
Drug Repositioning:

New Uses for Old Drugs

LTI Research Speaking Requirement

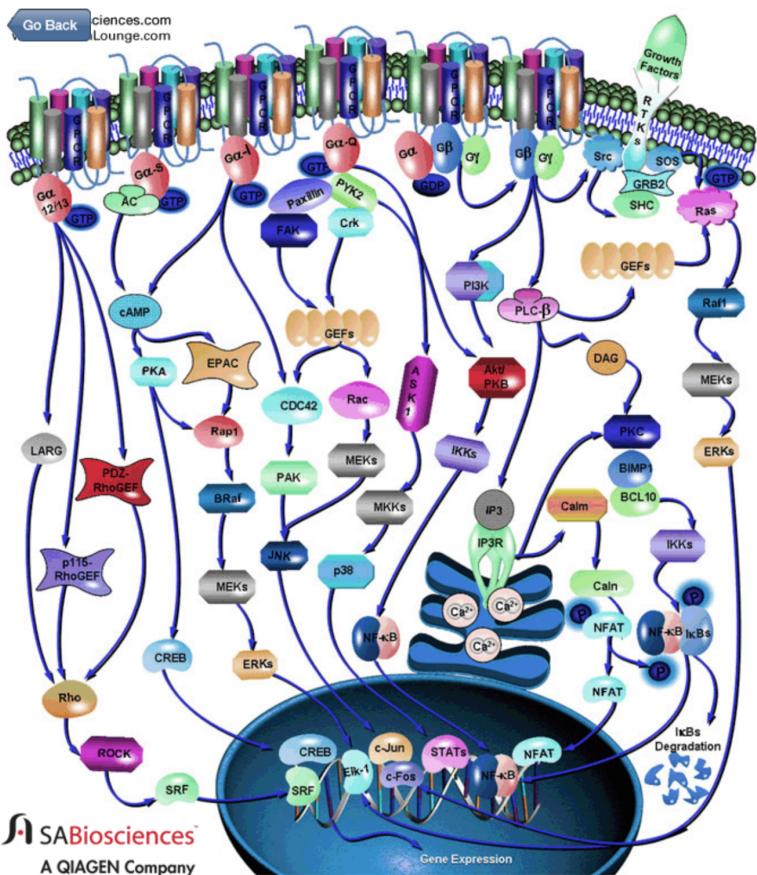
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6/30/2014

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- Introduction of drug repositioning
 - Network-based approach, ProphNet
 - Side effect information of drugs
 - QnA

