Analysis of bio-molecular networks through RANKS (RAnking of Nodes with Kernelized Score Funcions)

Giorgio Valentini
DI – Dipartimento Informatica
Università degli Studi di Milano

Computer Science Department

UNIVERSITÀ DEGLI STUDI DI MILANO

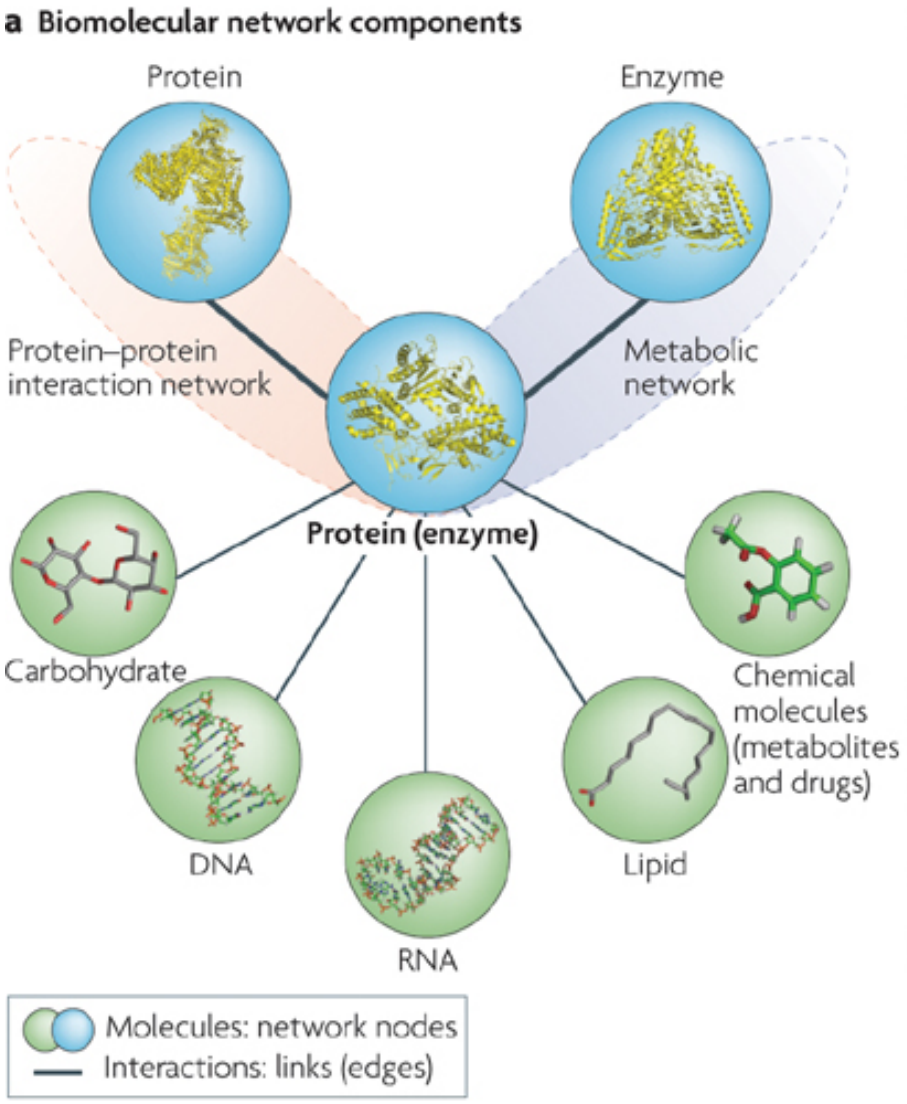
Anacleto Lab

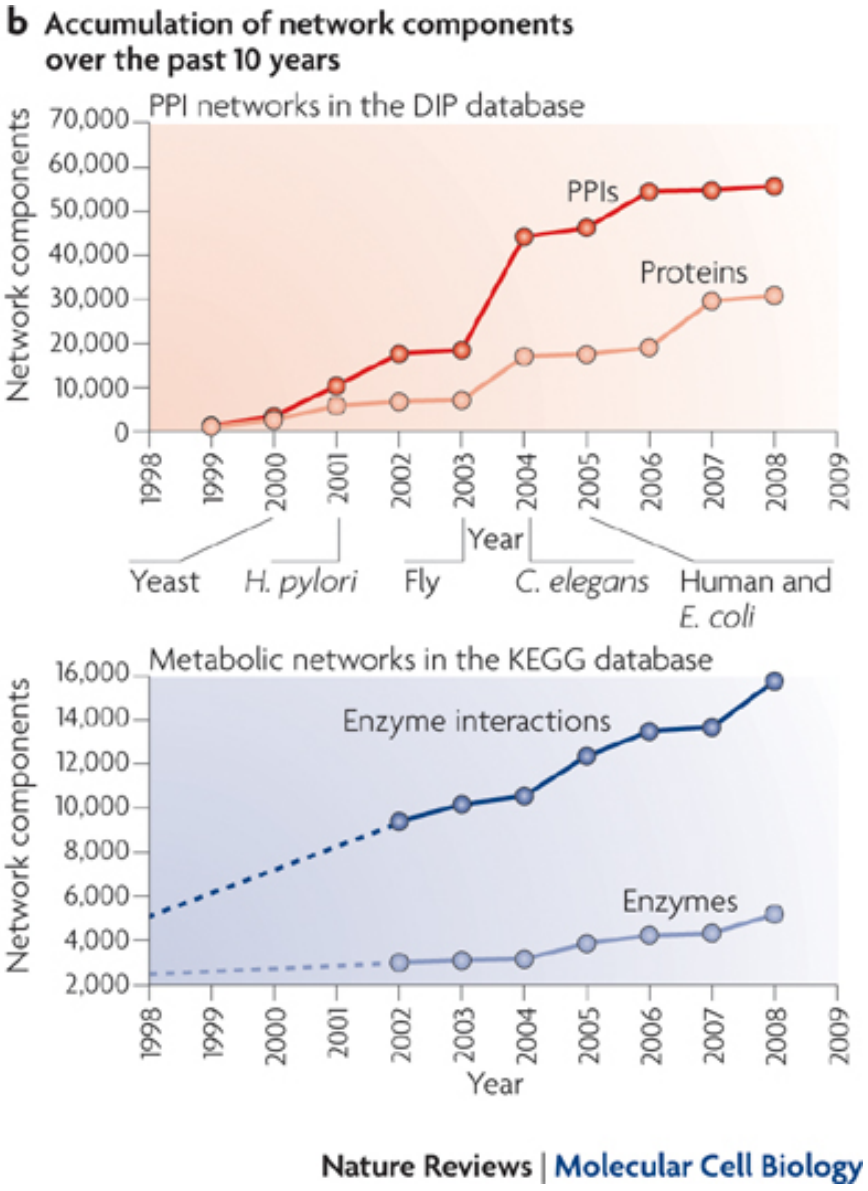
Computational Biology and Bioinformatics

Outline

- Relevant problems in molecular biology and medicine can be modeled through graphs
- Local and global semi-supervised learning strategies to learn node labels in graphs
- Merging local and global learning strategies: the *kernelized score functions* algorithmic scheme (*RANKS*)

