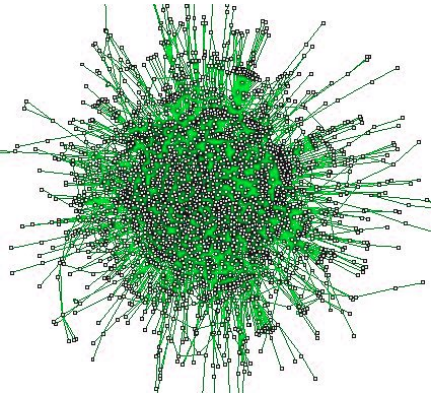
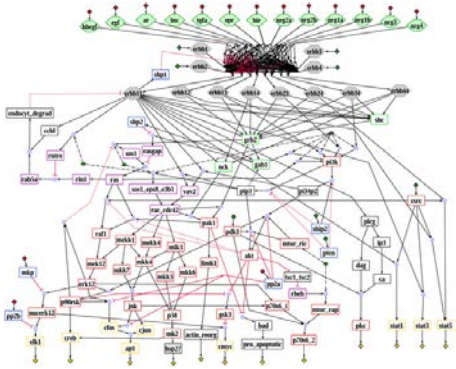
Protein networks: from topology to logic





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International Computer Science Institute at Berkeley

Motivation

- Goal: an executable model of a process of interest
- Current experimental techniques yield only the global wiring of proteins
- What is missing:
  - Directionality information
  - Process specific subnetwork
  - The underlying logic