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Drug and GPCR

GPCR Pathway

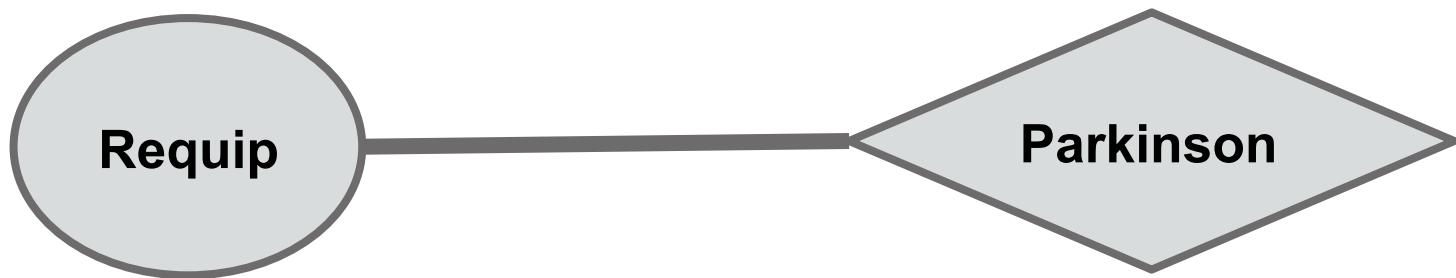


- Cell surface signalling proteins
- Control signaling pathways

➤ **Drug is designed to bind and activate GPCR to behave to cure disease**

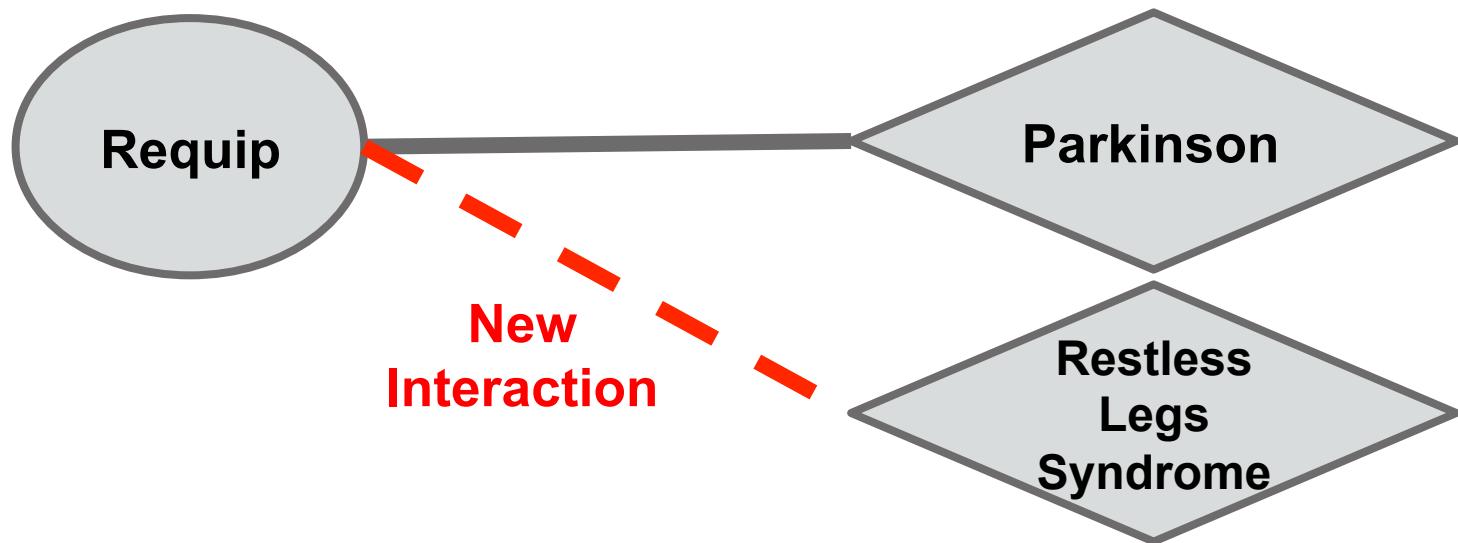
Introduction

- Traditional Drug Development
 - 10-15 years, \$1 billion, 90% of drug candidates fail
- Drug Repositioning?
 - Find new uses for existing, approved drugs



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Introduction

- Traditional Drug Development
 - 10-15 years, \$1 billion, 90% of drug candidates fail
- Drug Repositioning?
 - Find new uses for existing, approved drugs
- Not require new clinical trial
- Reduce Time, Money, and Risk of failure