Biomolecular networks

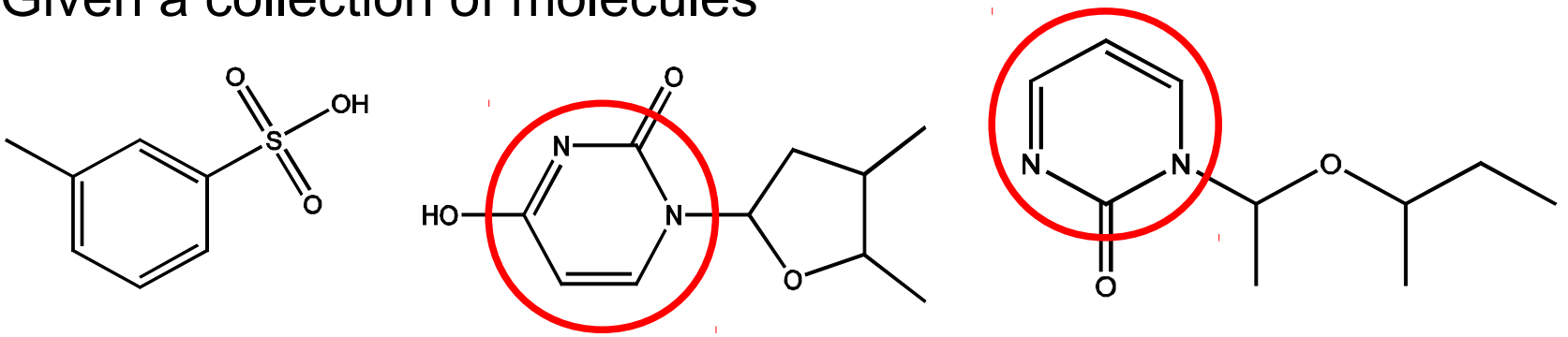




Nature Reviews | Molecular Cell Biology

Drug repositioning

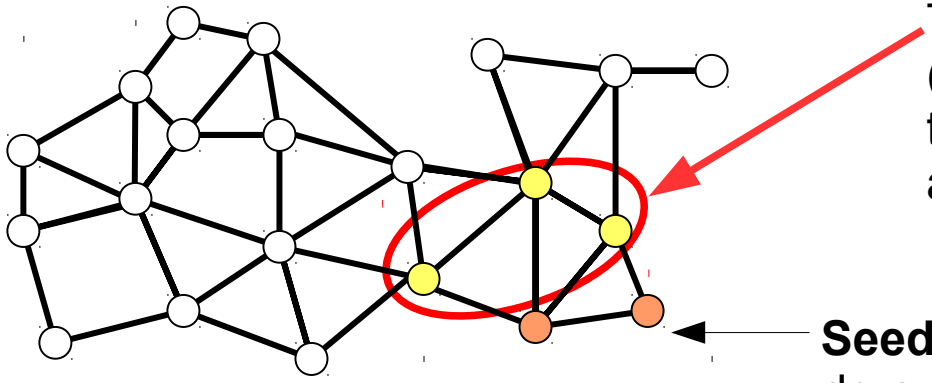
Given a collection of molecules



(A) (B) (C)

Find a meaningful way to express a similarity between them (i.e. binary profiles indicating the presence/absence of substructures used as proxy for the computation of a global similarity score between each pair of molecules).

Nodes: drugs
Edges: similarity between drugs



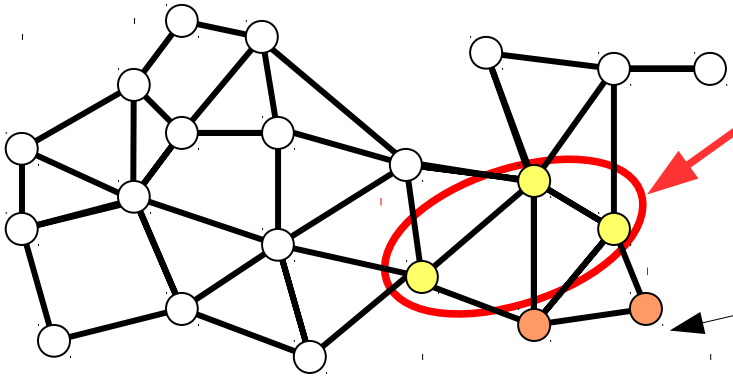
The **most similar** nodes (drugs) are candidates for the development of novel anticonvulsant drugs

Seed node, a **marketed** drug (i.e. anticonvulsant)

Automated Function Prediction (AFP)

Given a collection of proteins.

Find a meaningful way to express a similarity between them (i.e. binary profiles indicating the presence/absence of protein domains, 3D structure signatures, presence/absence of catalytic groups used as proxy for the computation of a global similarity score between each pair of ptoreins).

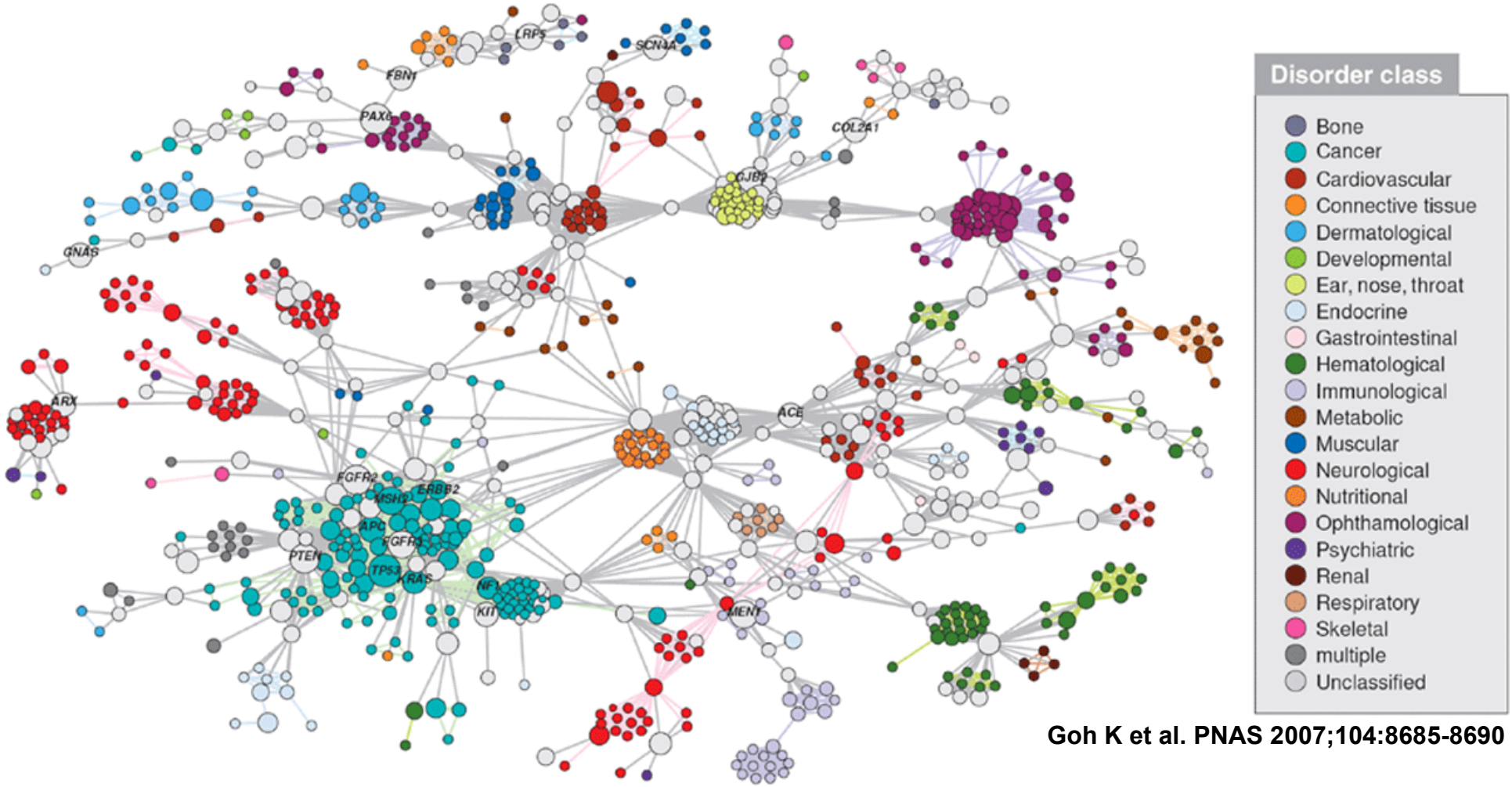


The **most similar** nodes (proteins) are candidates for the association to the functional term associated to the seeds

Seed node, associated to a **functional vocabulary term** (i.e. Gene Ontology)