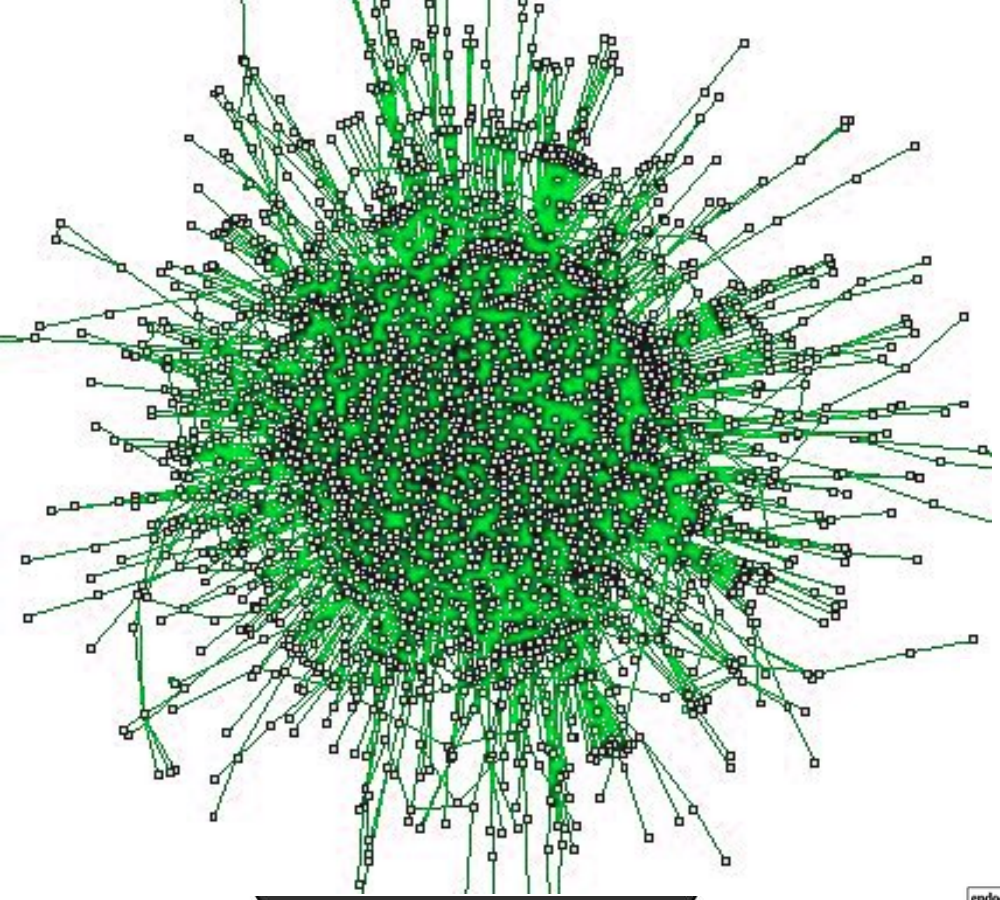
Sharan, EMBO Reports'13

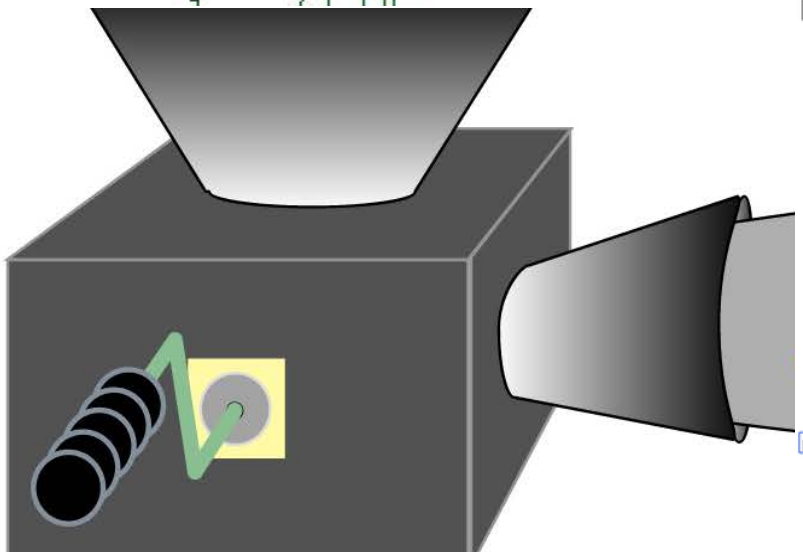
Our vision

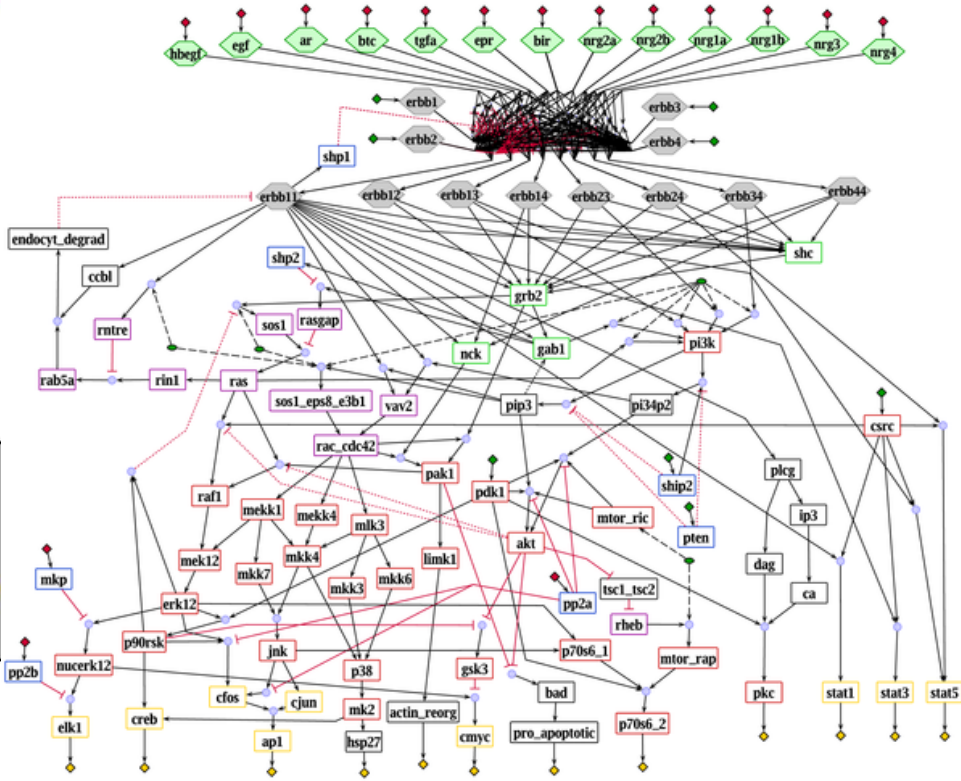
Network Orientation

Subnetwork inference

Logical model learning

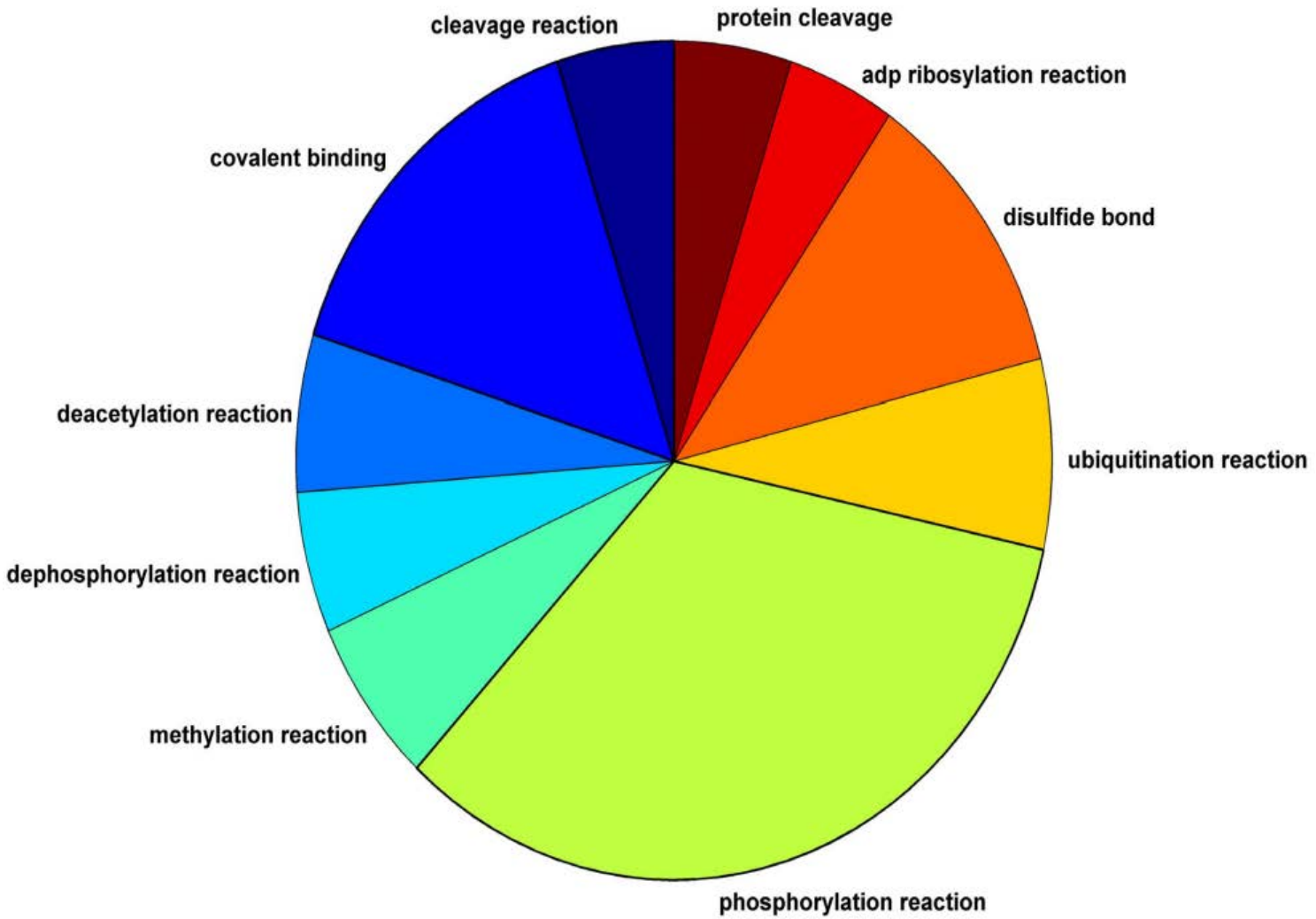






Network orientation

Are protein interactions directed?



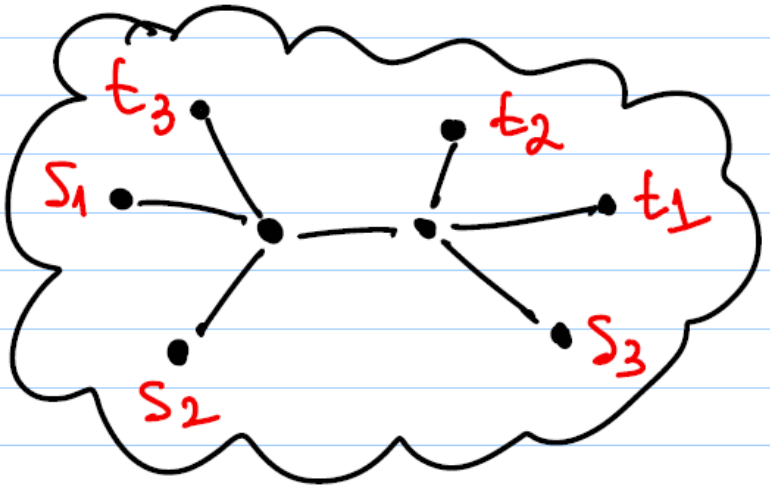
Silberberg et al., PLoS One'14

The computational problem

- Directionality is not revealed by the experiments
- Indirect information is obtained from knockout experiments:
  - Observe: knockout of protein *s* affects *t*
  - Assume: there is a directed *(s,t)* path
- Goal: predict directions to maximize #KO-pairs that can be "explained"

