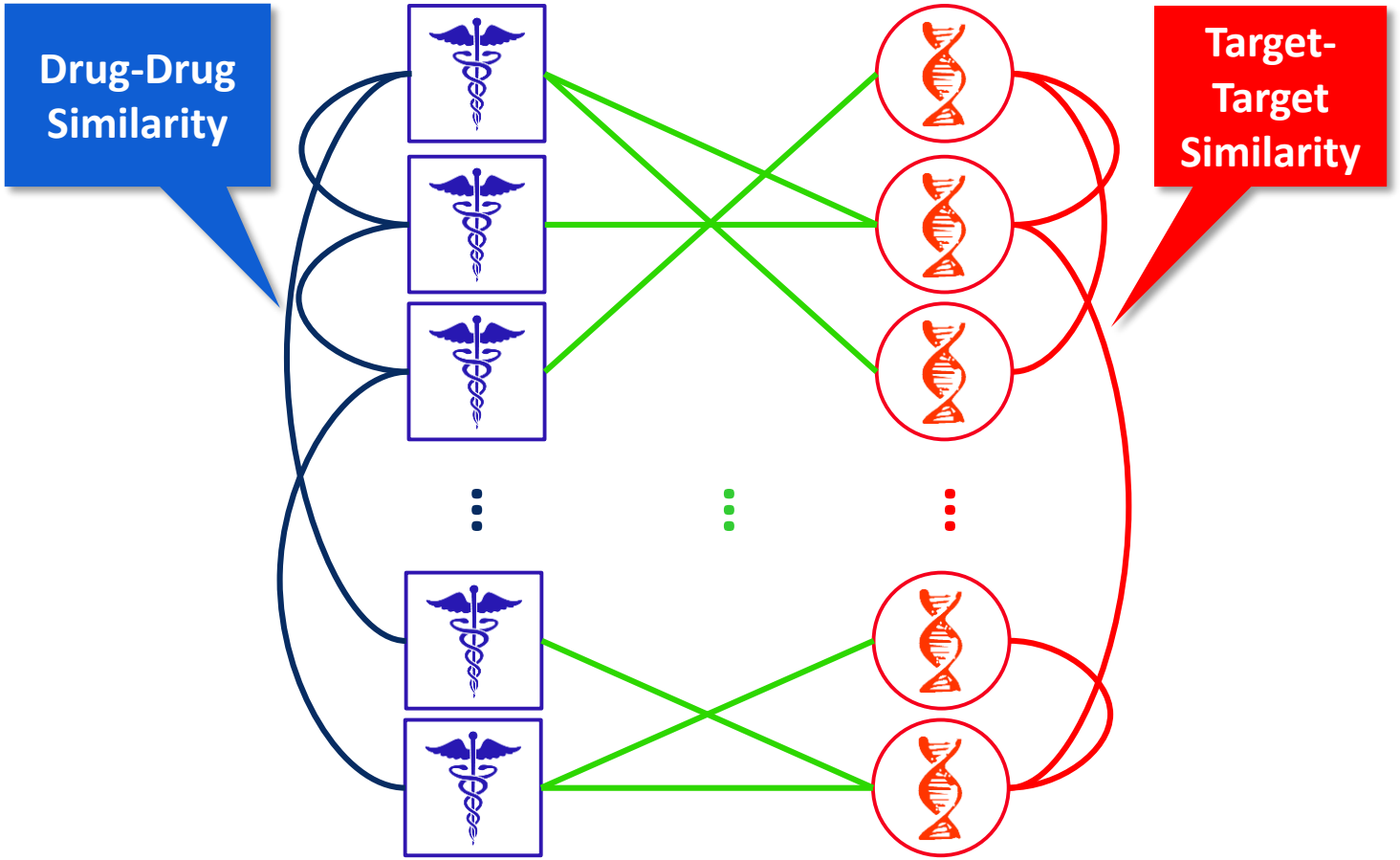
- A better solution?

