★°·。Drug Repurposing。·°☆
with Network-Based Analysis

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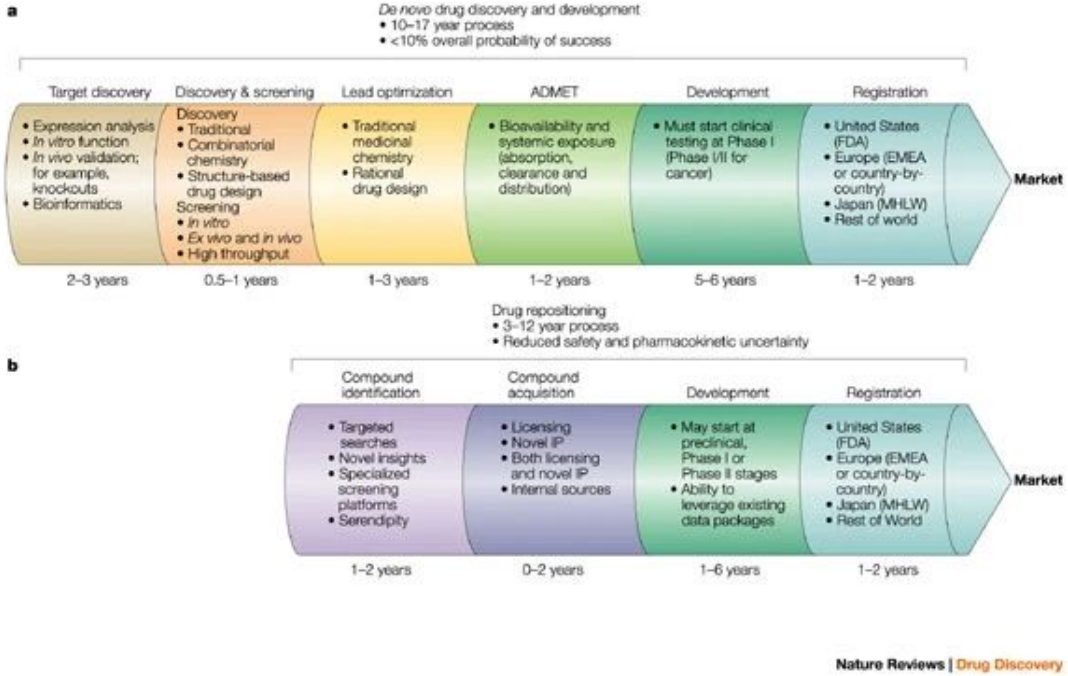
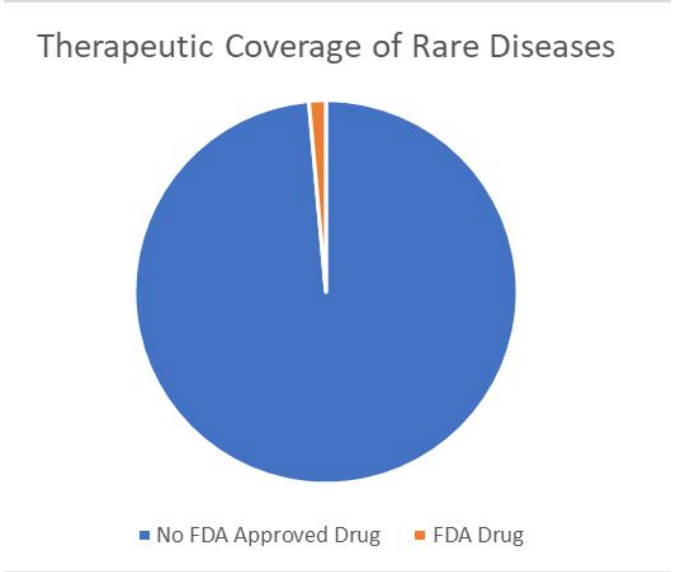
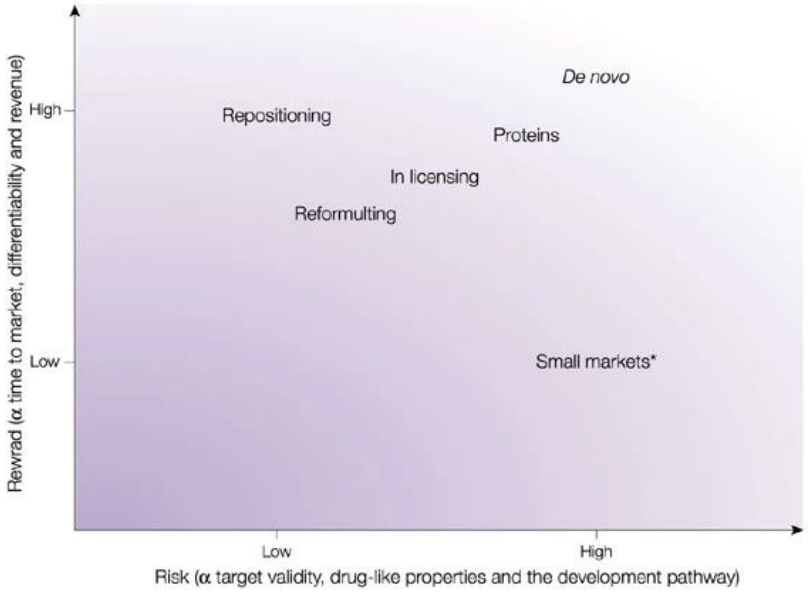
Why Pursue Drug Repurposing?