MAXIMUM GRAPH ORIENTATION

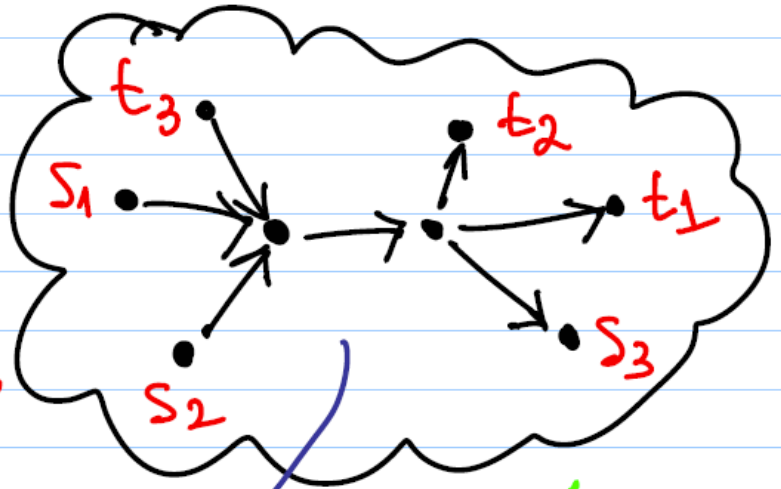
- Input: undirected graph $G=(V,E)$ with n vertices
  source-target pairs $(s_1,t_1),\dots,(s_k,t_k)$



MAXIMUM GRAPH ORIENTATION

- Input: undirected graph $G=(V,E)$ with n vertices
  source-target pairs $(s_1,t_1),\dots,(s_k,t_k)$

- goal: Compute an orientation in which the number of connected pairs is maximized



(s_1,t_1) ✓

(s_2,t_2) ✓

(s_3,t_3) ✗

MAXIMUM GRAPH ORIENTATION

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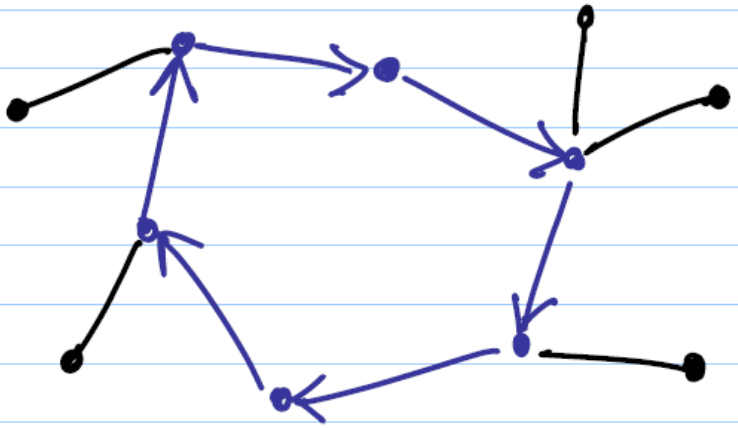


- remark: we may assume that the underlying graph is a tree

Complexity of Max. Tree Orientation

- NP-hard (reduction from MAX DI-CUT)
- Hard to approximate to within 12/13
- $\Omega(\log\log n / \log n)$ approximation
- Can we do better?

Medvedovsky et al., WABI 2008
Gamzu et al., WABI 2010
Elberfeld et al., Internet Math. 2011

An Integer Programming Formulation

- Assign a single direction for each edge

  $O(v,w) + O(w,v) = 1$

- Describe reachability relations

  $c(s,t) \leq O(x,y)$ for all edges in the path from s to t

- Objective: $\max \sum c(s,t)$

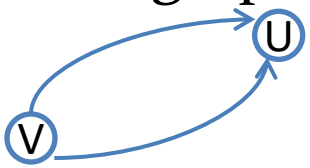
Medvedovsky et al., WABI 2008

A biological complication

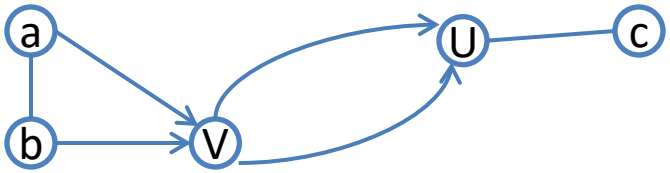
- In reality, some of the edges are pre-directed, e.g. kinase-substrate interactions.
- Can we deal with mixed graphs?
- On the theoretical side, large gap between upper (7/8) and lower ($\tilde{\Omega}(1/n^{1/\sqrt{2}})$) approximation bounds.

Mixed vs. undirected

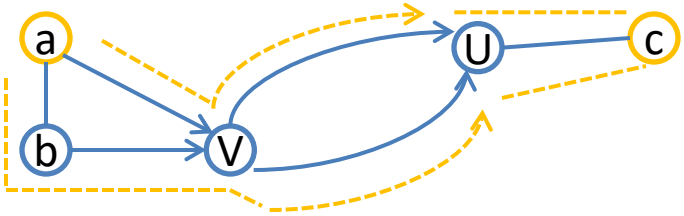
In the mixed graph there are cycles which cannot be contracted