# Using computational predictions to focus biological search

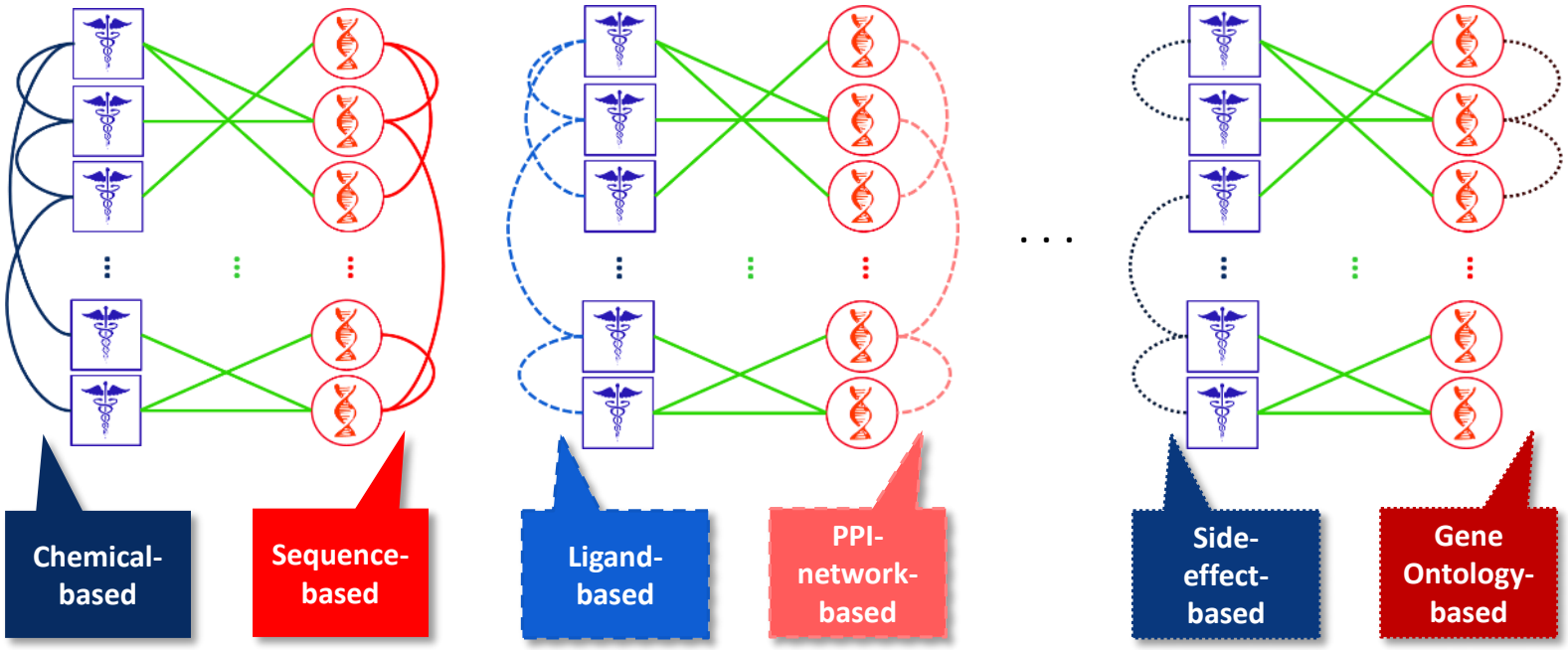
# Drug-Target Interaction Network



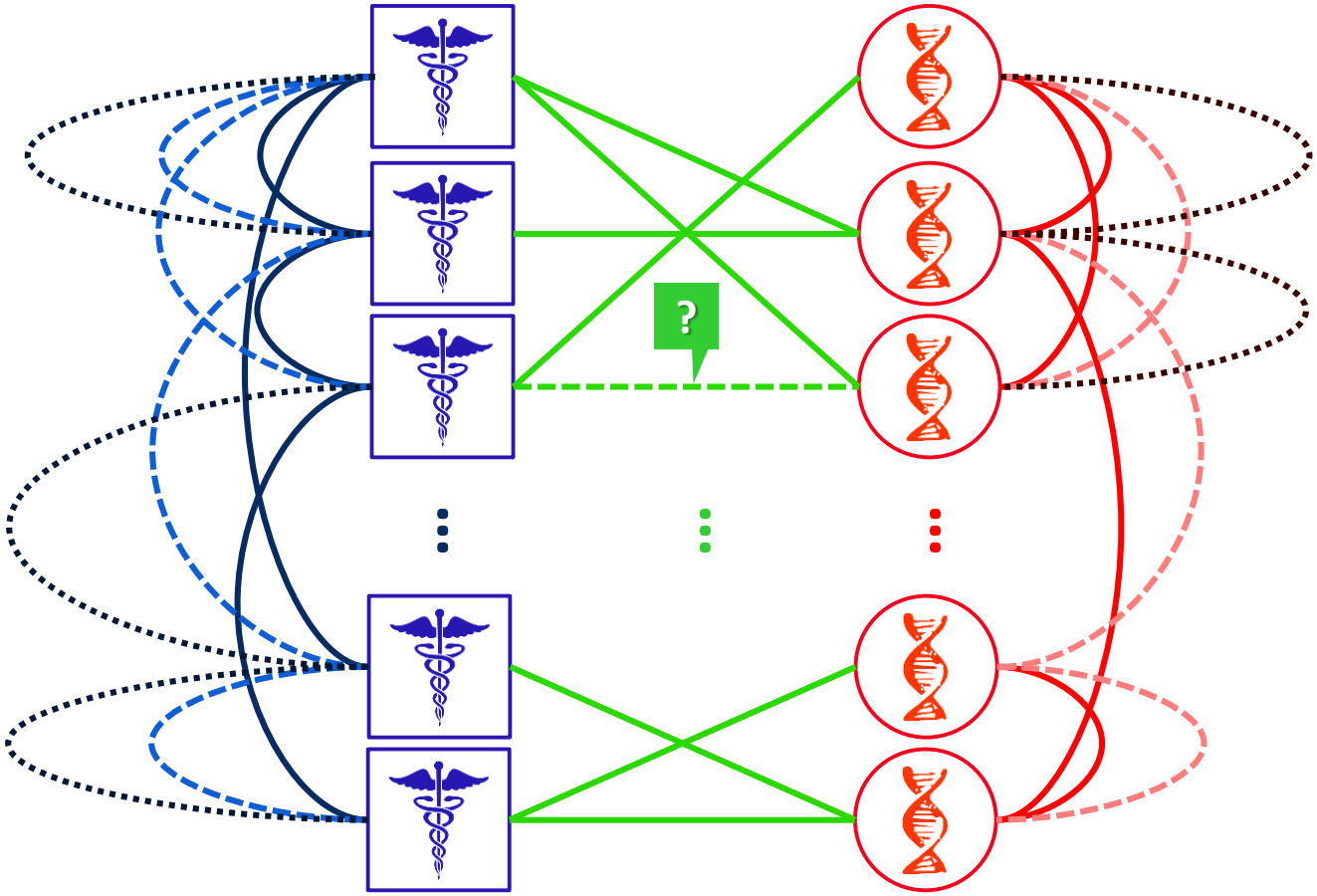
# Drug-Target Interaction Network + Similarities



# Multiple Similarities



# D-T Interaction Network + Multiple Similarities

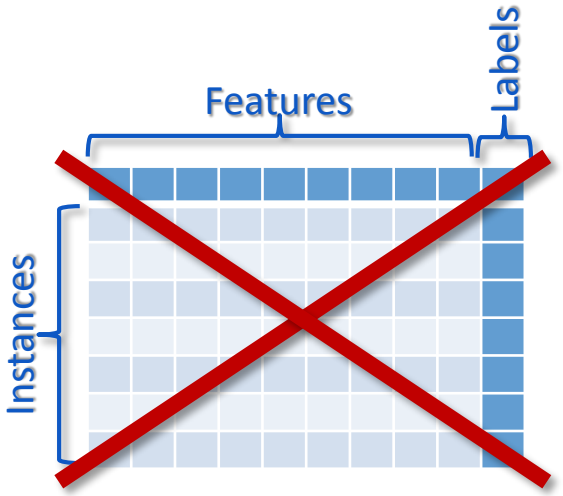


# Drug-Target Interaction Prediction

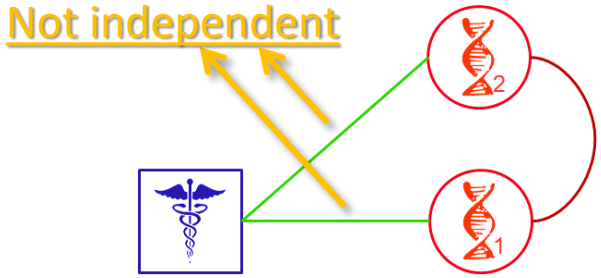

- Data:
  - Drug-target interaction network
  - Set of drug-drug similarities
  - Set of target-target similarities
- Task:
  - Link Prediction (New drug-target interactions)

# Challenges

- Data is not originally flat:
  - Classifiers need a set of features and instances.
  - Instances: all interactions in the network (pairwise)
    or only interaction of one drug or target.
  - Features: Feature engineering




- Not Independent and Identically Distributed (IID): Interactions depend on each other (a drug tends to interact with similar targets)