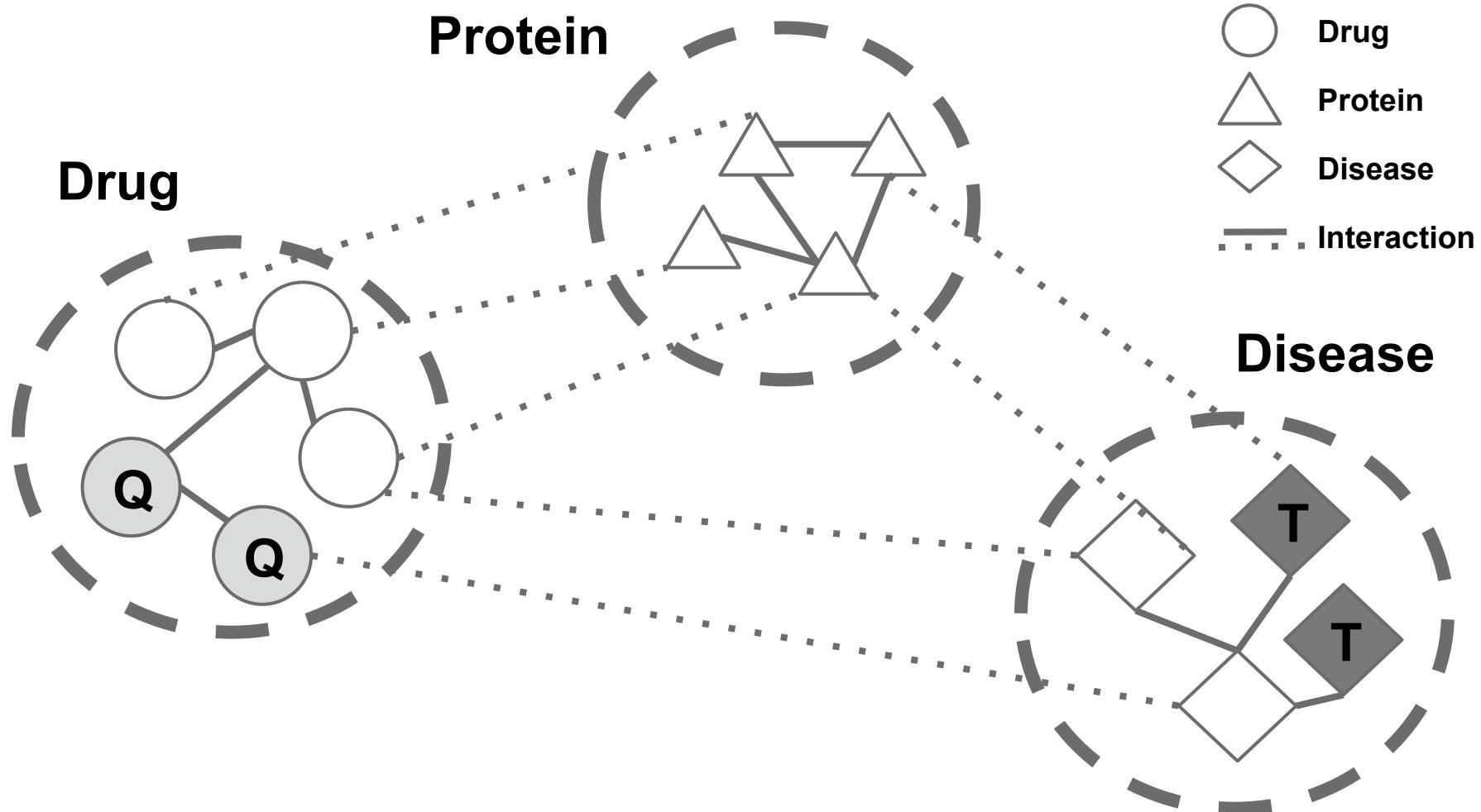
Background

- Availability of diverse biological data
 - Currently known drug-disease interaction
 - Chemical or molecular features of drug compound
 - Underlying processes of disease
- “*Guilt-by-association*” principle
 - Sharing interaction \Leftrightarrow same function, same biological process
- Challenge
 - Understand interconnection between diverse features and identify qualified one

Related Works

- Ligand-based approach
 - Ligand: molecule binds to protein
 - Chemical structure of drug compounds
 - Protein sequences
- Pharmacological approach
 - Infer whether two drugs share target disease
 - Observable effects of drugs
- Network based approach
 - Construct network and predict drug-target interaction
 - Based on known drug-target interactions