The graph cannot be reduced to a tree

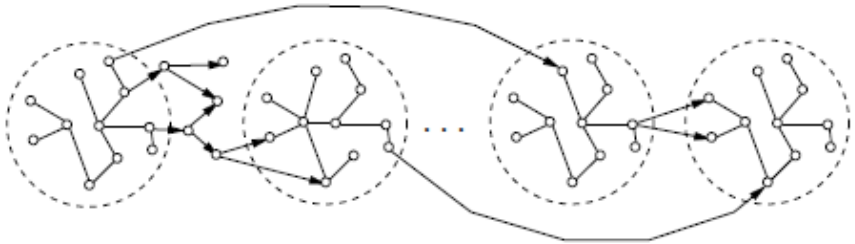


There may be multiple paths between a pair of vertices



An ILP for mixed graphs

- Contract all cycles, obtaining an acyclic graph
- Use topological sorting to create a graph of trees connected by left-to-right directed edges:



- Work recursively on pairs crossing from $G_i = T_1 \cup ... \cup T_i$ to T_{i+1}
- A path between trees decomposes to subpaths within trees and a single directed edge between the trees.

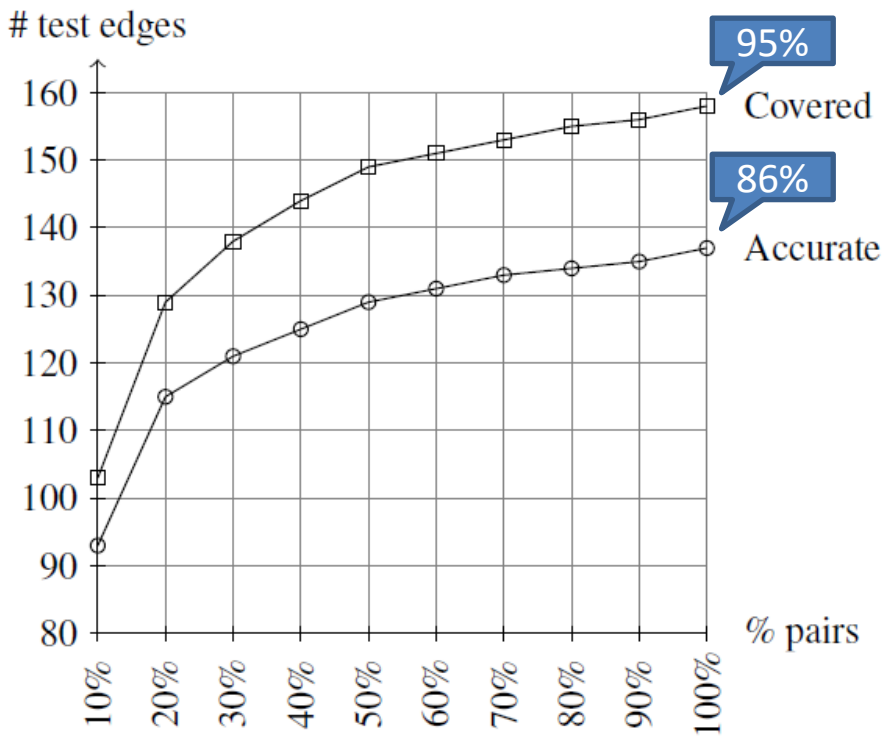
Silverbush et al., JCB 2011

A taste of the results

- Applied to yeast data: ~50K pairs, ~8,000 interactions (mixed) and 1361 test edges (KPIs) whose directions are hidden from the algorithm.

- After cycle contraction:
  - ~2,000 edges
  - 166 test edges

- Coverage: % oriented (with confidence)
- Accuracy: % correct (confident) orientations

