Network-based gene-disease prioritization using ProphNet

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Prioritization

Prioritization aims to identify the most promising biological entities among a larger pool of candidates through integrative computational analysis of genomic data. These methods are based on guilt-by-association hypothesis.

Guilt-by-association hypothesis

Biological entities showing a similar behaviour or sharing interactions/relations are more likely to belong to the same biological process, to be functionally related or to share molecular basis.

Prioritization strategies

Several prioritization strategies have been proposed:

- **Filtering**
- **Text-mining**
- **Profiling**
- **Network-based**

Network-based methods

Advantages

- Better average performance than other approaches under similar conditions.
- Biological information is usually easy to representate as networks.

Disadvantages

- Difficulties integrating an arbitrary number of data sources since network-based methods usually are limited to 2 networks.
- Very specific methods that do not allow to perform different types of queries.

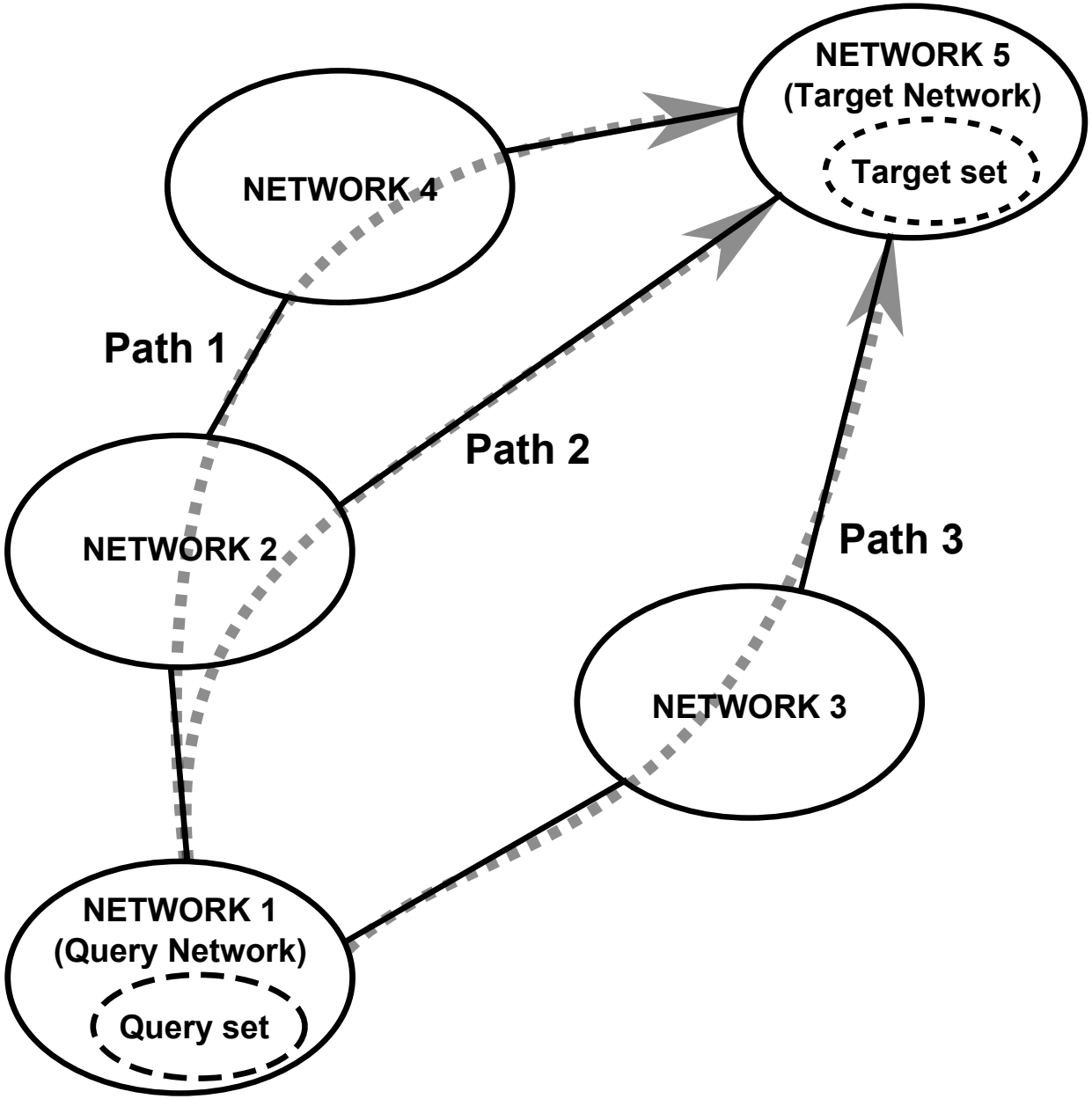
ProphNet

- **ProphNet** is a **network-based** prioritization method.
- Allows **integration** of an **arbitrary** number of networks.
- **Outperforms** recently proposed methods.
- **Flexibility in queries** allowing any prioritization task (e.g., genes-diseases or protein domains-genes).

Data representation

- **Data of a particular type** is represented by a **network**.
- **Nodes** represent **biological entities** (e.g., genes or diseases).
- **Arcs** represent **interactions or relations**.
- Networks are interconnected by other networks (e.g., gene-disease or domain-gene network) forming the **Global Graph**.