Disease gene networks

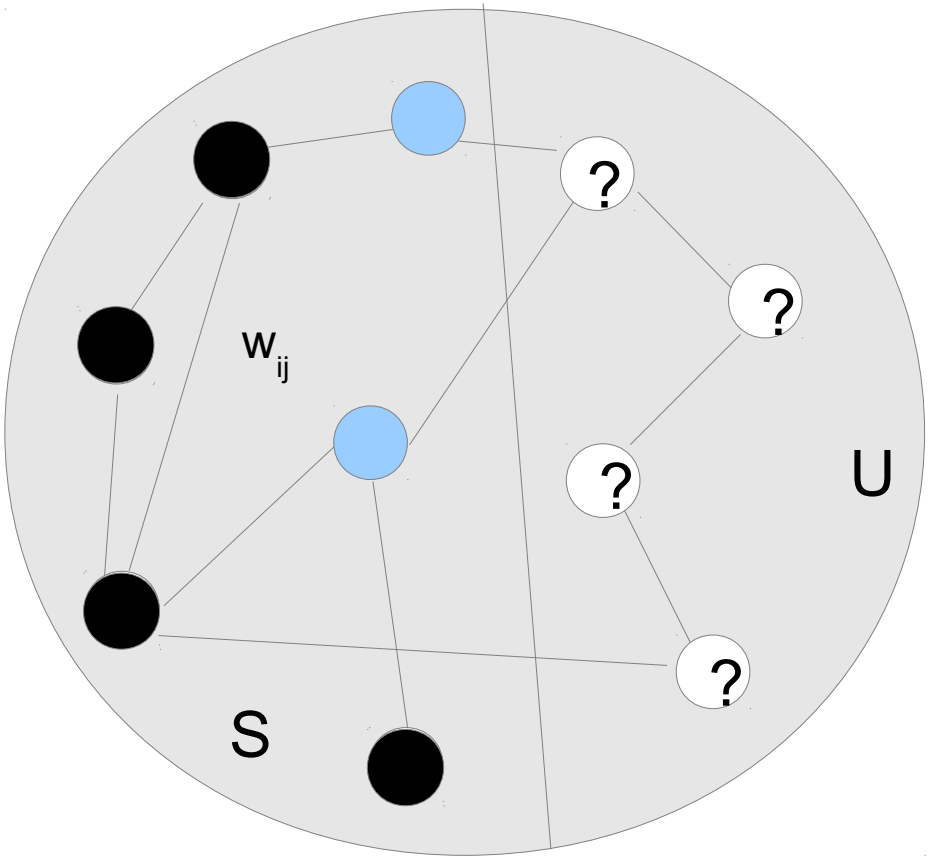
Given a collection of genes. Build a network whose nodes (genes) are connected only if they are involved into disorders of the same class.



Goh K et al. PNAS 2007;104:8685-8690

Graph Semi-Supervised Learning (GSSL) problem

$G = \langle V, E \rangle$



V : proteins,genes,drugs,...

E : functional similarities/relationships

W : similarity matrix

S : labeled nodes

U : unlabeled nodes

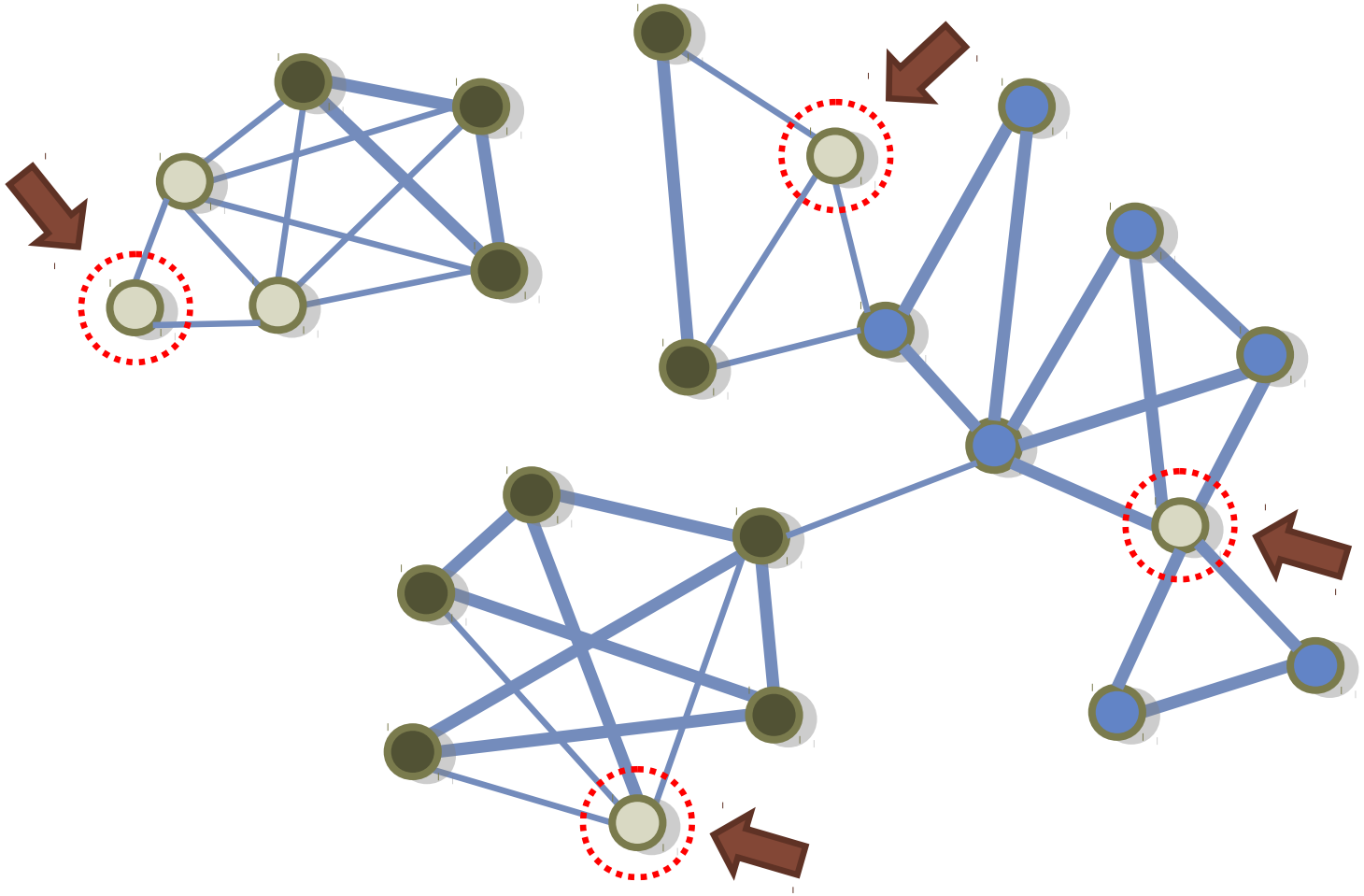
GOAL: predict labels for unlabeled nodes (*labeling problem*) or rank nodes with respect to the class to be predicted (*ranking problem*)

Node labeling/ranking methods in computational biology

- Guilt by association (*Marcotte* et al., 1999, *Oliver* et al. 2000)
- Evaluation of functional flow in graphs (*Vazquez* et al. 2003)
- Hopfield network-based methods (*Karaoz* et al. 2004, *Bertoni et al*. 2011)
- Local learning and weighed integration (*Chua* et al 2007)
- Label propagation based on Markov fields (*Deng* et al. 2004)
- Kernel methods for semi-supervised learning and integration of networks (*Tsuda* et al. 2005, *Borgwardt et al.* 2011)
- Label propagation based on Gaussian random fields and ridge regression (*Mostafavi* et al. 2008)
- Random walk-based algorithms (*Kohler et al*., 2008, *Bogdanov* and *Singh*, 2010)
- ...

