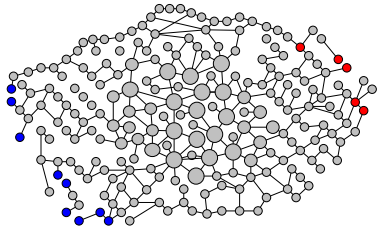
1- Human interactome network construction

Disease-genes (SEEDS)
DisGeNET and OMIM repositories

Protein-Protein Interactions (PPIs)
APID and HURI databases

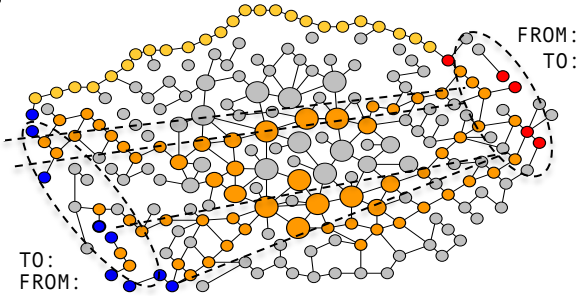


Node degree (number of edges)

2- Specific-Betweenness Count (BC)

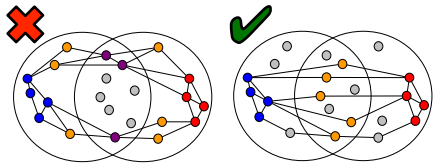
Specific Betweenness: Times a node is involved in shortest path* linking Disease A to B

* Shortest paths shorter than network mean distance



Node with high specific BC
Node with high specific BC in long shortest path (discarded)

Genes associated to both diseases are discarded to force S2B to find the disease modules' overlap



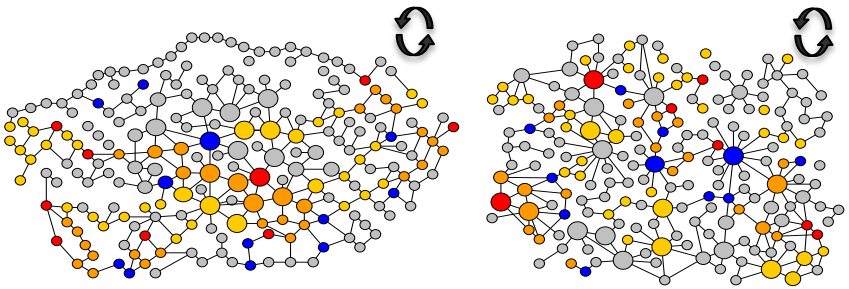
SEED of Disease A
SEED of Disease B
SEED of Disease A and B
S2B Candidates

3- Specificity scores: Specific-Specific Betweenness

Specificity scores: times the real BC is higher than in random networks

Random network A:
Shuffle SEEDS IDENTITY maintaining network's structure **100x**

Random network B:
Shuffle EDGES maintaining nodes' degree **100x**



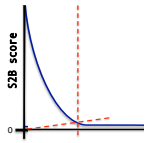
Specific nodes (high scores)
Unspecific nodes (low scores)

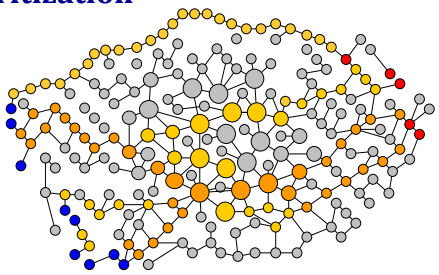
4- S2B candidates prioritization

S2B score: Specific BC is normalized dividing it by the number of shortest path linking SEEDs in the network

S2B candidates have to overcome:

- **Specificity Score A** and **B** ≥ 0.90
- **S2B threshold:** point at which ranked S2B score increase rate shifts upwards





S2B candidates
Discarded nodes