Definitions

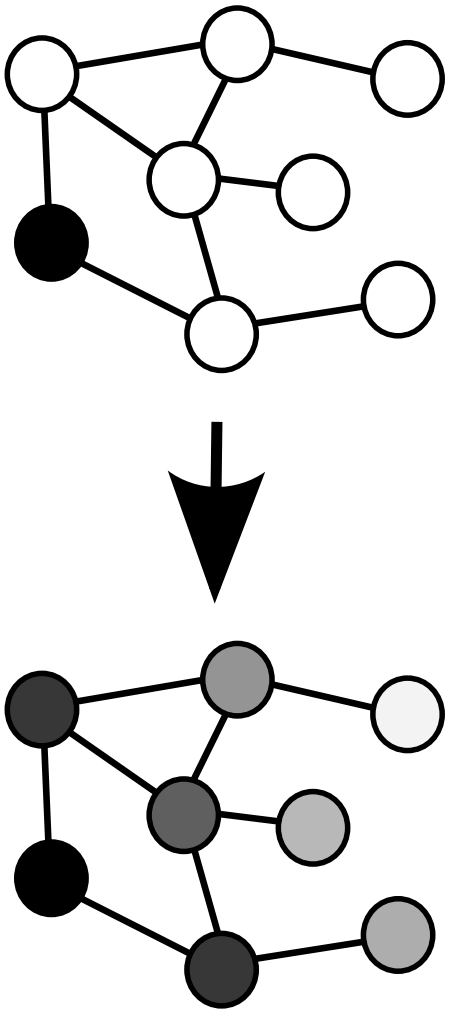


More details about data representation

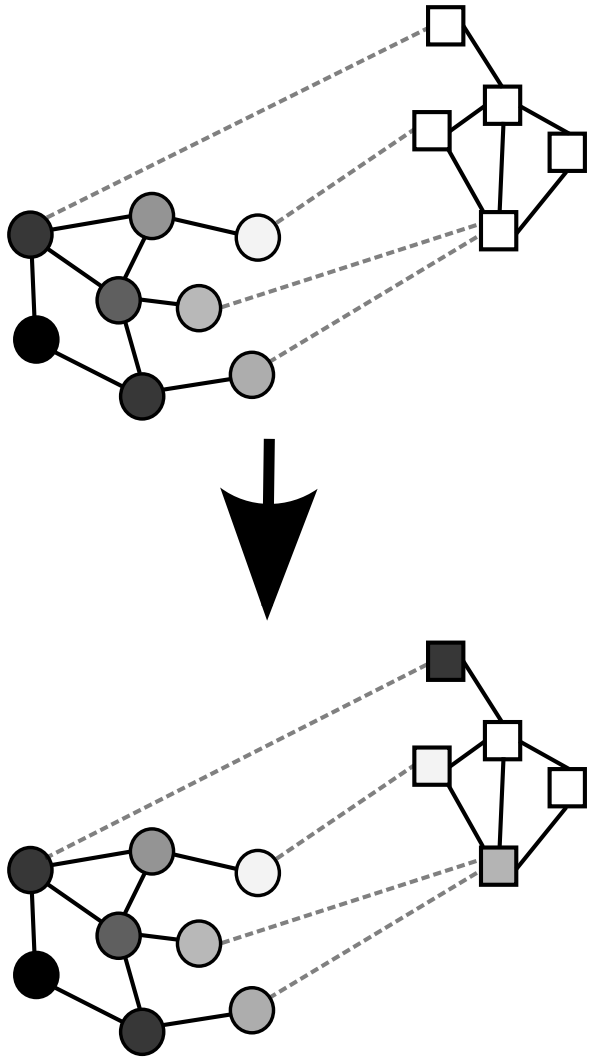
- Nodes have **variable values** which will be updated based on the **degree of relation** with the query or target sets.
- Query and Target set nodes are initially assigned with a value. The rest are assigned to zero.
- Arcs have **constant weights** representing the **strength** of the interaction or the relation.
- Networks are represented as **adjacency matrices**.
- A **normalization step** is performed in order to decrease the influence of each **node degree**.