Local learning strategy:

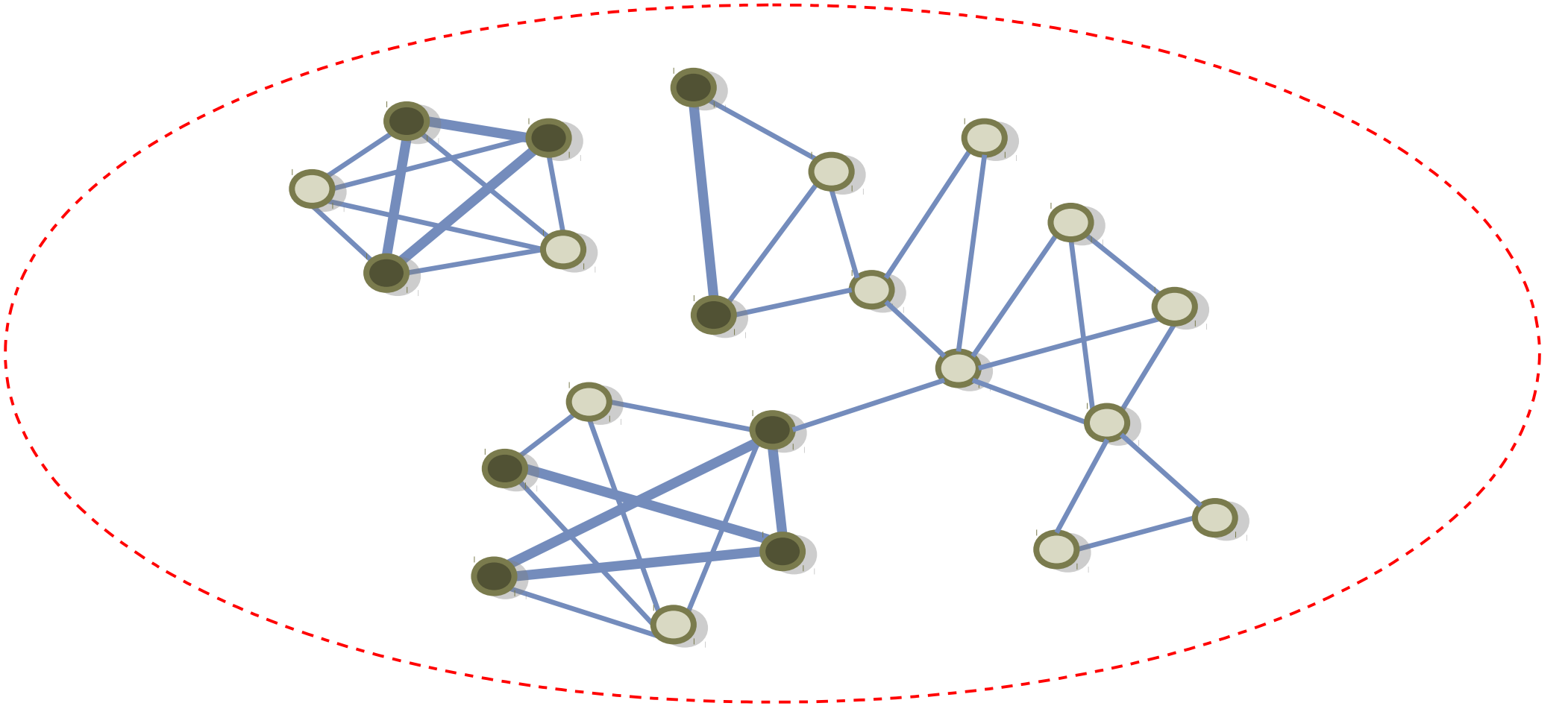
Guilt-by-association (*Marcotte* et al., 1999, *Oliver* et al. 2000)



Global learning strategy:

Exploitation of the overall network topology

(*Karaoz et al. 2004, Bengio et al. 2008, Borgwardt et al. 2011*)



Global learning strategy

Globlal learning strategies minimize a quadratic cost function

A. Consistency with the initial labeling:

$$\sum_{i=1}^{l}(\hat{y}_i - y_i)^2 = \|\hat{Y}_l - Y_l\|^2.$$

B. Consistency with the geometry of the data (internal consistency):

$$\begin{aligned}\frac{1}{2}\sum_{i,j=1}^{n}\mathbf{W}_{ij}(\hat{y}_i - \hat{y}_j)^2 &= \frac{1}{2}\left(2\sum_{i=1}^{n}\hat{y}_i^2\sum_{j=1}^{n}\mathbf{W}_{ij} - 2\sum_{i,j=1}^{n}\mathbf{W}_{ij}\hat{y}_i\hat{y}_j\right)\\ &= \hat{Y}^\top(\mathbf{D}-\mathbf{W})\hat{Y}\\ &= \hat{Y}^\top L\hat{Y}\end{aligned}$$

A + B + regularization

$$C(\hat{Y}) = \|\hat{Y}_l - Y_l\|^2 + \mu\hat{Y}^\top L\hat{Y} + \mu\epsilon\|\hat{Y}\|^2$$

Kernelized score functions: putting together local and global learning strategies (Valentini *et al. 2016*)

Global learning

Kernel

Any kernel. E.g.:
- *Linear kernel*
- *Gaussian kernel*
- *Graph kernels*

Score function

Node ranking

Local learning

Average score : $S_{AV}(v,V_C)=\frac{1}{|V_C|}\sum_{x\in V_C} K(v,x)$

kNN score : $S_{kNN}(v,V_C)=\sum_{x\in kNN(v)} K(v,x)$

NN score : $S_{NN}(v,V_C)=max_{x\in V_C} K(v,x)$

Example of a kernel well-suited to capture the topology of the graph: the Random Walk Kernel (Smola and Kondor, 2003)

$$L = D - W \quad d_{ii} = \sum_j w_{ij}$$

Normalized graph Laplacian

$$\tilde{L} = D^{-\frac{1}{2}} L D^{-\frac{1}{2}} = D^{-\frac{1}{2}}(D - W)D^{-\frac{1}{2}} =$$
$$D^{-\frac{1}{2}} D D^{-\frac{1}{2}} - D^{-\frac{1}{2}} W D^{-\frac{1}{2}} = I - D^{-\frac{1}{2}} W D^{-\frac{1}{2}}$$

$$K_{rw} = aI - \tilde{L} = aI - I + D^{-\frac{1}{2}} W D^{-\frac{1}{2}} =$$
$$(a-1)I + D^{-\frac{1}{2}} W D^{-\frac{1}{2}}$$

1 - step RW kernel

$$K_{rw}^{q} = (aI - \tilde{L})^{q}$$

q - step RW kernel

Derivation of kernelized score functions

$$\phi : X \rightarrow \mathcal{H} \qquad D_{AV}(i, V_C) = \left|\left| \phi(\boldsymbol{x}_i) - \frac{1}{|V_C|} \sum_{j \in V_C} \phi(\boldsymbol{x}_j) \right|\right|^2$$

$$D_{AV}(i, V_C) = < \phi(\boldsymbol{x}_i), \phi(\boldsymbol{x}_i) > - \frac{2}{|V_C|} \sum_{j \in V_C} < \phi(\boldsymbol{x}_i), \phi(\boldsymbol{x}_j) > + \frac{1}{|V_C|^2} \sum_{k \in V_C} \sum_{j \in V_C} < \phi(\boldsymbol{x}_k), \phi(\boldsymbol{x}_j) >$$

$$Sim_{AV}(i, V_C) = -K(\boldsymbol{x}_i, \boldsymbol{x}_i) + \frac{2}{|V_C|} \sum_{j \in V_C} K(\boldsymbol{x}_i, \boldsymbol{x}_j - \frac{1}{|V_C|^2} \sum_{k \in V_C} \sum_{j \in V_C} K(\boldsymbol{x}_k, \boldsymbol{x}_j)$$

$$S_{AV}(i, V_C) = -K(\boldsymbol{x}_i, \boldsymbol{x}_i) + \frac{2}{|V_C|} \sum_{j \in V_C} K(\boldsymbol{x}_i, \boldsymbol{x}_j)$$