Why Pursue Drug Repurposing?

- Contribute to the pool of therapeutics for rare diseases / orphan drugs
- May offer commercial benefits in the form of alternative uses for existing therapeutics
- Informs novel off-label prescriptions for clinicians
- Provides mechanistic and chemical insights for basic researchers



Nature Reviews | Drug Discovery

Existing Methods and Examples

Methodologies

- Data Mining / Semantic Associations
- Machine Learning
- Network-Based Methods

Drugs

- Aspirin
- Thalidomide
- Sildenafil
- Dimethyl fumarate

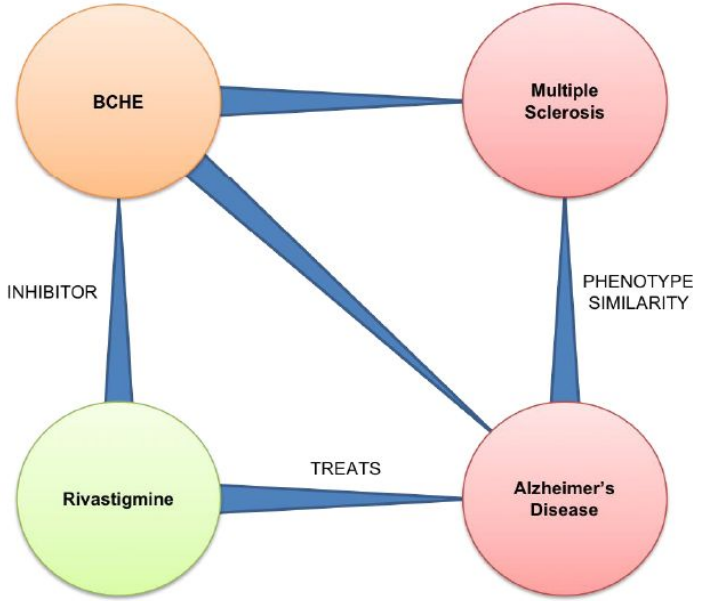


Figure 2: The potential relationship between Rivastigmine and MS is only revealed through connected data sources

Challenges in Drug Repurposing

Scientific Issues

- Identifying significant associations
- Scale of comparisons
- Validation of computational insight