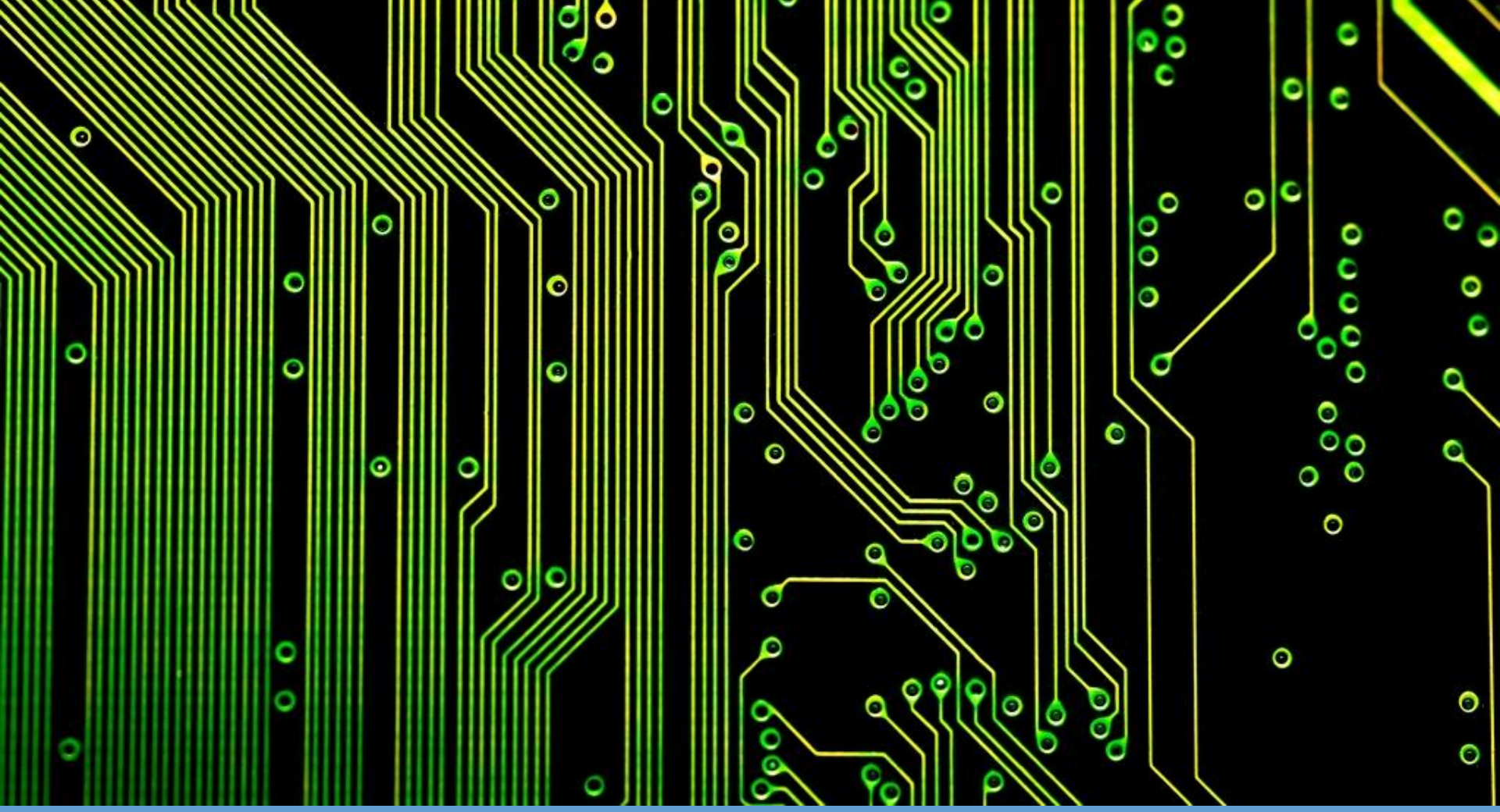

- Multi-relational:
  - Drug-Target Interactions
  - Different Drug-Drug Similarities
  - Different Target-Target Similarities


Probabilistic
Similarity
Logic

# Probabilistic Similarity Logic

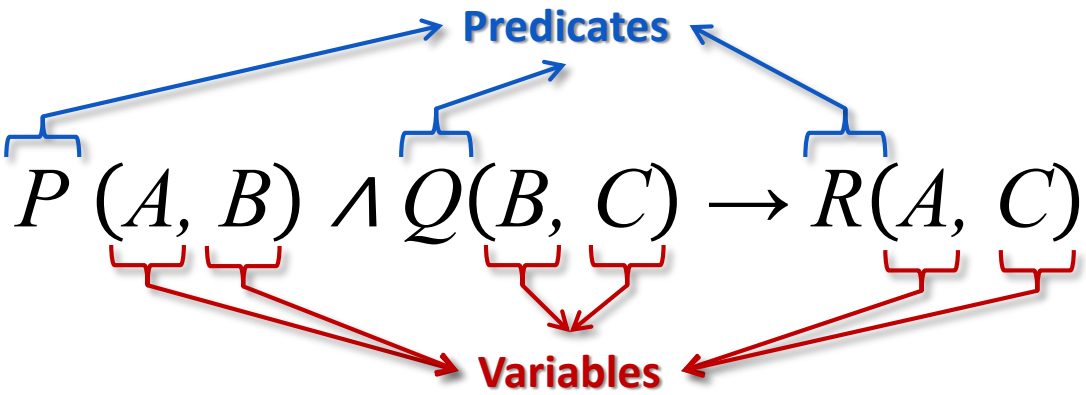
# Probabilistic Similarity Logic (PSL)

- Declarative language based on logic to express collective probabilistic inference problems.
  - Logical foundation
  - Probabilistic foundation
  - Weight Learning



# Logic Foundation

# General Rules

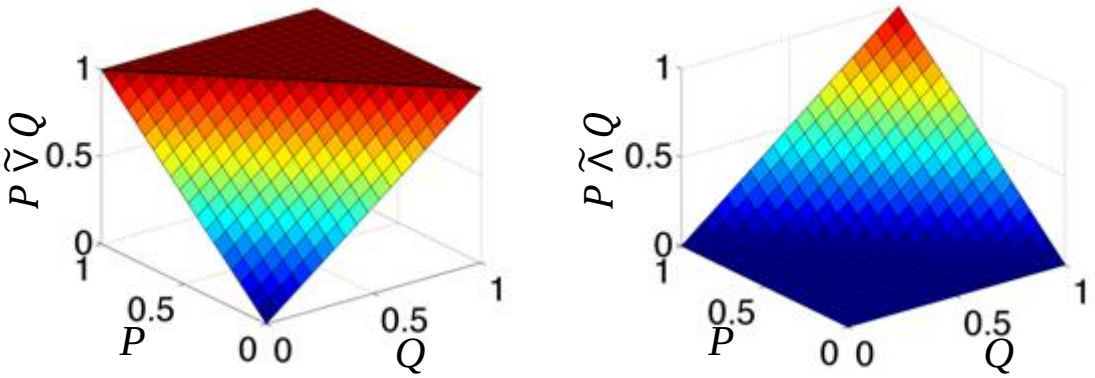



e.g., $Interacts(D, T_2) \wedge SimilarTarget(T_1, T_2) \rightarrow Interacts(D, T_1)$

- Can use predicate to define relations between variables.
  e.g. Interacts(D, T)
- Grounding: Instantiation of predicates with data.
  e.g. Interacts(acetaminophen, cox2)
- Groundings have a soft-truth values between [0, 1]

# Lukasiewicz t-norm and co-norm

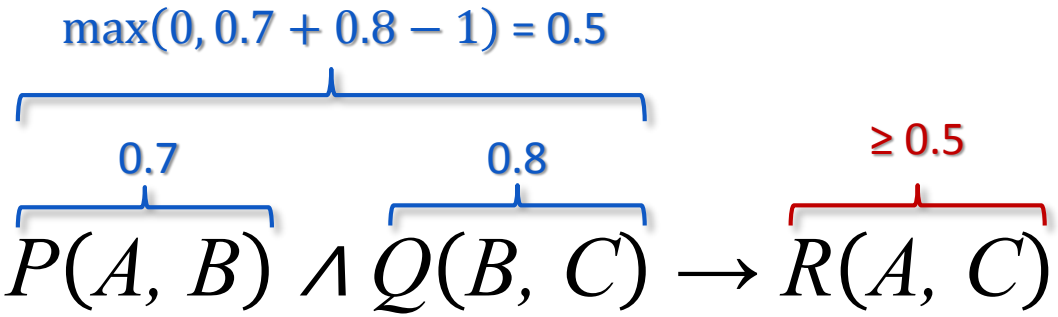
$$P(A, B) \wedge Q(B, C) \rightarrow R(A, C)$$




- $P \tilde{\wedge} Q = max(0, P + Q - 1)$
- $P \tilde{\vee} Q = min(1, P + Q)$
- $\neg P = 1 - P$