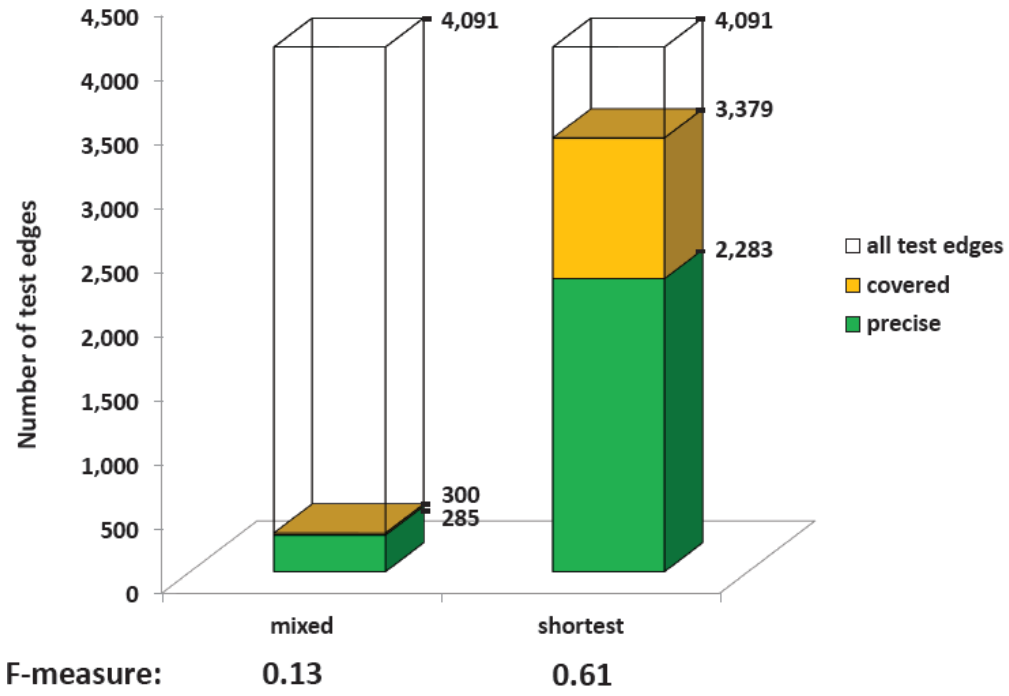


Increasing coverage

- Most edges are eliminated by the cycle contraction phase, hence their directions remain ambiguous.
- One “biologically-meaningful” attack is to require the connecting path to be SHORTEST
- Can be efficiently tackled via ILP by:
  - For any given pair (s,t) build a graph of all shortest paths
  - Perform flow computations in this graph to determine if the pair is connected under a given orientation.

Silverbush et al., Bioinformatics’14

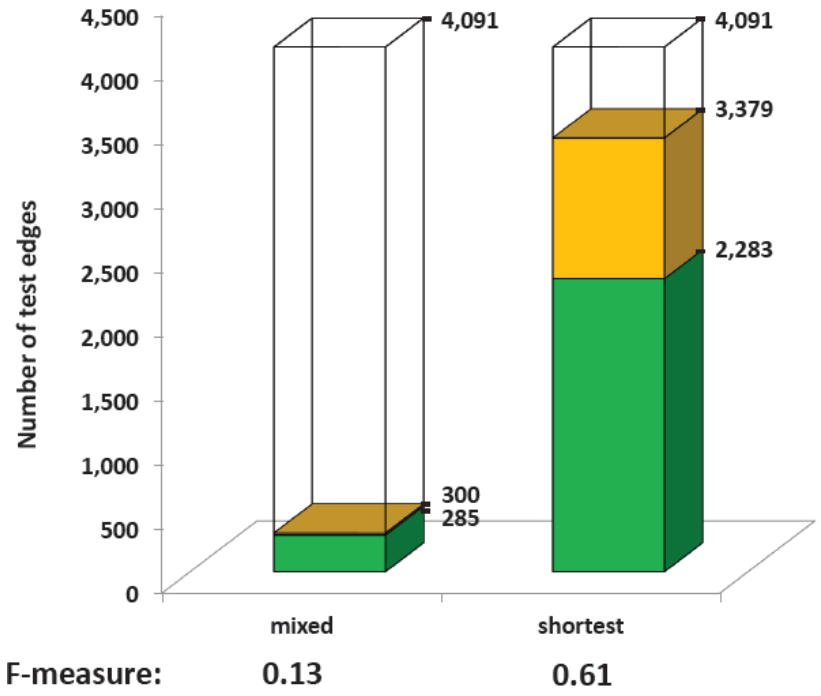
The SHORTEST approach (application)



- Yeast: similar accuracy, 8-fold more coverage!