Real-World Issues

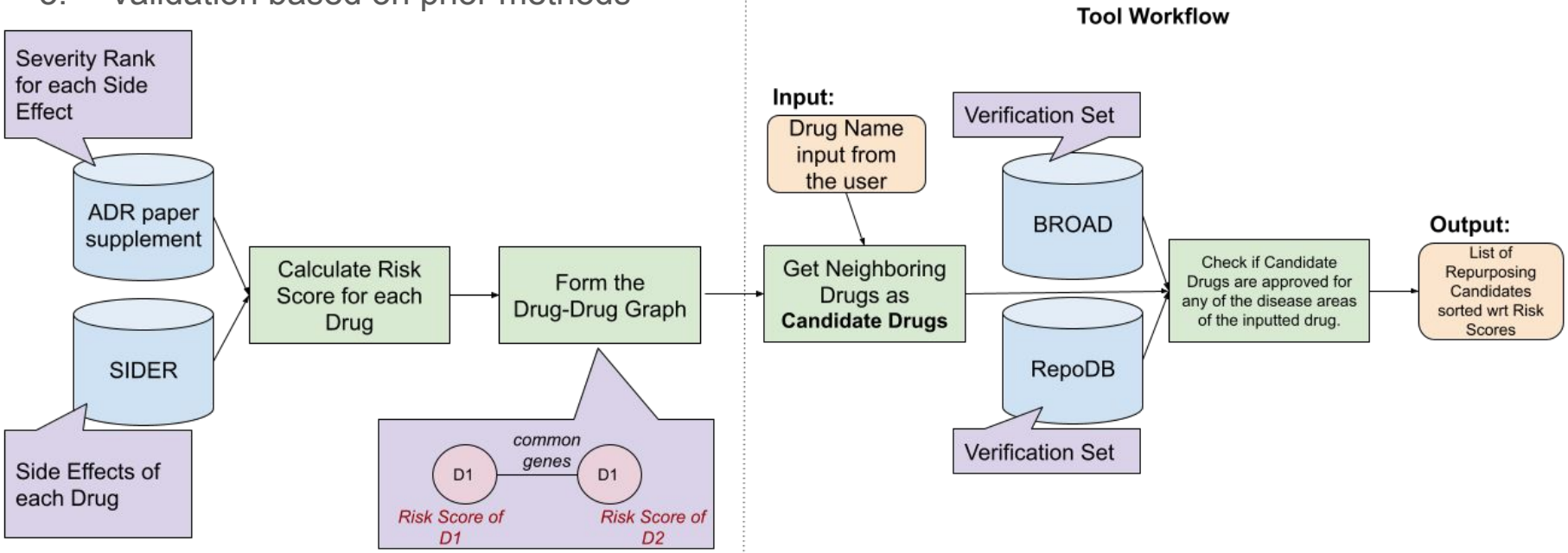
- Due diligence on validation
- Intellectual property issues / Organizational issues

Hypothesis

Given multiple compounds which target the same gene-product/protein, those which have the lowest relative user risk (as calculated on the basis of the number, frequency, and severity of compound side-effects) would make them better candidates than others connected to the same genes for repositioning.

Initial Approach

1. Creation of a unified drug to drug network which considered relative risk
2. Ranking of drugs based on relative risk
3. Validation based on prior methods