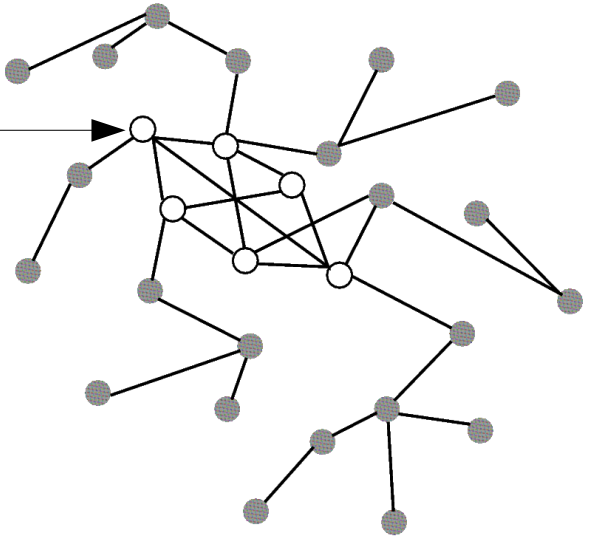
Score functions are used to rank nodes in a undirected graph

A modular approach:

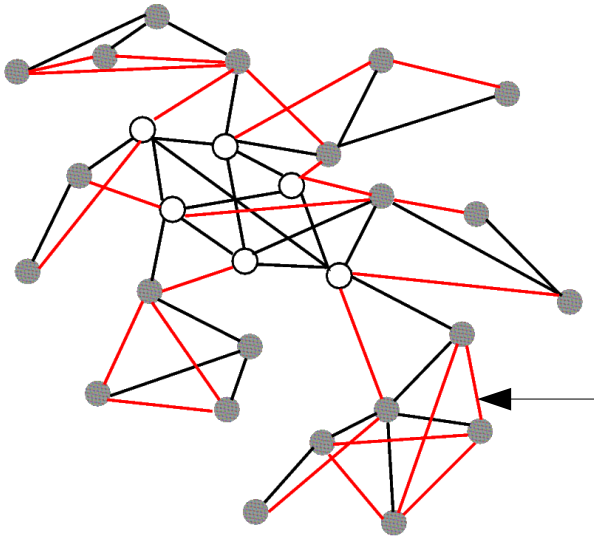
1. Select a distance - score function
2. Select a suitable kernel

Kernelized score functions: a picture of the ranking method

A positive node

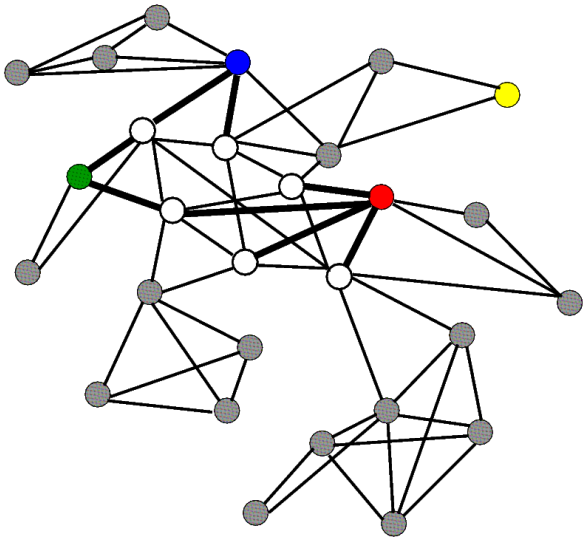


Original network



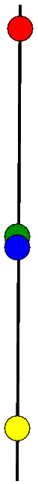
Random walk kernel

Augmented connectivity



Scoring of unlabeled nodes

high rank



connected with 4 positives

connected with 2 positives

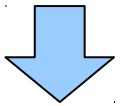
. . .

low rank

Kernelized score functions : a drug repositioning case study

M. Re, and G. Valentini, Network-based Drug Ranking and Repositioning with respect to DrugBank Therapeutic Categories, IEEE ACM Transactions on Computational Biology and Bioinformatics 10(6), pp. 1359-1371, Nov-Dec 2013

- A network G=(V,E) connecting a large set of drugs: { Nodes → drugs; Edges → similarities }
- A subset $V_C \subset V$ of drugs belonging to a given therapeutic category *C*



Rank drugs $v \in V$ w.r.t. to a given therapeutic category *C*

Many strategies for drugs networks construction: pairwise chemical similarity, bipartite network projection (projection in drug space of drug-target networks : drugs connected if they target the same protein/s).

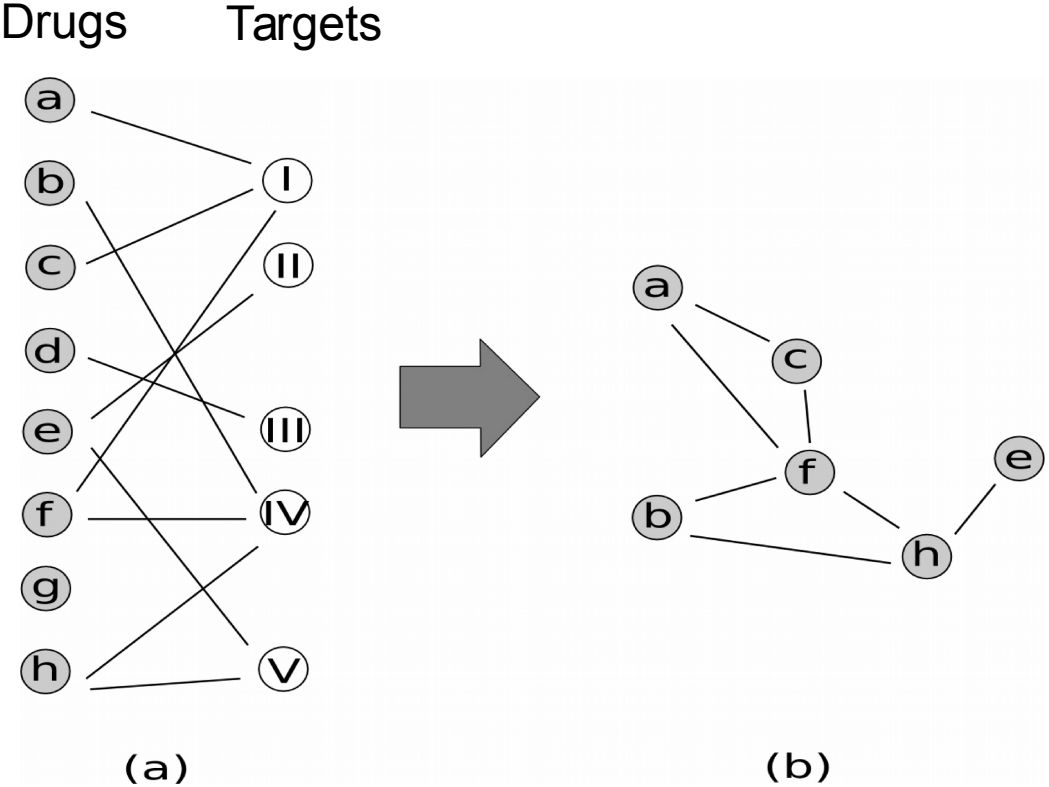
Kernelized score functions: experiments

- 1253 FDA approved drugs
- 51 DrugBank therapeutic classes
- 3 pharmacological networks:
  - $N_{structSim}$: pairwise chemical similarity (*Tanimoto* coefficients)
  - $N_{drugTarget}$: projection from drug-target interactions (from *DrugBank 3.0*)
  - $N_{drugChem}$: projection from chemical interactions (from *STITCH 2.0*)

Problem: <u>inhomogeneous coverage</u> in the 3 networks. Solution: networks integration.