Network-based method

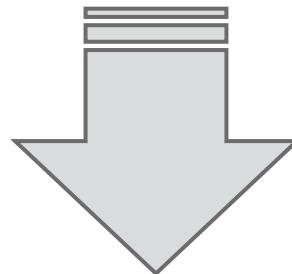


Approach

- Side effects of drugs
 - Network-based algorithm:
 - ProphNet (Martinez, et al. 2012)
 - Combine diverse biological data
- Goal: Applying Side-effect information into network-based model to discover new drug-disease interaction more accurately

Network-based method

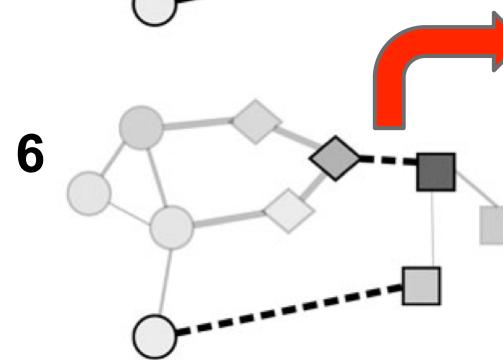
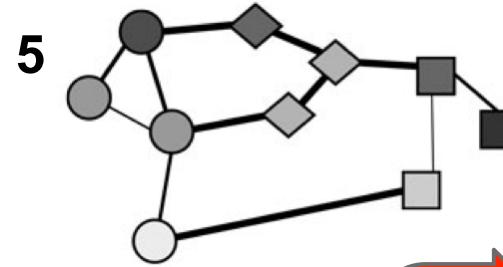
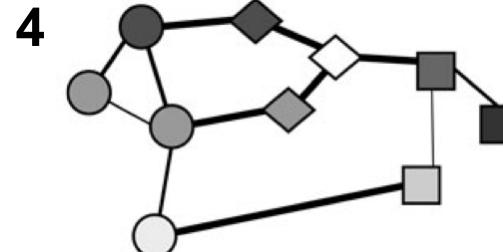
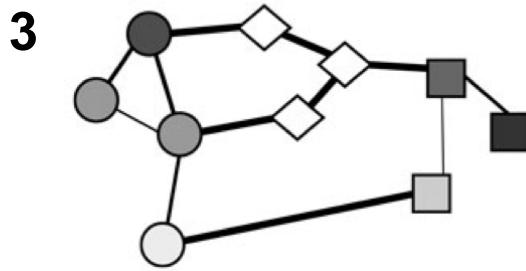
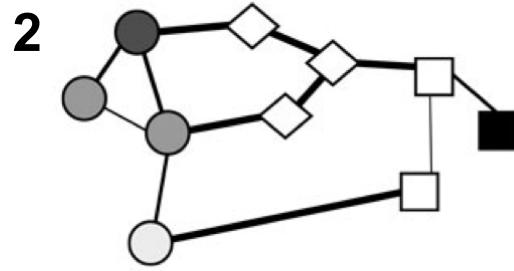
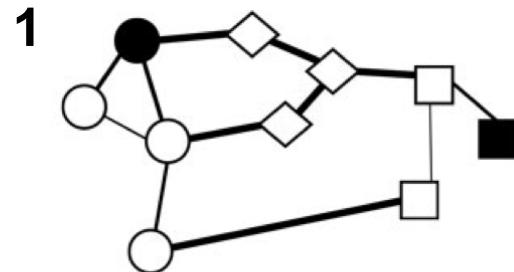
By propagating node value
through the path
from query/drug to target/disease,



obtain the prioritized target/disease list
suggesting degree of interaction with query/drug