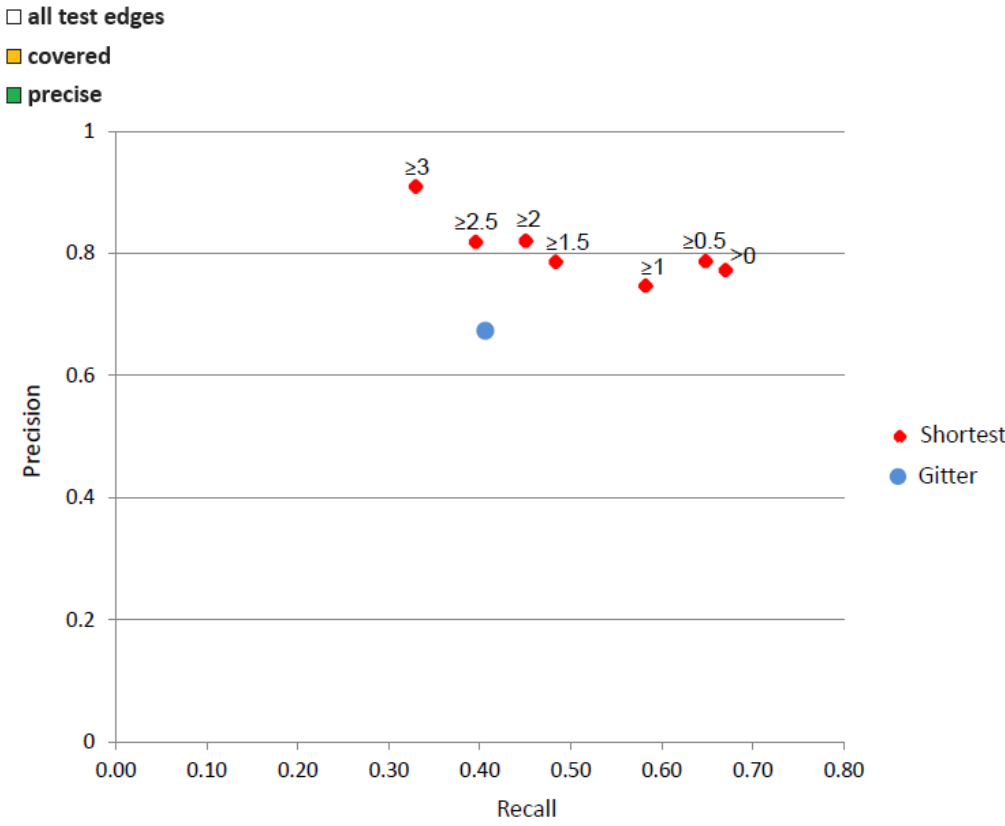
Silverbush et al., Bioinformatics'14

The SHORTEST approach (application)



- Yeast: similar accuracy, 8-fold more coverage!

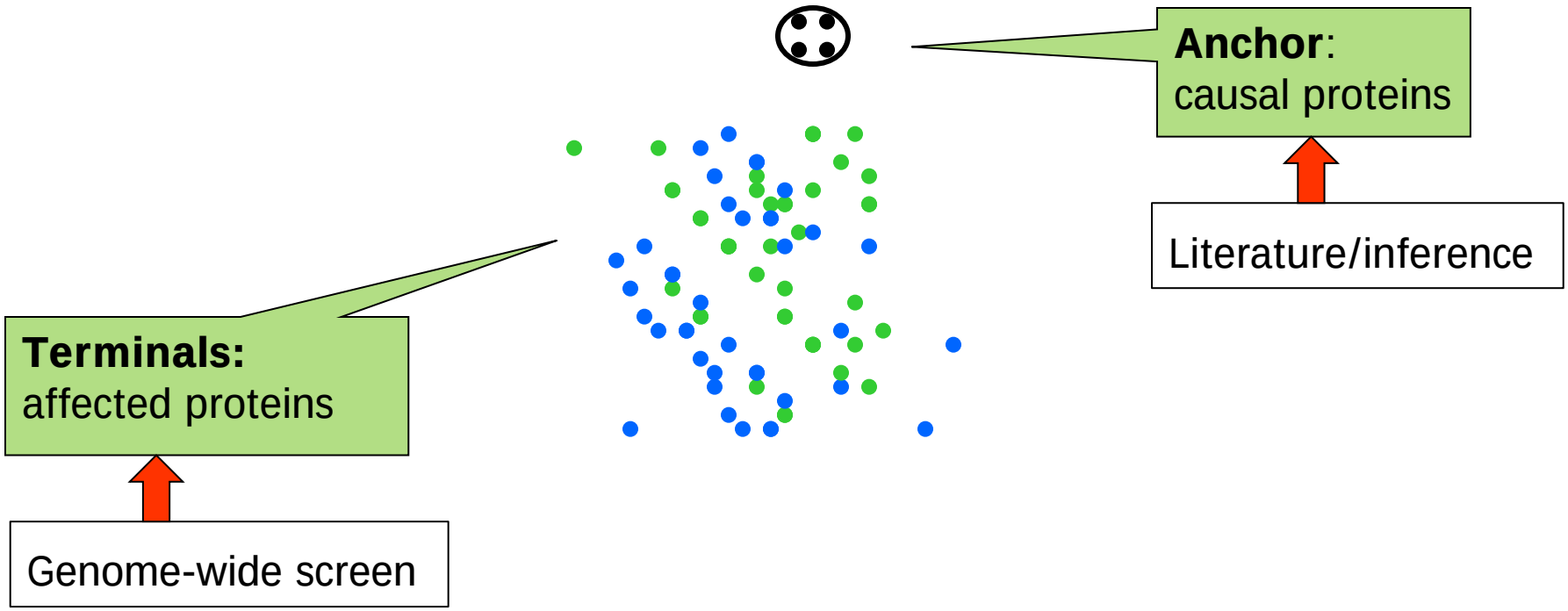
- Human: outperforms a previous method by Gitter et al.