Calculating Relative Risk

For any given drug …

Risk = Relative Severity * Frequency

For any given drug pair, linked by a gene …

Relative Risk = Risk * Overlap Score

For any two connected drugs …

Overlap Score $= \dfrac{\binom{k}{x}\binom{N-k}{n-x}}{\binom{N}{n}}$

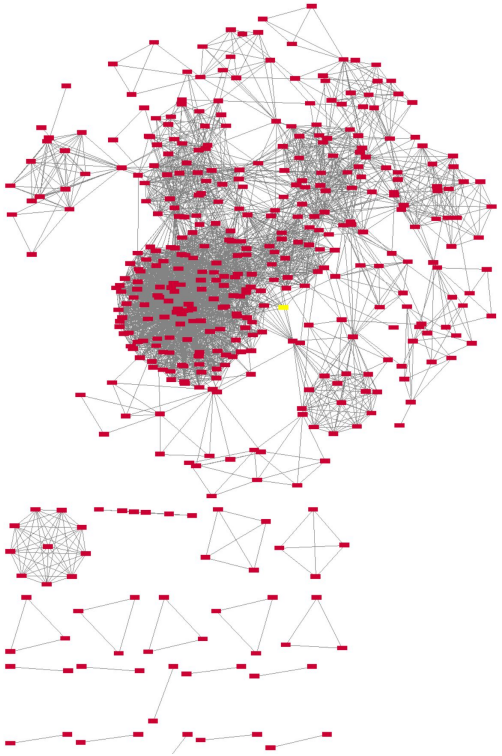
k = Drug B's target genes

x = the total overlapping genes

n = Drug A's target genes

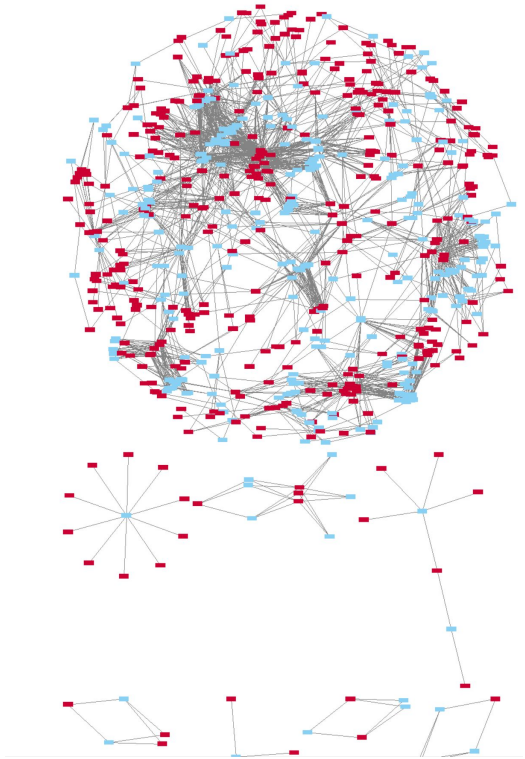
N = estimate of total human genes (23271)