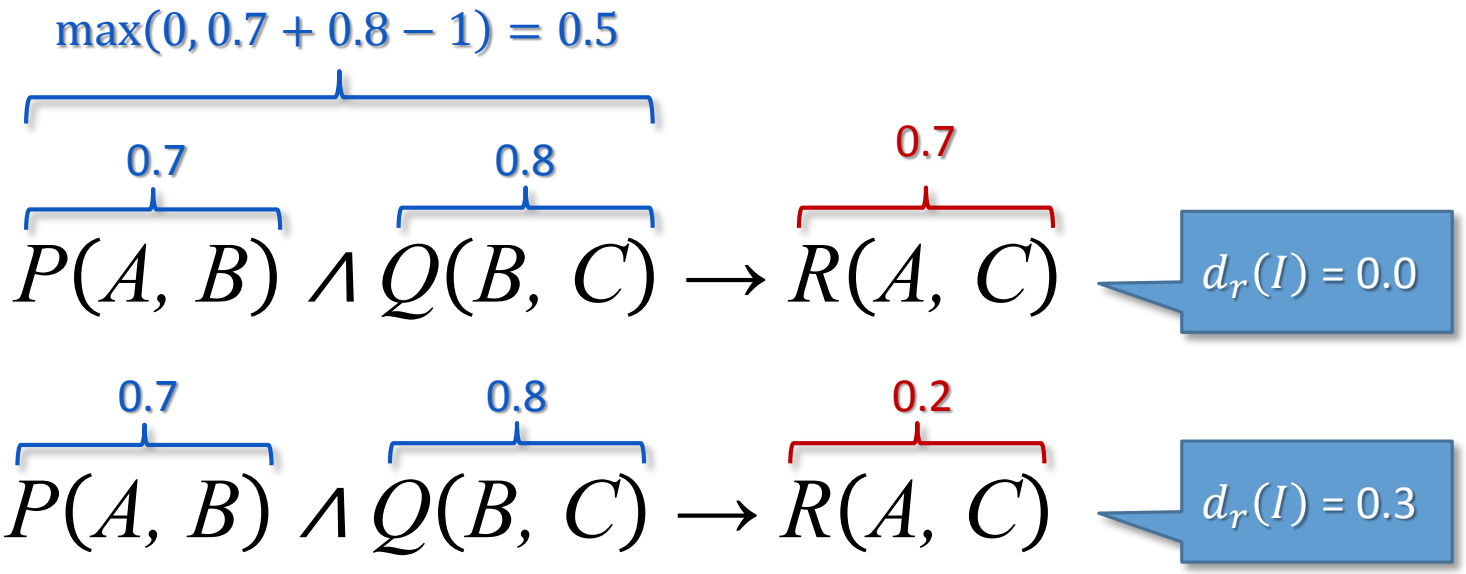
# Satisfaction

- Interpretation (I) : an assignment of soft-truth values to a set of groundings.
- Rule satisfaction: $r_{body} \rightarrow r_{head}$ is satisfied when $I(r_{body}) \leq I(r_{head})$



# Distance to Satisfaction

$$d_r(I) = max\left( I\left(r_{body}\right) - I\left(r_{head}\right), 0\right)$$



# Rule Weights

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

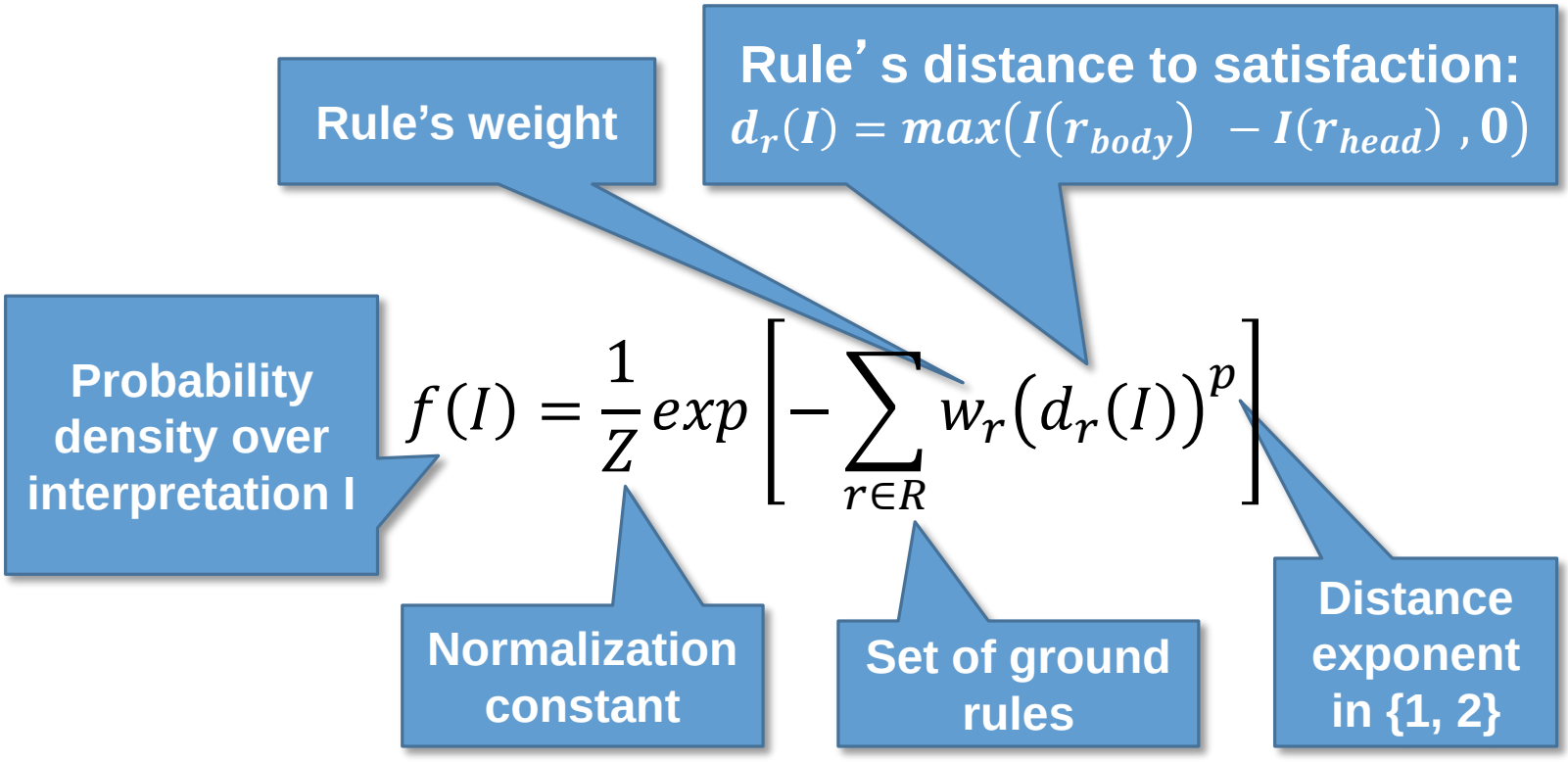
- Rule can have weights which corresponds to importance of the rule.
  - Can come from domain knowledge
  - Can be learned from data

# Review

- PSL program + Dataset → Set of ground rules
- Some groundings (predicates) have known truth values and some have unknown truth values.
- Every Interpretation of unknown groundings (predicates) → different weighted distances to satisfaction
- How to decide which Interpretation is best?

# Probabilistic Foundation

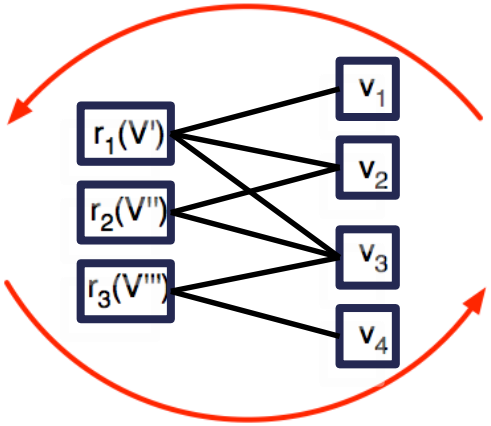
# Probabilistic Model



# Inferring Most Probable Explanations

- Given a set of observed groundings infer the values of unknown groundings
- e.g., Given a set of drug-target interactions + a set of D-D and T-T similarities infer the value of other interactions.