Kernelized score functions

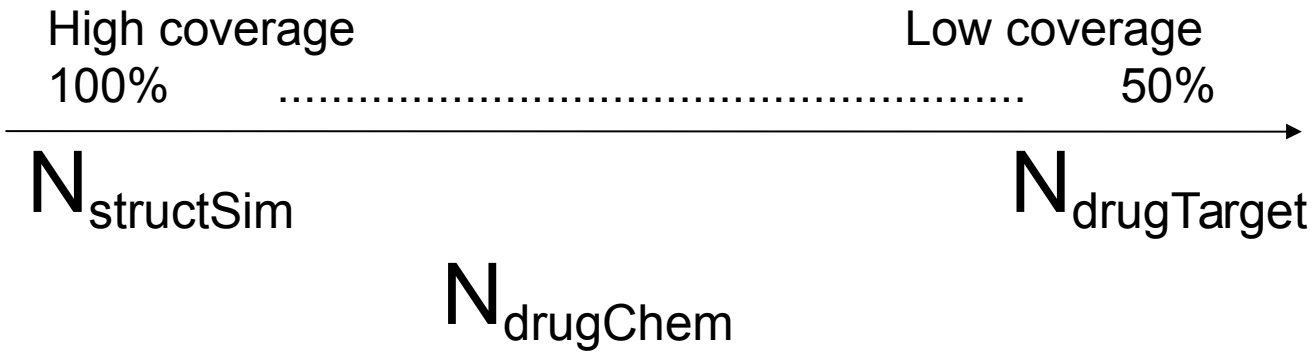
Network construction by bipartite network projection



Bipartite network
(e.g. drug-target,
drug-drug interaction)

One-mode drug network

Kernelized score functions: experiments



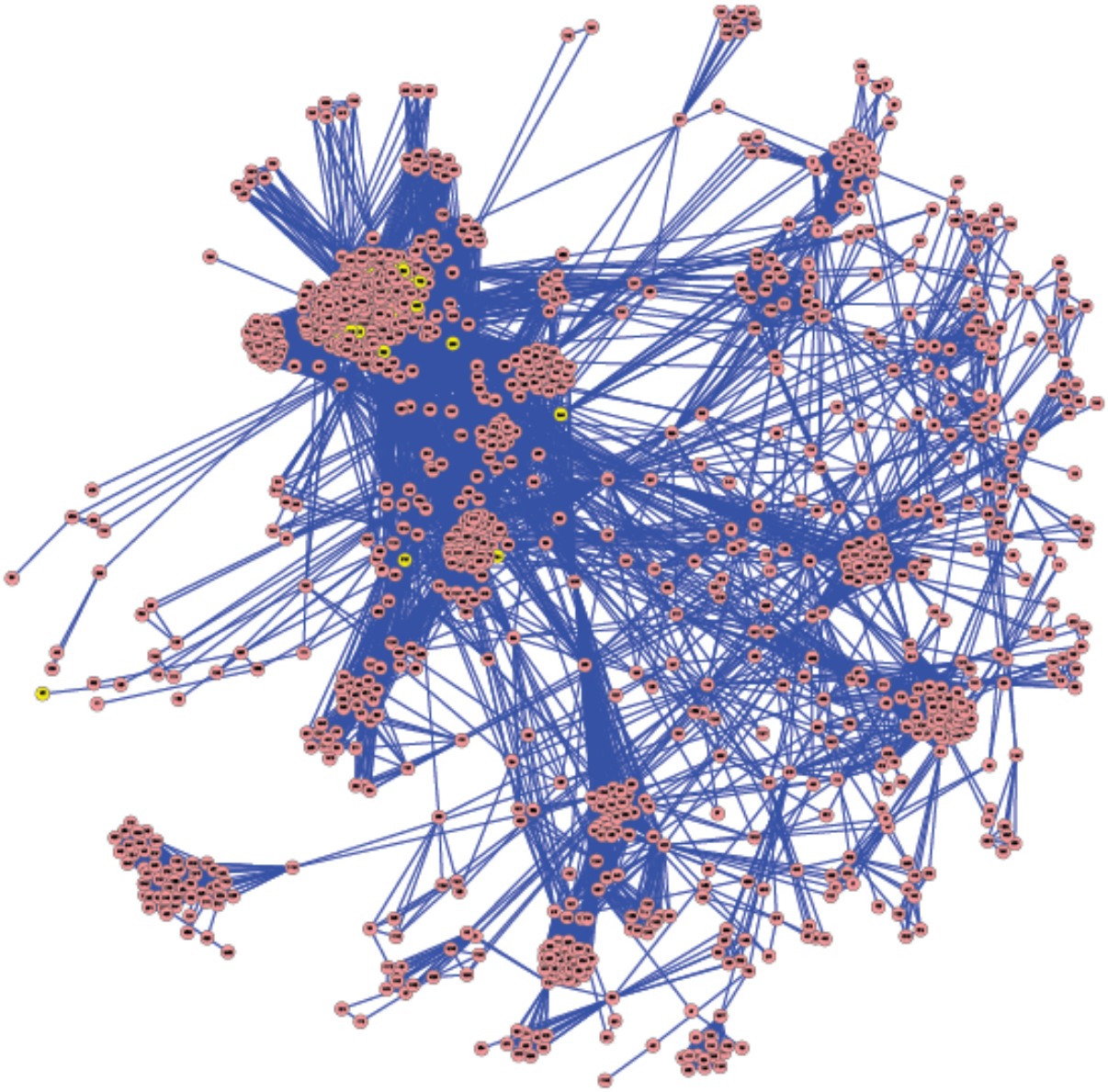
$N_{structSim} \rightarrow W_1$ (1253 nodes, **13010** edges)

$N_{structSim} + N_{drugTarget} \rightarrow W_2$ (1253, **43827**)

$N_{structSim} + N_{drugTarget} + N_{drugChem} \rightarrow W_3$ (1253, **96711**)

NB: networks integration **increase the connectivity**!

A view of the integrated pharmacological network



Kernelized score functions: results (AUC)

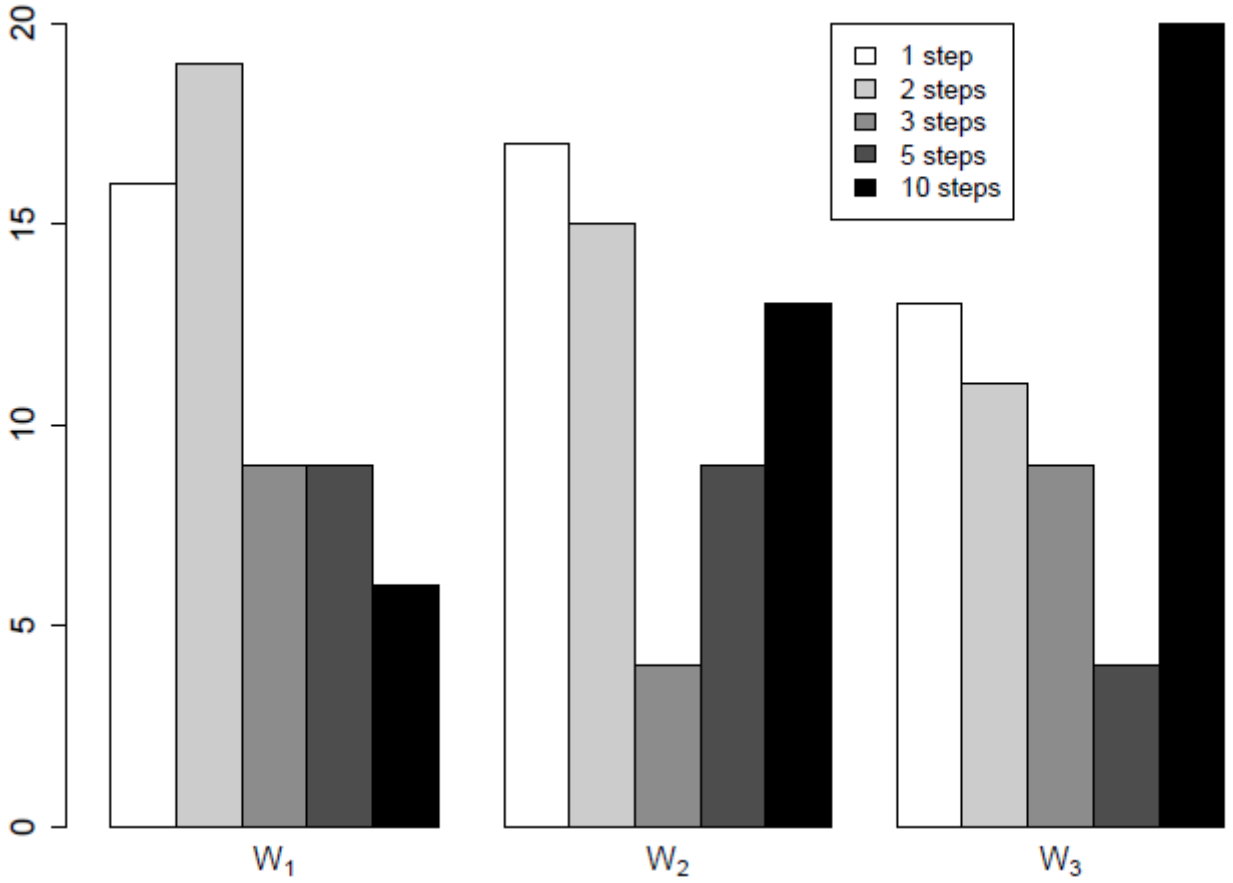
Kernelized score functions with random walk kernels **compared with *Random Walk* (RW) and *Random Walk with Restart* (RWR) algorithms**:

- 5-fold CV
- Results averaged across 51 DrugBank therapeutic classes having more than 15 drugs:

Methods	AUC			P40R		
	W_1	W_2	W_3	W_1	W_2	W_3
S_{AV} 3 steps	0.8332	0.9233	**0.9372**	0.5330	**0.6497**	0.6931
S_{kNN} 2 steps k=31	**0.8373**	**0.9261**	0.9361	**0.5334**	0.6480	**0.7012**
S_{NN} 3 steps	0.8271	0.9067	0.9224	0.3803	0.4300	0.4653
$RWR\ \theta = 0.6$	0.8078	0.9203	0.9299	0.5238	0.6278	0.6839
RW 1 step	0.8175	0.9201	0.9272	0.4910	0.6240	0.6799
GBA	0.8027	0.9028	0.9095	0.3273	0.4127	0.4634
RW	0.6846	0.5780	0.5334	0.2224	0.0608	0.0366

- $W_1 \rightarrow W_2 \rightarrow W_3$: AUC increments are statistically significant (Wilcoxon rank sum test, α=0.01)
- S_{AV} and S_{kNN} significantly better than the other methods (Wilcoxon rank sum test, α=0.01)

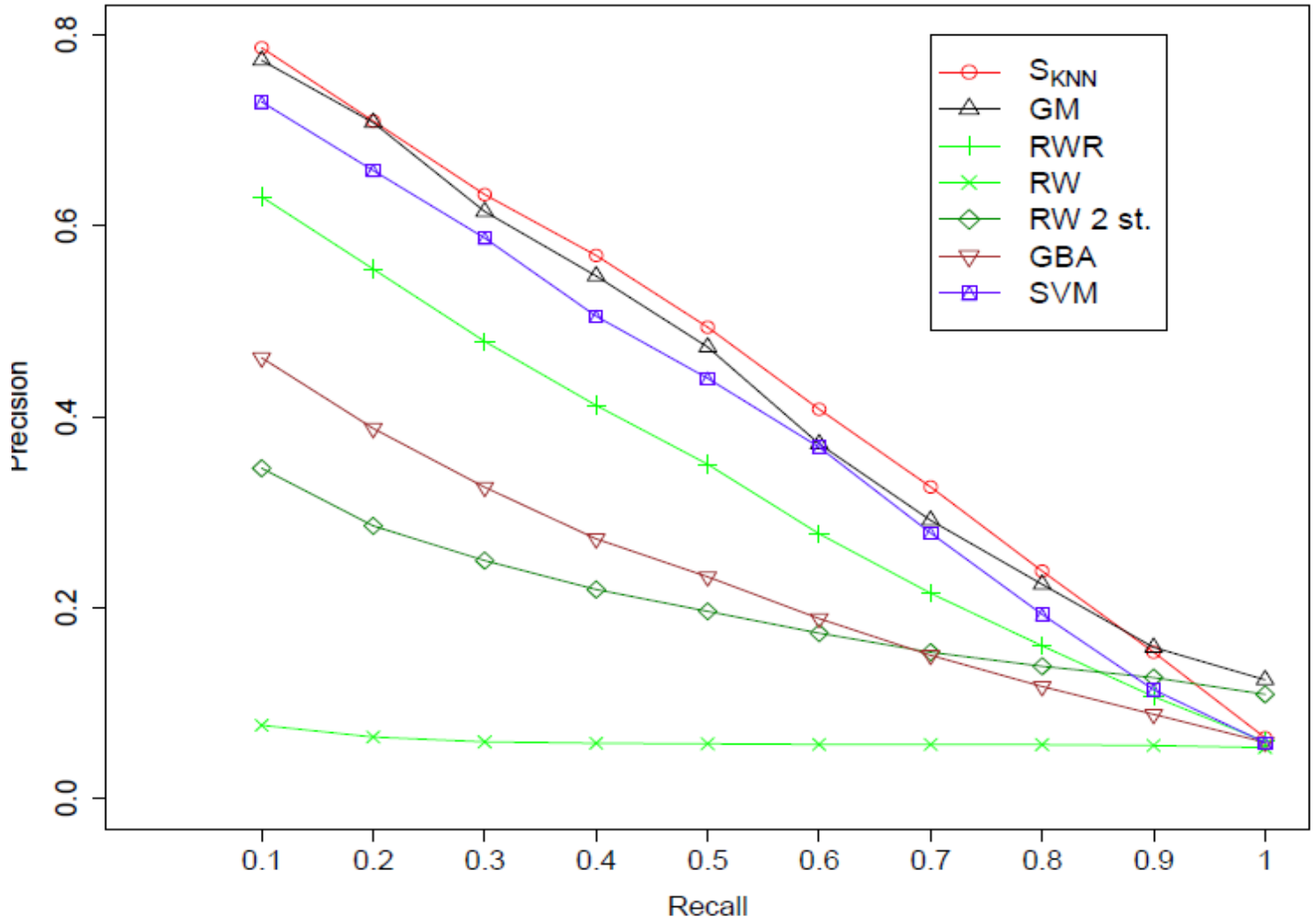
Kernelized score functions: Exploring deeply the integrated pharmacological space yields better results



Counts of the ”wins” across the 1254 therapeutic classes for the average score with 1, 2, 3, 5 and 10 steps random walk kernels

Kern. score functions : a gene function prediction case study

M. Re, M. Mesiti, and G. Valentini, "A Fast Ranking Algorithm for Predicting Gene Functions in Biomolecular Networks," IEEE ACM Transactions on Computational Biology and Bioinformatics, vol. 9, no. 6, pp. 1812–1818, 2012.



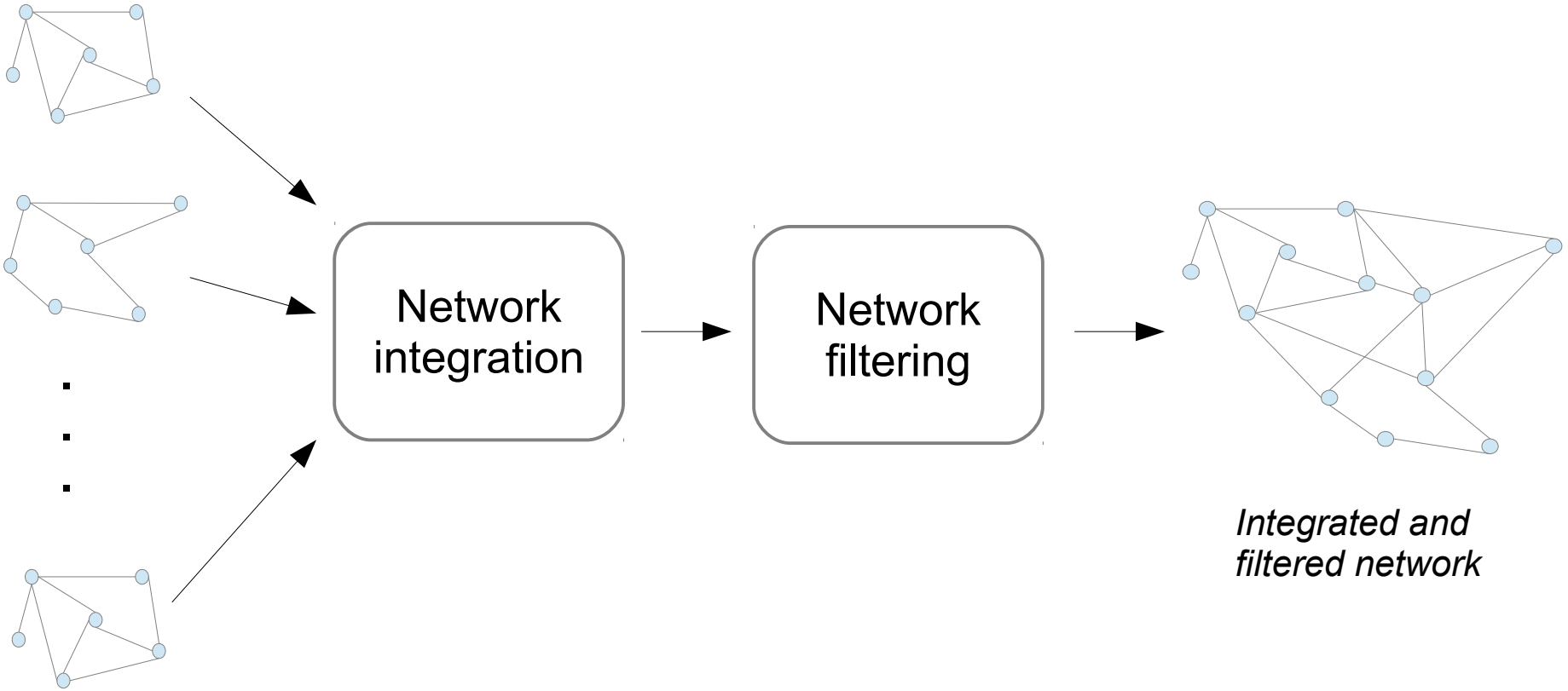
Kern. score functions : a gene disease prioritization case study