Drug-to-Drug by Risk (DDR) Network



Drug Node

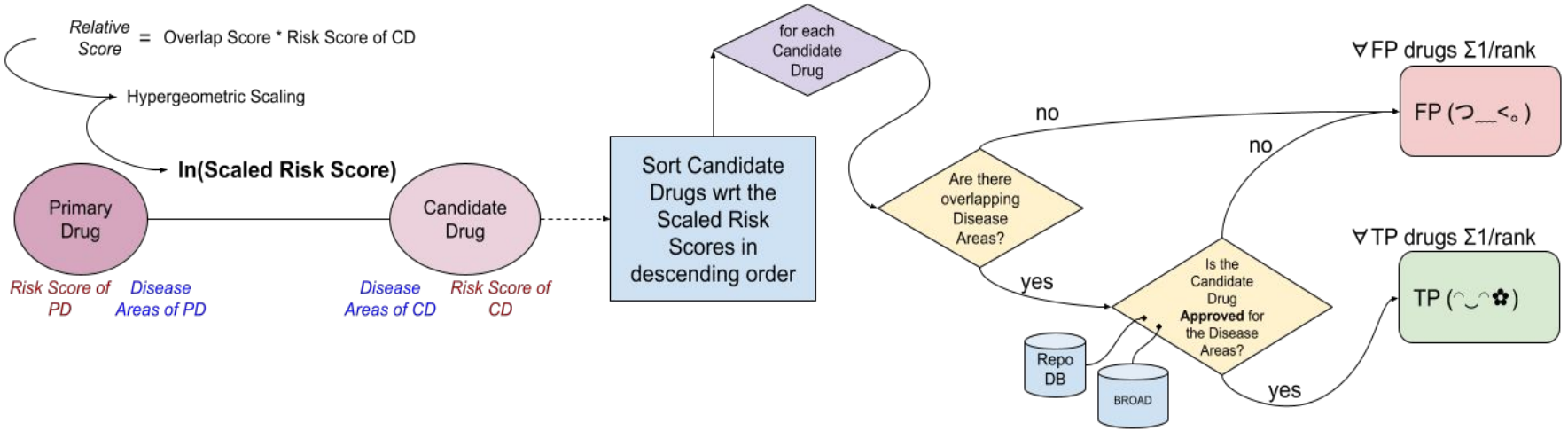
Gene Node



Drug-to-Drug Network (438 nodes, 18742 edges)

Drug-to-Gene Network (767 nodes, 18742 edges)

Finalized Approach and Validation Methodology



Sample Output

```
PS C:\Users\Admin\OneDrive\Masaüstü\SYSBIO\p\459-drug-proj> python .\calc_relative_risks_drugs.py -i amlodipine

*★*----*★**★*----*★**★*----*★* 𝕽𝖆𝖓𝖐𝖎𝖓𝖌𝖘 𝖋𝖔𝖗 amlodipine *★*----*★**★*----*★**★*----*★*

Rank 1: ibutilide with relative risk of -12.144 of amlodipine | Validation: TP (◠‿◠✿), can be repurposed for diseases: cardiology
Rank 2: lercanidipine with relative risk of -12.720 of amlodipine | Validation: TP (◠‿◠✿), can be repurposed for diseases: Hypertensive disease,cardiology
Rank 3: pinaverium with relative risk of -14.226 of amlodipine | Validation: FP (つ﹏<。)
Rank 4: diltiazem with relative risk of -26.879 of amlodipine | Validation: TP (◠‿◠✿), can be repurposed for diseases: Angina Pectoris, Variant,Hypertensive disea
se,Angina Pectoris,cardiology
Rank 5: isradipine with relative risk of -29.795 of amlodipine | Validation: TP (◠‿◠✿), can be repurposed for diseases: Hypertensive disease,cardiology
Rank 6: verapamil with relative risk of -30.398 of amlodipine | Validation: TP (◠‿◠✿), can be repurposed for diseases: Hypertensive disease,Angina Pectoris, Varia
nt,Angina Pectoris,cardiology
Rank 7: dronedarone with relative risk of -30.472 of amlodipine | Validation: TP (◠‿◠✿), can be repurposed for diseases: cardiology
Rank 8: gabapentin with relative risk of -36.233 of amlodipine | Validation: FP (つ﹏<。)
Rank 9: nisoldipine with relative risk of -37.749 of amlodipine | Validation: TP (◠‿◠✿), can be repurposed for diseases: Hypertensive disease,cardiology
Rank 10: nifedipine with relative risk of -40.344 of amlodipine | Validation: TP (◠‿◠✿), can be repurposed for diseases: Angina Pectoris, Variant,Hypertensive dis
ease,Angina Pectoris,cardiology

𝕻𝖗𝖊𝖈𝖎𝖘𝖎𝖔𝖓:･ﾟ✧          0.844

*★*----*★**★*----*★**★*----*★**★*----*★**★*----*★**★*----*★**★*----*★**★*----*★**★*----*★**★*----*★**★*----*★**★*----*★**★*----*★**★*----*★**★*----*★**★*----*★*
```