Network-based method

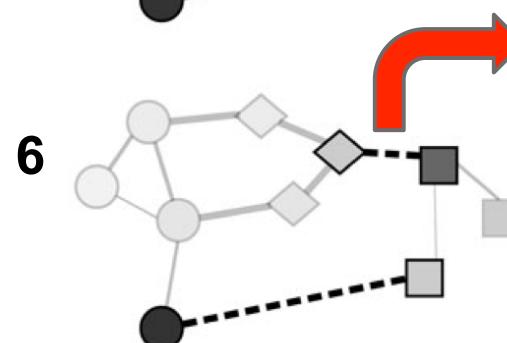
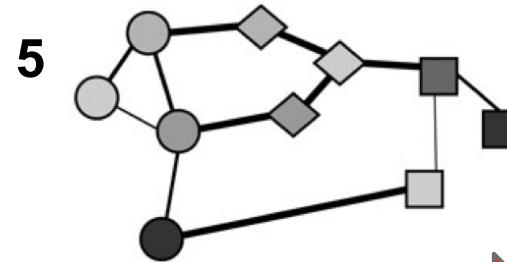
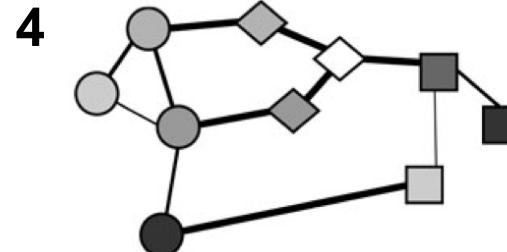
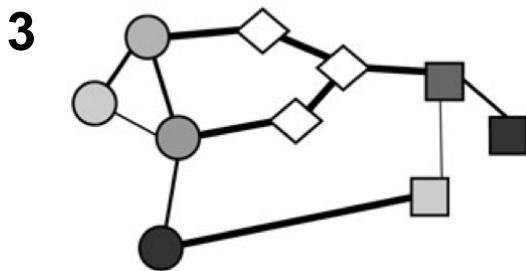
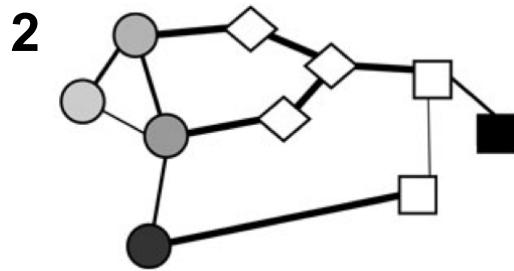
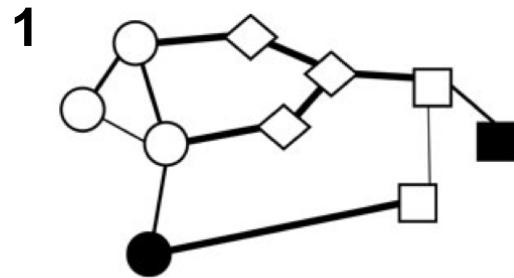
Example A.



Highly
Correlated

Network-based method

Example B.