- Convex optimization: perform inference using the alternating direction method of multipliers (ADMM) [Bach et al., NIPS 2012]
- Fast, scalable, and straightforward
- Optimize sub-problems (ground rules) independently.

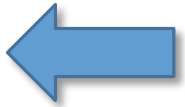



# Weight Learning

# Weight Learning

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

- Learn the weights from training data
- Various methods:
  - Approximate maximum likelihood [Broecheler et al., UAI 10]
  - Maximum pseudo-likelihood
  - Large-margin estimation



# PSL Summary

- Design probabilistic models using declarative language
  - Syntax based on **first-order logic**
- Inference of most-probable explanation is fast **convex optimization** (ADMM)
- Learning algorithms for training rule weights from labeled data.

# Drug-Target Interaction Prediction with PSL

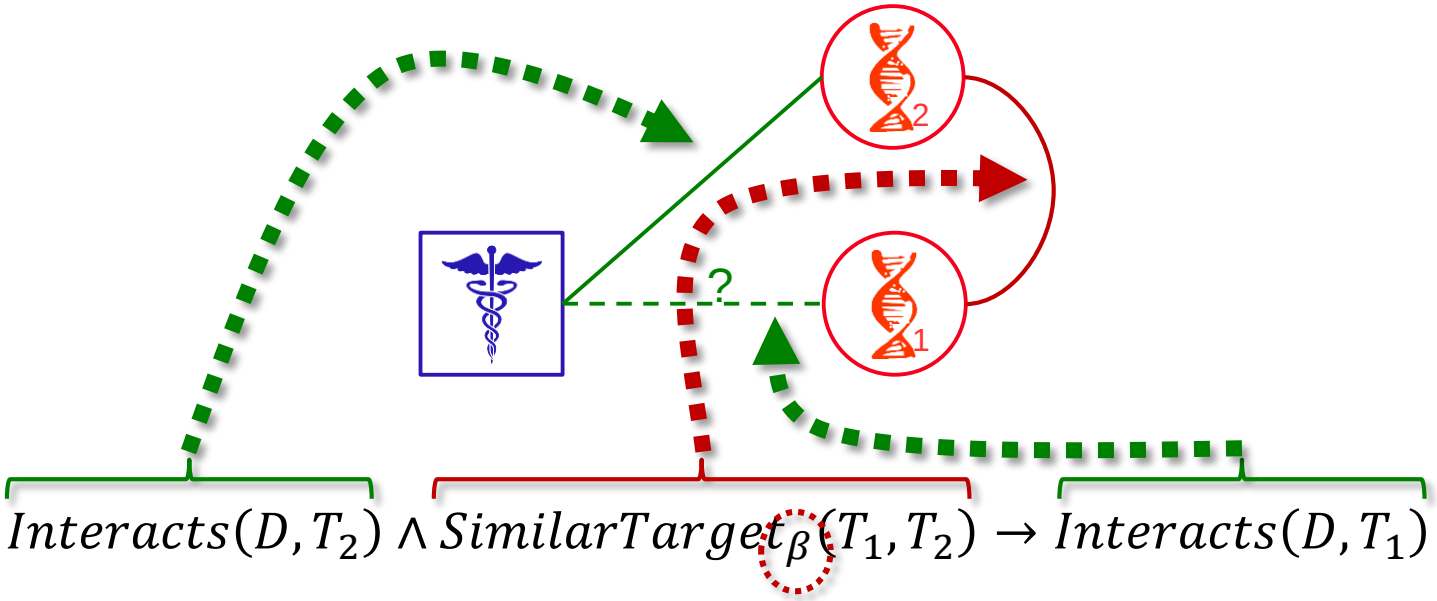
# Predicates

- $\mathrm{Interacts}(\mathrm{D}, \mathrm{T})$
- $\mathrm{SimilarTarget}_{\beta}(\mathrm{T}_1, \mathrm{T}_2)$
  - e.g. $\beta$ can be Sequence-based, PPI-network-based, Gene Ontology-based.
- $\mathrm{SimilarDrug}_{\alpha}(\mathrm{D}_1, \mathrm{D}_2)$
  - e.g. $\alpha$ can be Chemical-based, Ligand-based, Expression-based, Side-effect-based, Annotation-based.


# Drug-Target Interaction Prediction Rules

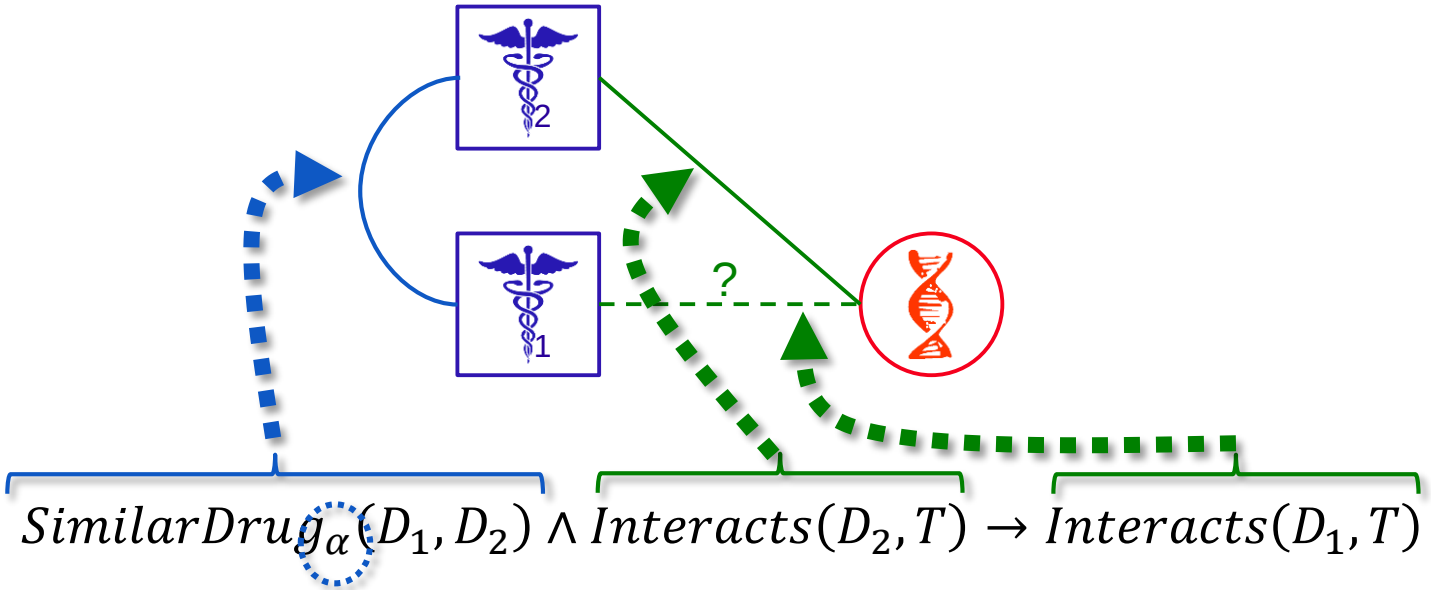
# Triad-based rules (Targets)

- Drugs tend to interact with similar targets
  (friend of friend is a friend)