Propagation operations

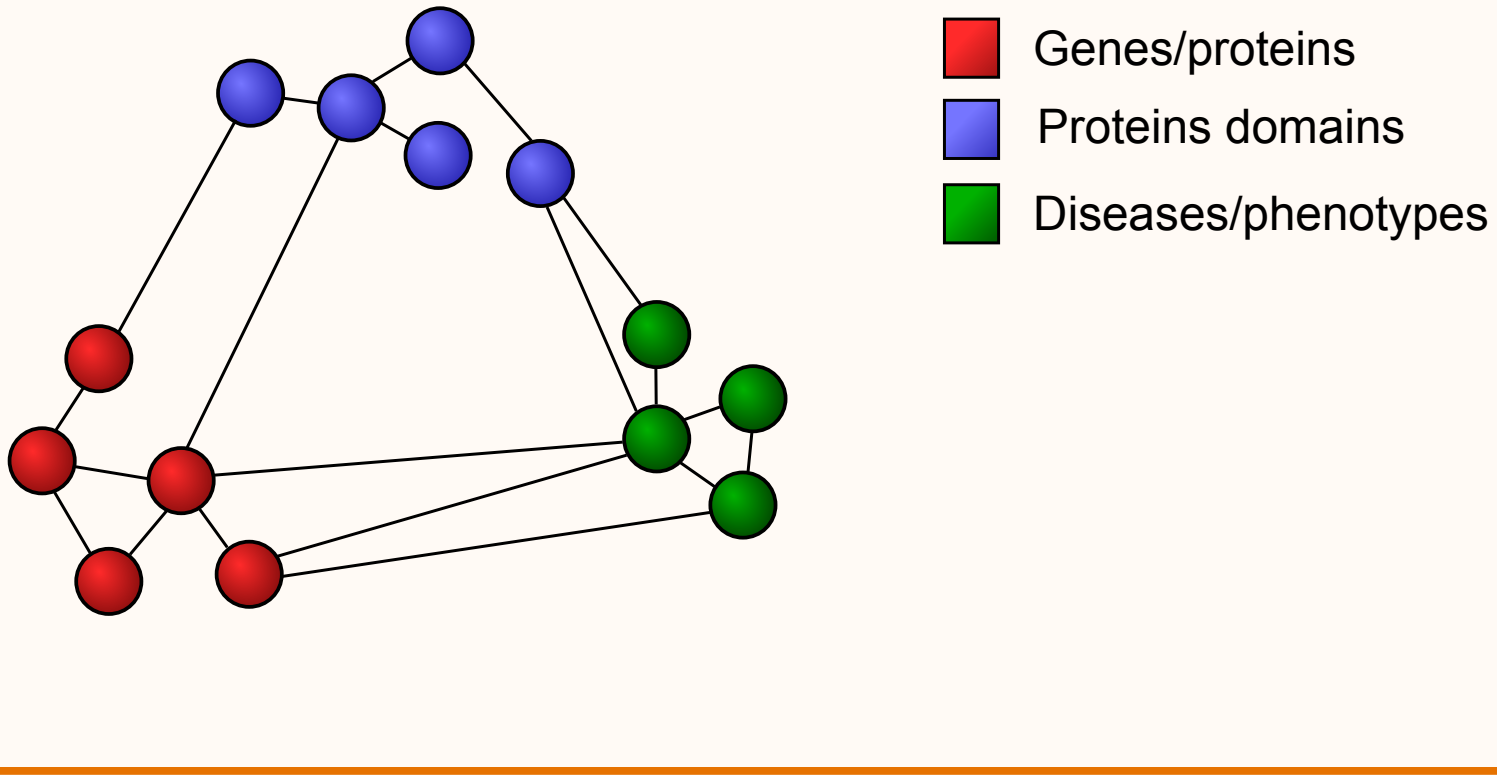
Propagation inside network



Propagation to the next network



Used Global graph



Algorithm

ProphNet algorithm pseudocode

1: Query set values are propagated inside Query Network.
2: paths $\leftarrow$ Compute all paths from Query to Target Net.
3: **for each** node e **in** Target Network **do**
4: Set node e as Target Set and propagate values inside Target Network
5: **for each** path **in** paths **do**
6: **for each** step **in** path **do**
7: Propagate from current network to next network
8: Propagate inside next network
9: **end for**
10: **end for**