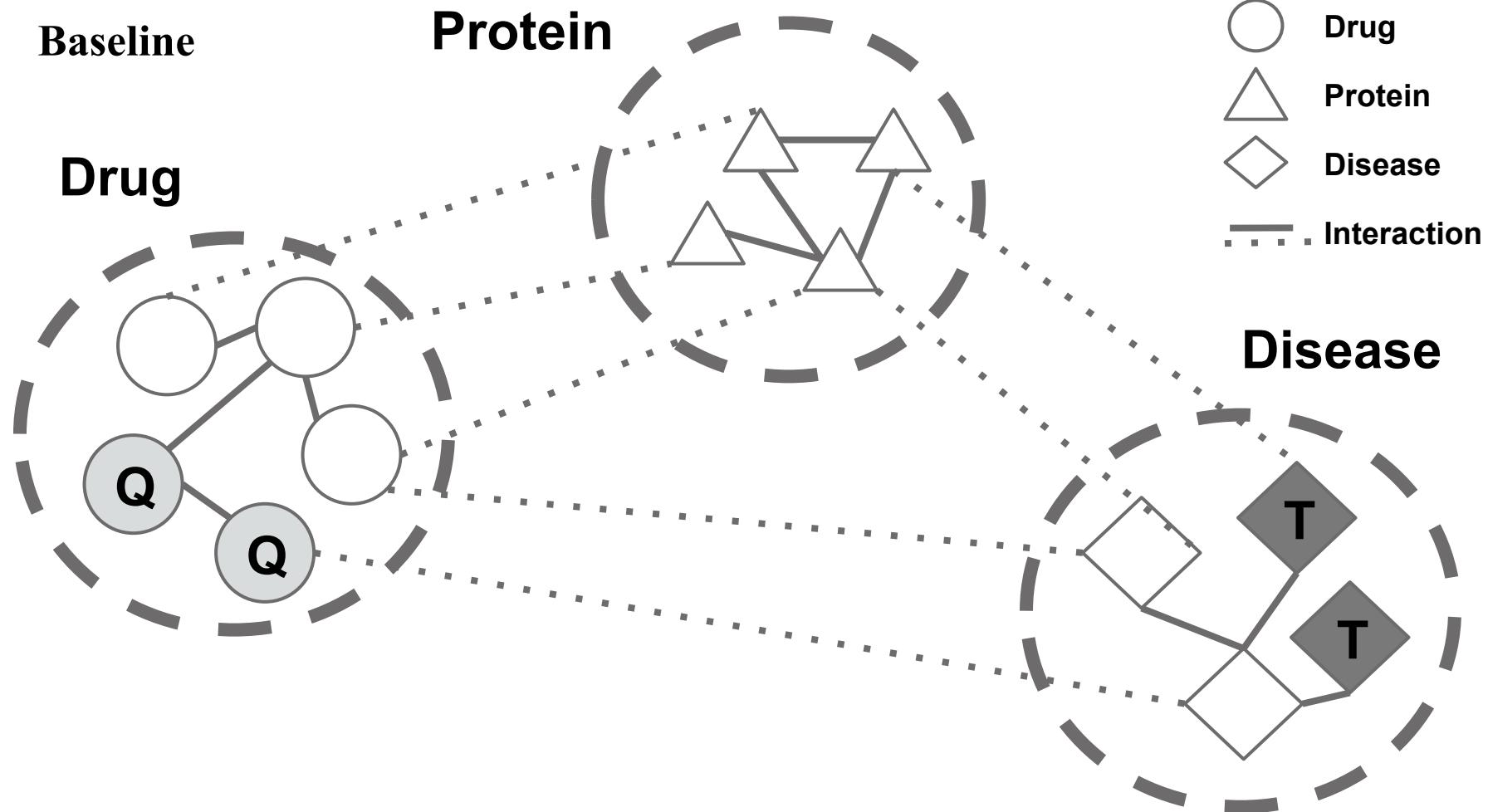


NOT
Correlated

-
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-

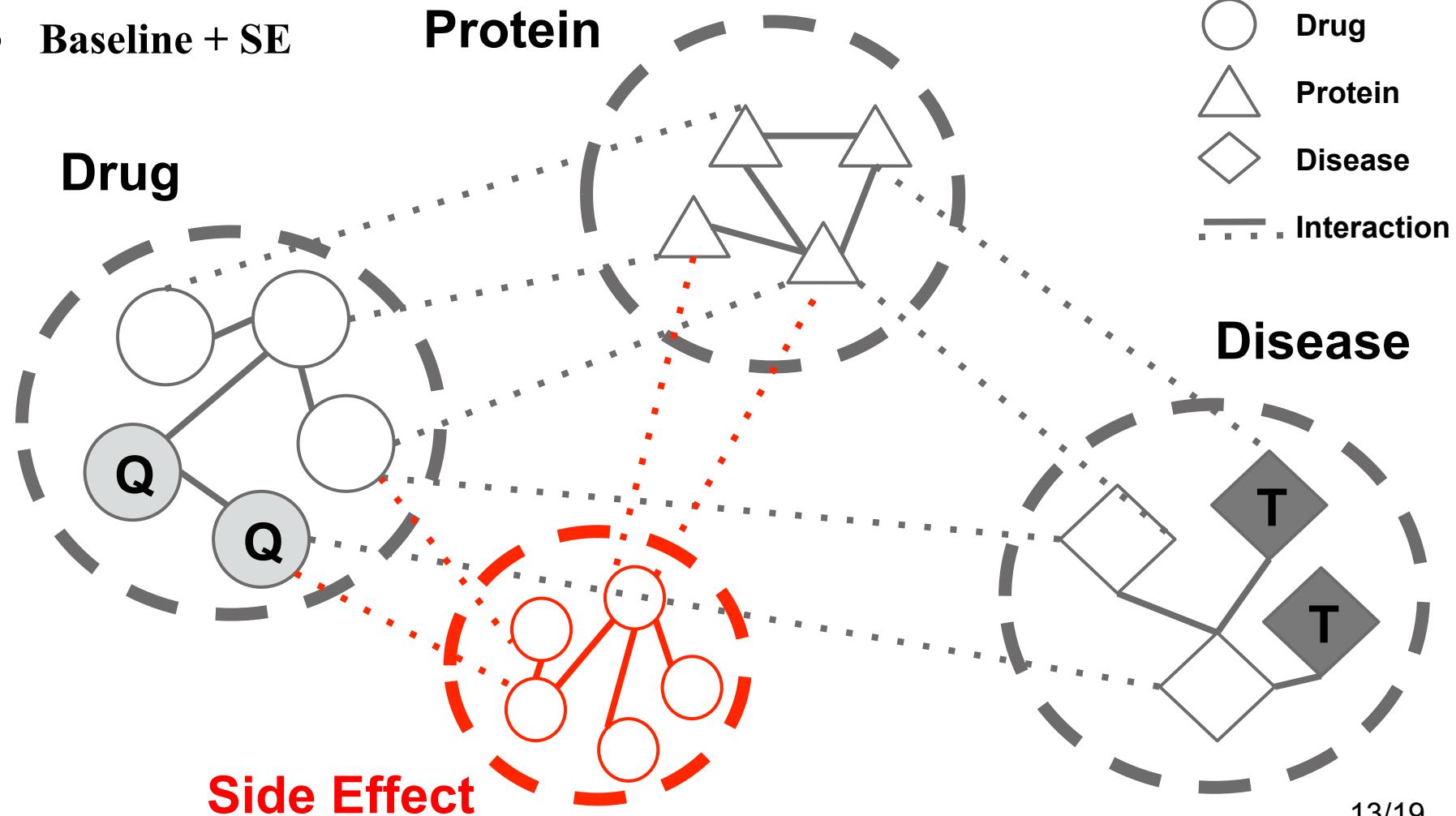
Side Effect of Drugs

- Baseline



Side Effect of Drugs

- Baseline + SE

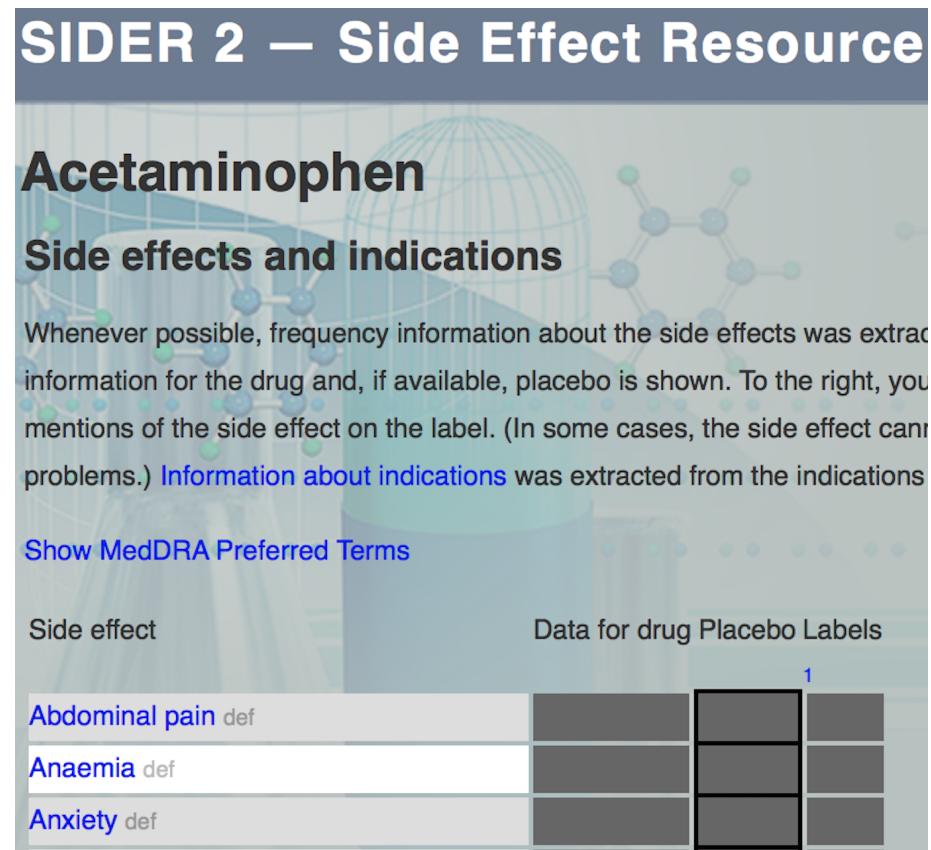


Side Effect of Drugs

- SIDER2
 - Marketed medicines and their side effects, frequency of side effects
 - Extracted from public medical documents, by text mining

# of Side Effect	4,192
# of Drugs	996

<http://sideeffects.embl.de>



Side Effect of Drugs

- Network → Drug-Drug adjacency matrix
- Node → Drug
- Edge value → **Side Effect (SE) Similarity between two drugs**

★ All SE are **NOT** equally informative

1. **Rareness** score → how SE appears rarely?

Ex) “dizziness” << “yellow skin”