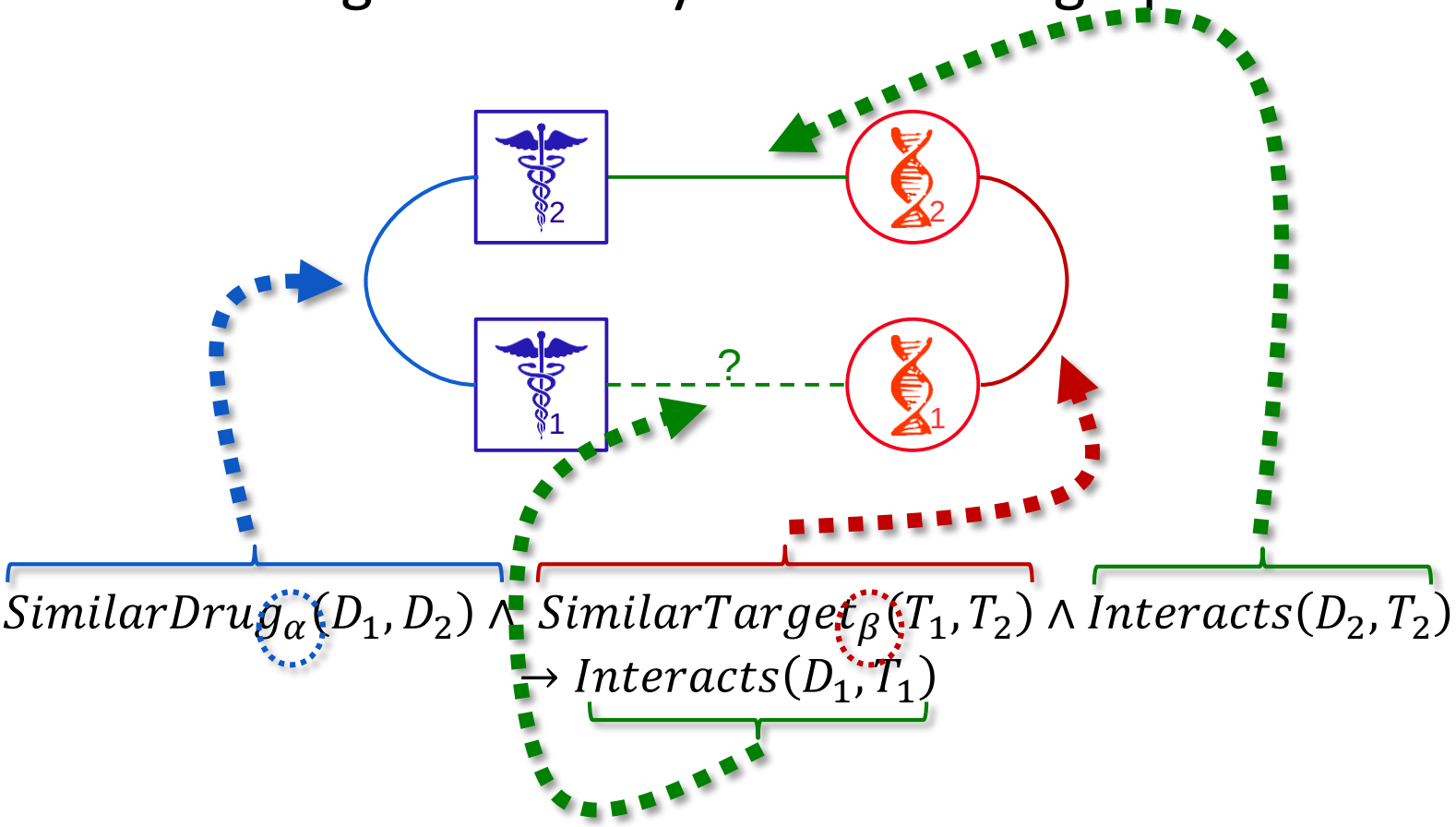
# Triad-based rules (Drugs)

- Targets tend to interact with similar drugs
  (friend of friend is a friend)



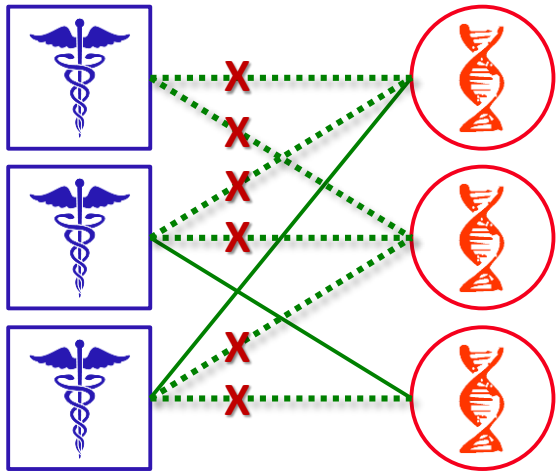
# Tetrad-based Rules (Similar Edges)

- Similar edges are likely to form in a graph



# Negative Prior

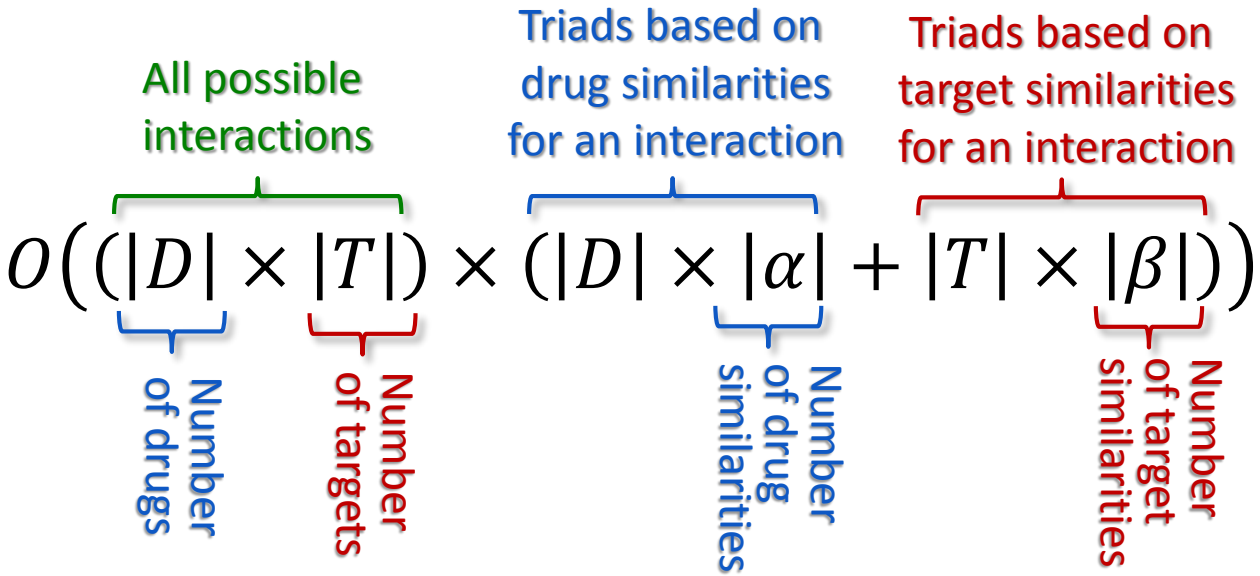
- Negative prior indicates “Interacts” predicate is most likely false
- i.e., most drugs and targets do not interact



$$\neg\, Interacts(D, T)$$

# Size of the problem

- Total ground triad-based rules can be:




- e.g., in our experiments it was **180M**
- For tetrad-based rules the situation is even worst!