G. Valentini, A. Paccanaro, H. Caniza, A. Romero, M. Re, An extensive analysis of disease-gene associations using network integration and fast kernel-based gene prioritization methods, Artificial Intelligence in Medicine 61 (2) (2014)

Goals:

- An extensive analysis of gene-disease associations, considering a large set of diseases (708 MeSH diseases)
- Finding novel gene-disease associations for unannotated genes
- Analysis of the impact of network integration on gene prioritization

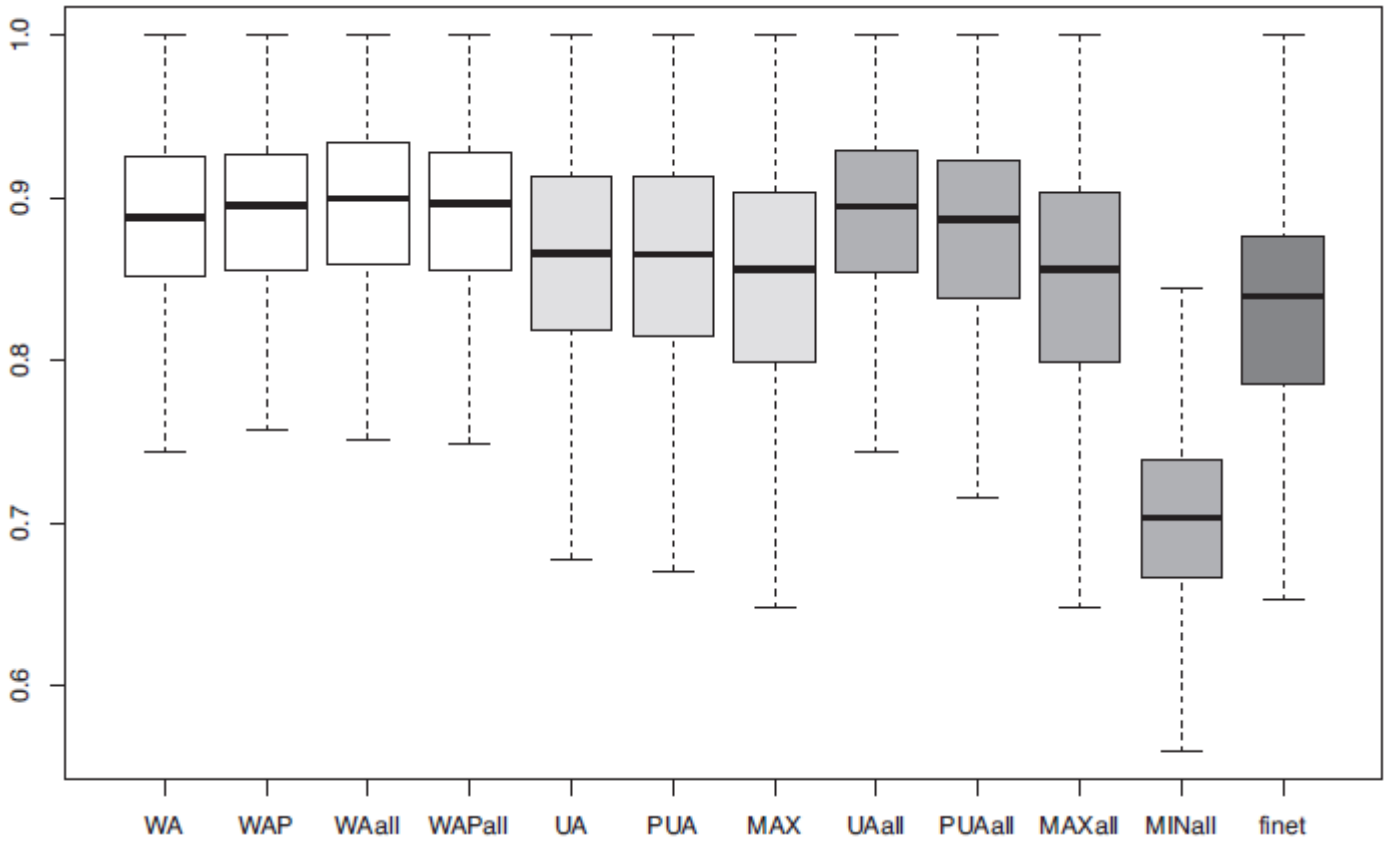
Analysis of the impact of network integration on gene prioritization



But also proper pre-processing and normalization of the networks is fundamental ...

Analysis of the impact of network integration on gene prioritization

Network	Description	Type	Nodes	Edges	Density
finet	Obtained from multiple sources of evidence	Binary	8449	271466	0.0038
hnnet	Obtained from multiple sources of evidence	Binary	8449	502222	0.0070
cmnet	Network projections from cancer modules	Binary	8449	3414722	0.0478
gcnet	Network projections from CTD	Binary	7649	1421298	0.0242
bgnet	Network projections from BioGRID	Binary	8449	120169	0.0016
dbnet	Direct relationships obtained from BioGRID	Binary	8449	3023084	0.0423
bpnet	Semantic similarity network from GO BP	Real valued	6923	44506147	0.9286
mfnet	Semantic similarity network from GO MF	Real valued	6145	26611887	0.7047
ccnet	Semantic similarity network from GO CC	Real valued	6693	39652637	0.8851



Summary

- Semi-supervised graph-based methods are widely applied in several relevant problems in computational biology and medicine
- Kernelized score functions is a flexible algorithmic framework that can be applied in a broad range of interesting bioinformatics problems
- Kernelized score functions and the others state-of-the-art semi-supervised learning methods for biological network analysis are affected by serious scalability problems on big networks
- RANKS software library is available as a R package from CRAN: `https://cran.r-project.org/web/packages/RANKS`

References:

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- M. Mesiti, M. Re, G. Valentini Think globally and solve locally: secondary memory-based network learning for automated multi-species function prediction, *GigaScience*, 3:5, 2014
- G. Valentini, A. Paccanaro, H. Caniza, A. Romero, M. Re, An extensive analysis of disease-gene associations using network integration and fast kernel-based gene prioritization methods, *Artificial Intelligence in Medicine*, Volume 61, Issue 2, pages 63-78, June 2014
- M. Re, and G. Valentini, Network-based Drug Ranking and Repositioning with respect to DrugBank Therapeutic Categories, *IEEE ACM Transactions on Computational Biology and Bioinformatics* 10(6), pp. 1359-1371, Nov-Dec 2013
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