1. **Correlation** score

Ex) “chest discomfort”, “chest pressure”, ... << “eye pain”

Dataset

- Disease-Disease (OMIM)
 - 5,080 x 5,080
- Protein Domain-Protein Domain (DOMINE)
 - 5,490 x 5,490
- Drug-Drug (DrugBank)
 - 1,109 x 1,109
- Protein-protein Interaction (HPRD)
 - 8,919 x 8,919
- Protein Domain-Drug (Pfam UniProt)
- Drug-Domain (DrugBank)
- Protein-Protein Domain (OMIM)

Evaluation

- 1,337 test cases (explicit drug-disease pairs)
- **Leave-one-out (LOO) test:**
 - Remove one known A-B interaction, using A as query, and measure where B is ranked
- Areas under the ROC curves (AUC),
 - TP/Positives vs. FP/Negatives at various thresholds
 - TP = Rank of case disease is below the threshold,
 - FP = Rank of case disease is **NOT** below the threshold

Results

	Baseline	Baseline + SE
AUC	0.956	0.965
Mean Ranking (5,080)	222.53	177.66
STDEV	566	514

- SE improves AUC to predict new interaction
- Predicted disease was ranked 177 out of 5,080 on average

Discussion

- ★ Incorporating **Side Effect** information of drugs can help to predict **new drug-disease** interaction **more accurately**.
- ★ **Adverse reaction** of marketed drugs, can help to uncover the **new uses** for known drugs.

Thank You!



QnA

Appendix

★ Rareness score

$$r_i = -\log_{10} \frac{|I|}{|N|}$$

★ SE similarity score

$$\sum_{i \in D \cap E} (r_i)(c_i)$$

★ Pairwise Correlation

- ★ Individual Correlation score
 - Hierarchical Clustering

$$\text{Corr}(i, j) = \frac{|I \cap J|}{|I \cup J|}$$

A	B	C
20	20	50
30		
Ca=35	Cb=35	Cc=50