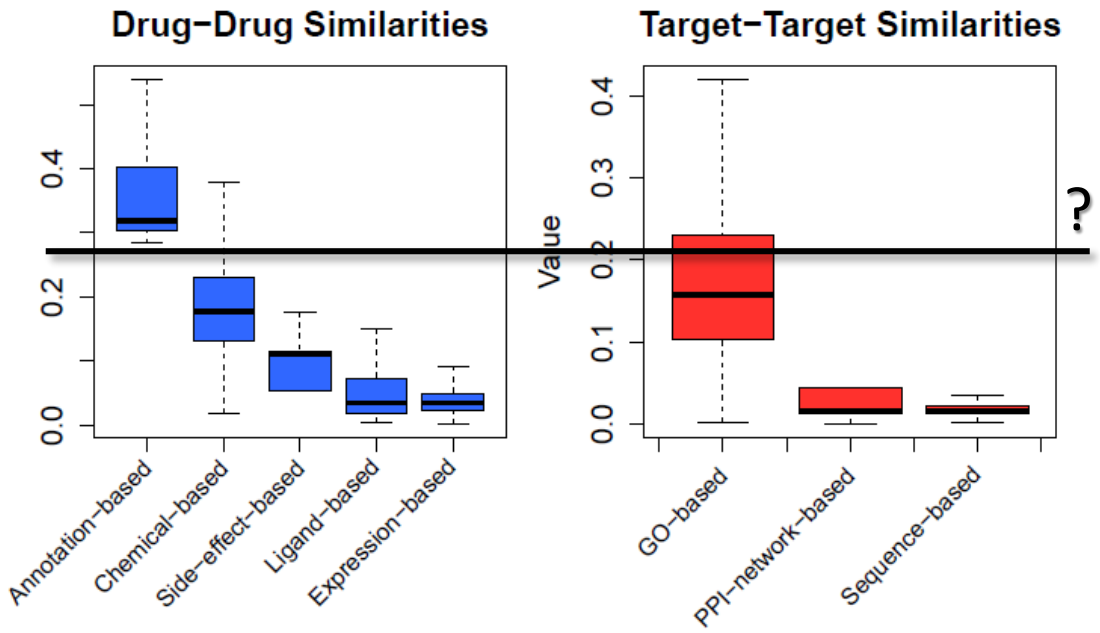

# Blocking

# Blocking

- Limit some of the rules from being grounded
- Ignore some of the less significant similarities between drugs and between targets.

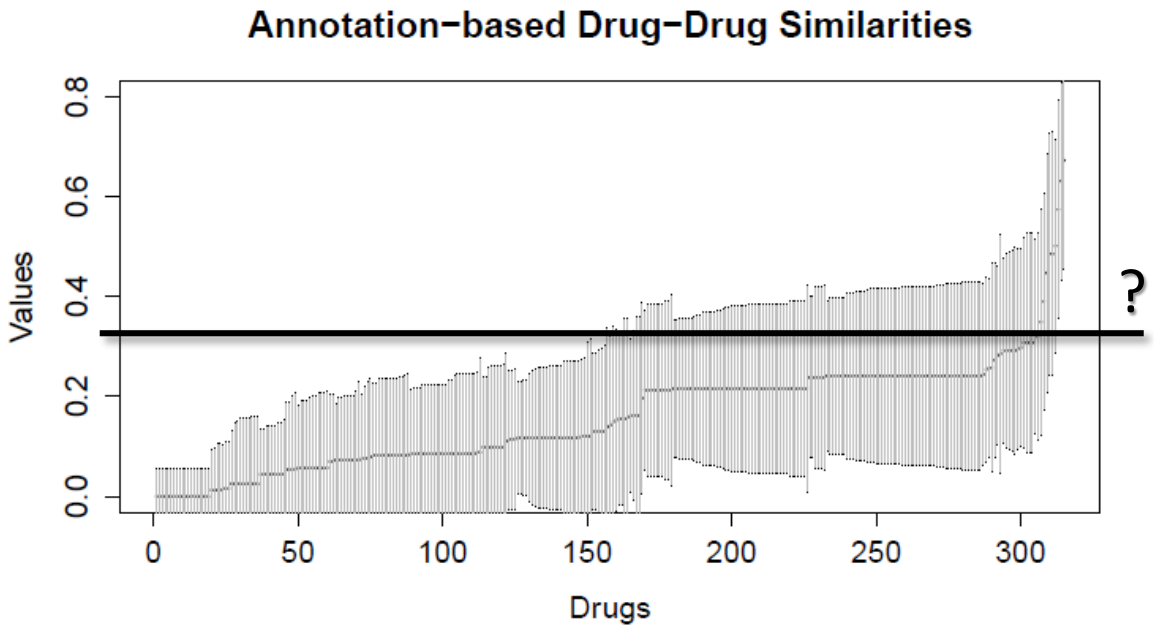
# Same Threshold for All Similarities

- Fixed threshold either ignores most of the values in one similarity or includes most of the values from the other



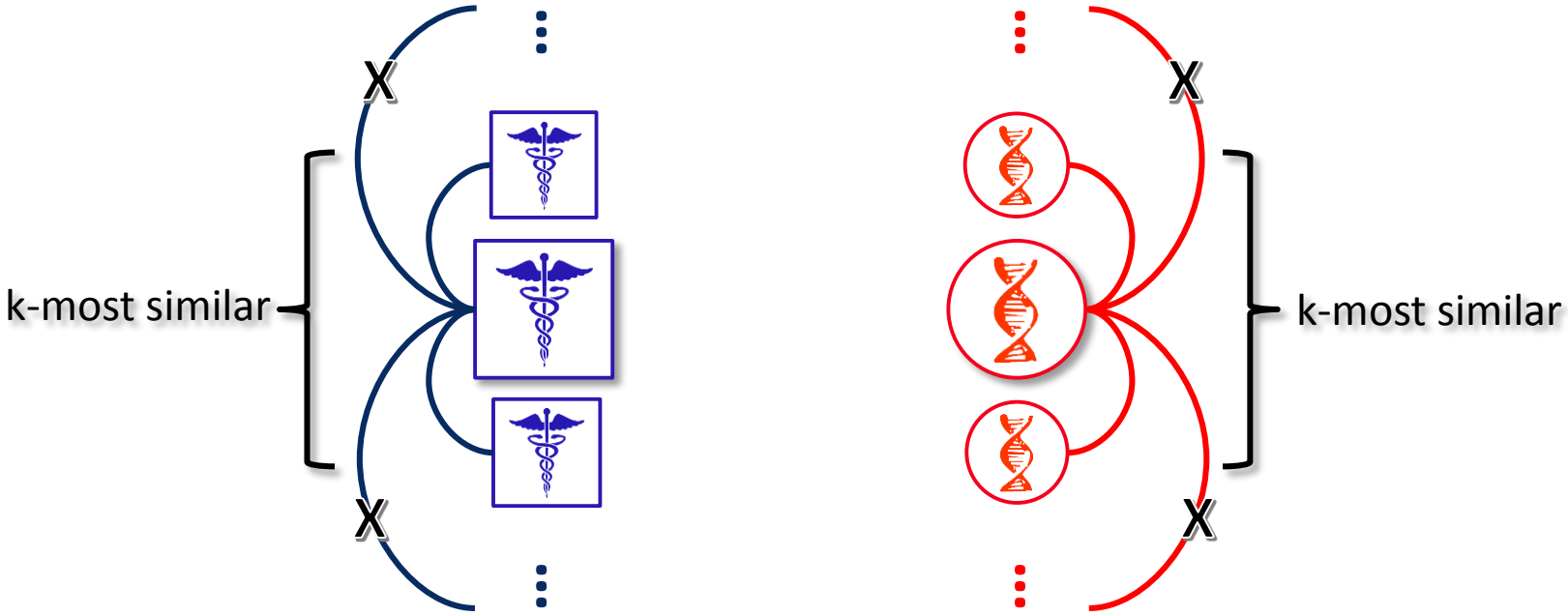
# A Threshold for Each Similarity

- Same problem for individual drug or target!