Validation Results

Mean Precision = **0.488**

STD of Precision = **0.349**

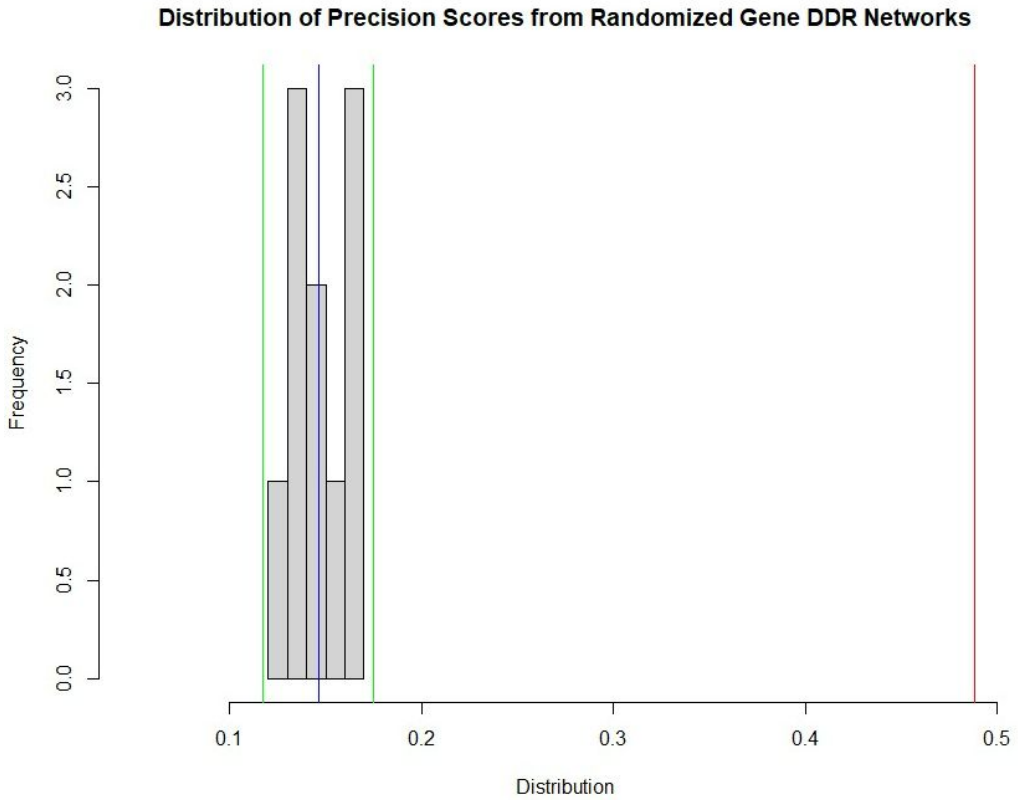
From 425 drug inputs

Validation → Permutation test of n = 10

DDR reconstructed from individual drugs with shuffled gene target sets

Characteristics of Random Set:

- Range: 0.122 to .1677
- Mean: 0.1462



Red = Calc. Precision **>** Mean(Random) + 2 SDs

Discussion and Limitations

- The severity of the risk scores in the RADR are scaled with respect to the side effects present in the list. **->** Limited side effects to consider.

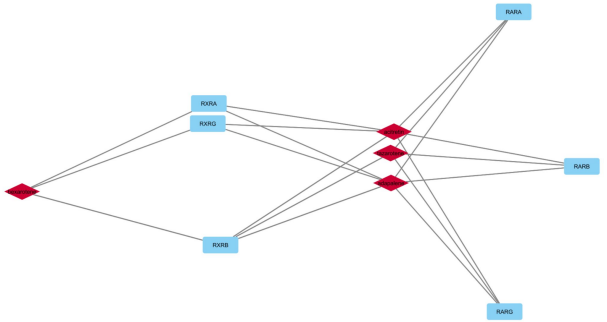
- Our tool does not generate negative predictions **->** Prevents us from doing a specificity-based evaluation.

Future Direction?

- Further validation and alternative strategies for building randomized networks

$$D_R -- G^* -- D_R$$

$$D_{R^*} -- G -- D_{R^*} ?$$



- Exploring known relationships shown in DDR

- Clustering and alternative relative risk metrics

$$RR = O^*R^* ?$$

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