11: $S_e \leftarrow$ Correlate paths with Target Network values
12: **end for**
13: Sort S_x decrementally to obtain prioritized list

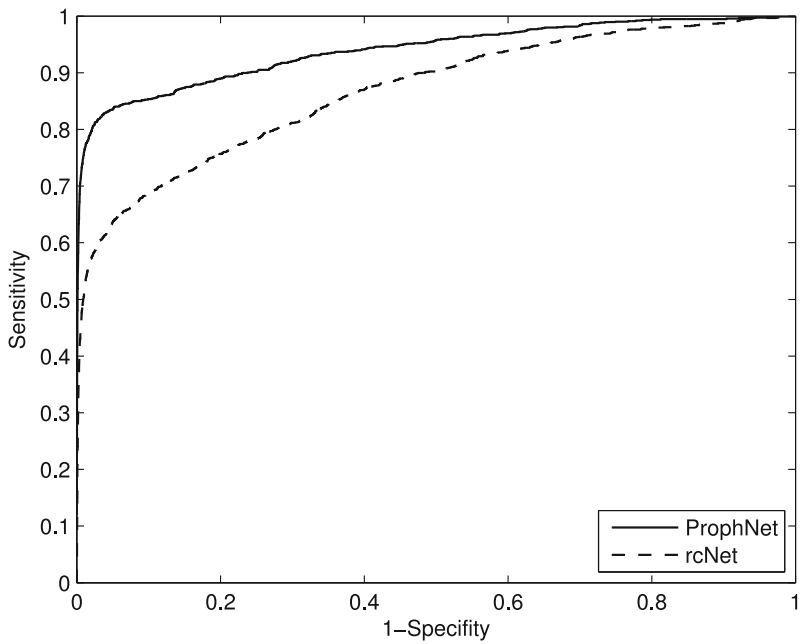
Validation tests

- ProphNet has been applied to **obtain a prioritized list** of genes for some diseases. Top ranked genes were related with query diseases.
- **Three test** have been performed to **validate** ProphNet.
- Against **rcNet**: **LOO gene-disease** prioritization and **new associations** prioritization.
- Against **domainRBF**: **LOO domain-disease**.
- **Leave-one-out (LOO) test:** Remove known A-B association, prioritize using A as Query Set and measure where B is ranked.