# K-Nearest Neighbors-based

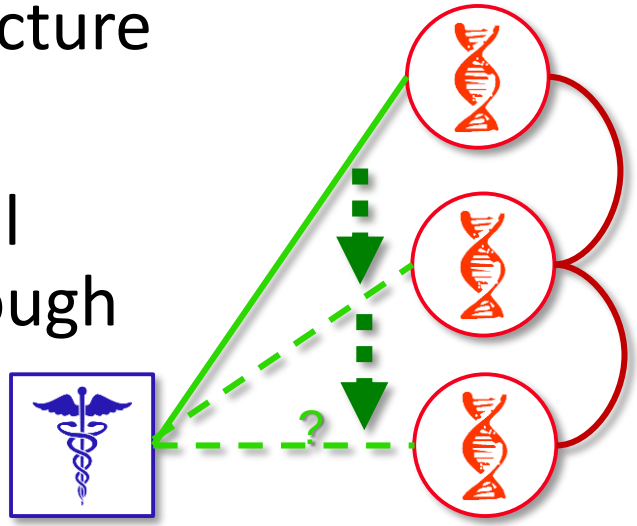
- Preserve the k-highest values in each similarity for each drug and each target and set the others to zero.



# PSL Advantages

# PSL Advantages

- PSL captures the original structure
- Collective Inference (No IID assumption): Results in global information propagation through the network.
- Inference based on Interpretable rules




- Class Imbalance: PSL can handle huge class-imbalance problems in link prediction problems.

# Experimental Evaluation

# Dataset

- 315 Drugs
- 250 Targets
- Interaction: [Knox et al. 2011]
  - 1,306 observed interactions
  - 78,750 possible interactions
- Similarities: [Perlman et al. 2011]
  - 3 target-target similarities
  - 5 drug-drug similarities

# Drug-Drug Similarities [Perlman et al. 2011]

- **Chemical-based:**
  - Jaccard similarity of the SMILES fingerprints
- **Ligand-based:**
  - Jaccard similarity between protein receptor families extracted via matched ligands with drugs SMILES
- **Expression-based:**
  - Spearman correlation of gene expression responses to drugs using Connectivity Map.
- **Side-effect-based:**
  - Jaccard similarity between drugs side-effects from SIDER
- **Annotation-based:**
  - Semantic Similarity of Drugs based on the World Health Organization ATC classification system

# Target-Target Similarities [Perlman et al. 2011]

- **Sequence-based:**
  - Smith-Waterman sequence alignment scores
- **Protein-protein interaction network-based:**
  - The distance in the protein-protein interactions network using all-pairs shortest path.
- **Gene ontology-based:**
  - Semantic similarity between Gene ontology annotations

# Triad Rules

| | Rule | AUROC |
|---|---|---|
| Drug-Drug Similarity | Annotation-based | 0.685 ± 0.026 |
| | Chemical-based | 0.714 ± 0.030 |
| | Ligand-based | **0.751 ± 0.030** |
| | Expression-based | 0.584 ± 0.025 |
| | Side-effect-based | 0.614 ± 0.030 |
| Target-Target Similarity | PPI-network-based | 0.816 ± 0.026 |
| | GO-based | 0.608 ± 0.029 |
| | Sequence-based | **0.842 ± 0.019** |
| **All rules (similarities)** | | **0.931 ± 0.018** |

# Triad Rules: Comparison with reported results

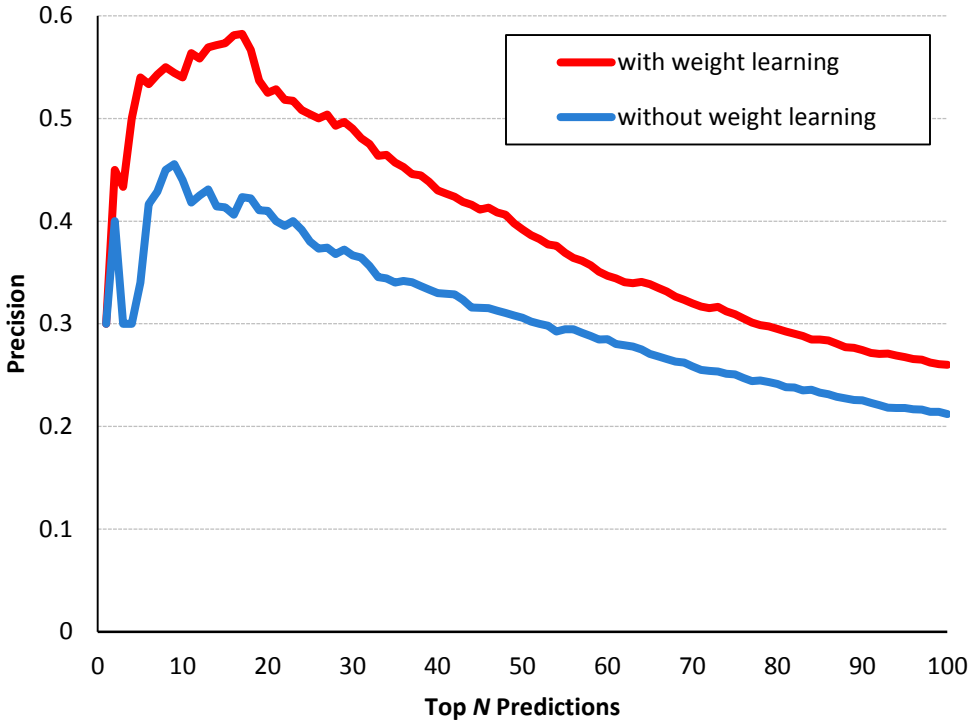
| Method | AUROC | Condition |
|---|---|---|
| PSL | 0.931 ± 0.018 | Without Sampling (10 Fold C.V.) |
| Perlman et al. 2011 | 0.935 | With Sampling (Reported Results) |
| Yamanishi et al. 2008 | 0.884 | |
| Bleakley et al. 2009 | 0.814 | |

# Triad Rules: Blocking and Weight Learning

| Condition | AUROC | | |
|---|---|---|---|
| | K=5 | K=15 | K=30 |
| All weights fixed | 0.926 ± 0.016 | 0.929 ± 0.020 | 0.923 ± 0.021 |
| + Weight learning | 0.930 ± 0.016 | **0.931 ± 0.018** | 0.924 ± 0.21 |

| Condition | Time to Complete (10-folds) | | |
|---|---|---|---|
| | K=5 | K=15 | K=30 |
| All weights fixed | 12 mins | 3 h | 9 h |
| + Weight learning | 1 h | 10 h | 28 h |

# Triad Rules:
# Precision of Top 100 Predictions



# Triad and Tetrad based rules

| Method | AUROC with k=5 |
|---|---|
| Triad-based Rules | 0.930 ± 0.016 |
| Tetrad-based Rules | 0.796 ± 0.025 |
| Triad-based & Tetrad-based | 0.913 ± 0.017 |

# Conclusion

- Identified challenges of network-based drug-target interaction prediction.
- Described PSL framework to address them:
  - Captures original network structure
  - Is a declarative language to implement different rules
  - Performs collective inference (No IID assumption)
  - Weight learning based on training data
- Matched performance of the state-of-the-art with simple triad-based rules.
- The proposed method can easily be applied to other tasks with similar structures.

# Thank you

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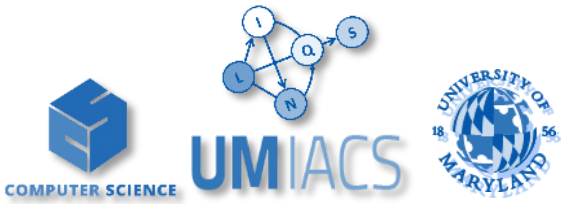

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