Tests against rcNet

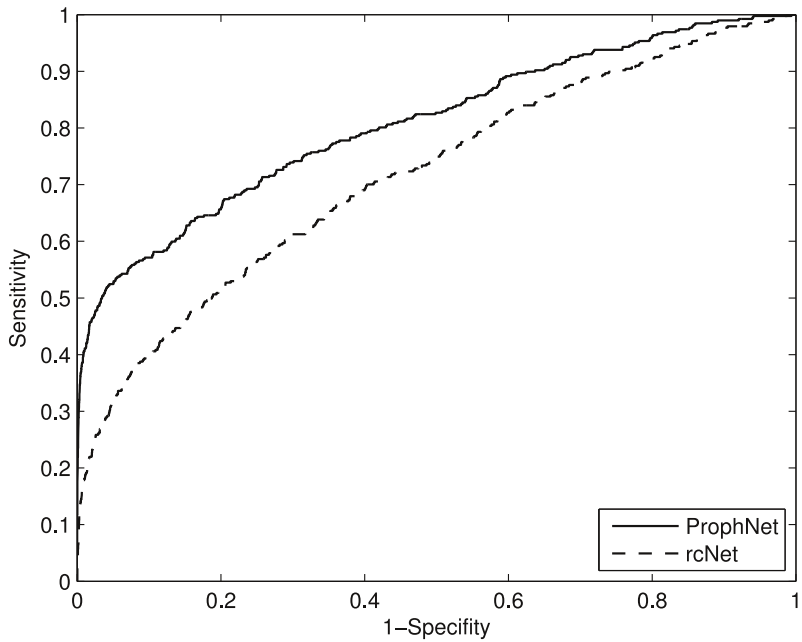
LOO gene-disease validation

16 % AUC gain



New gene-disease relation validation

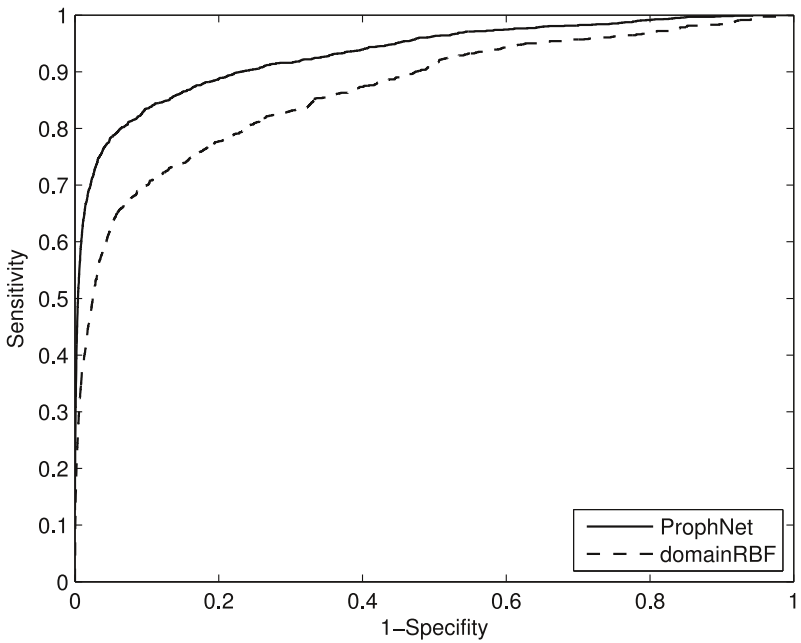
13 % AUC gain



Tests against domainRBF

LOO protein domain-disease validation

8 % AUC gain



Conclusions

- We have proposed a method that **overcomes some limitations** in network-based methods.
- Data integration allows **better performance** than some state-of-the-art methods.
- **Integration** of other type of data has shown an **increase** in ProphNet performance (e.g., drugs or pathways).

Thanks for your attention!

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