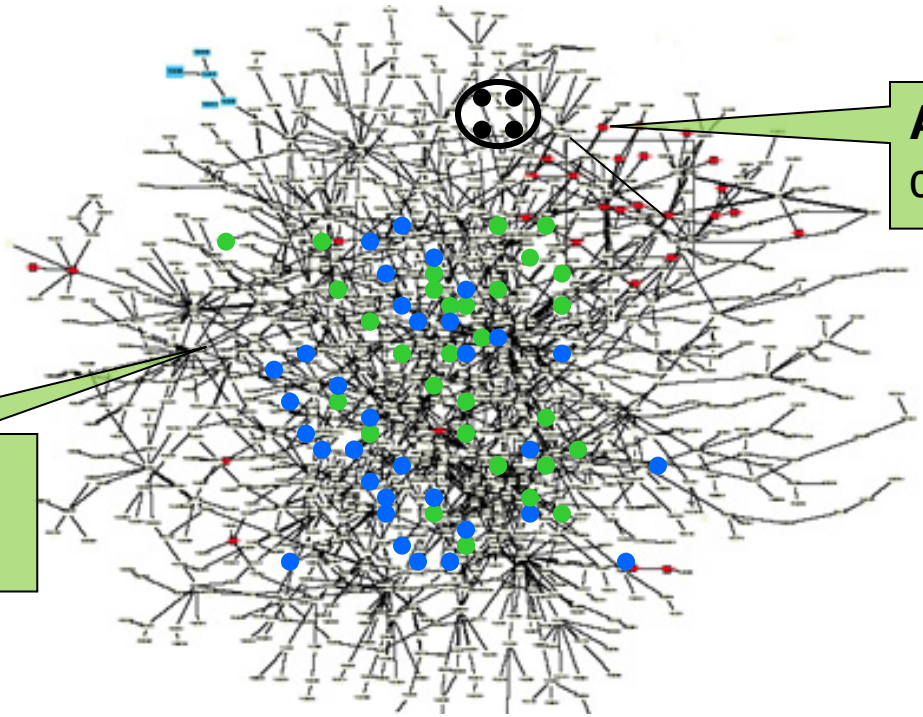
Silverbush et al., Bioinformatics'14

Subnetwork inference

Identifying process-specific proteins



From components to a map



Anchor:
causal proteins

Terminals:
affected proteins

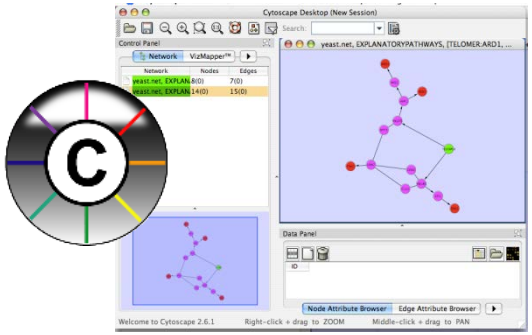
Goal: Infer the underlying subnetwork

Shachar et al., MSB 2008
Yosef et al., MSB 2009
Atias et al., MBS 2013

From components to a map (cont.)

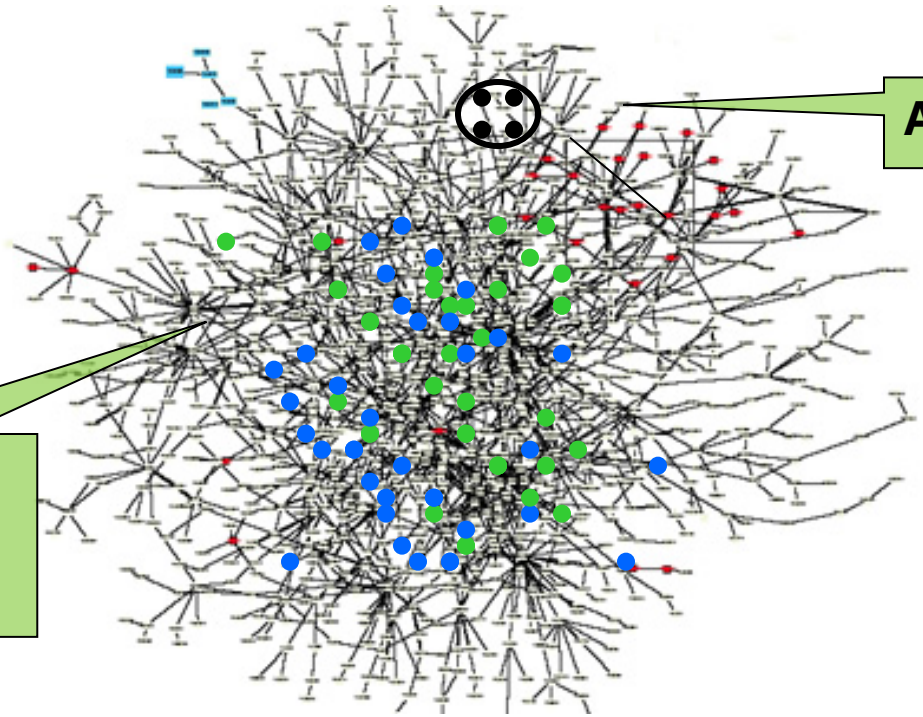
- Unique approach to simultaneously optimize subnetwork size and length of anchor-terminal paths.
- Shown to outperform existing tools on yeast and human data
- Implemented as a cytoscape plugin called **ANAT**

(www.cs.tau.ac.il/~bnet/ANAT)



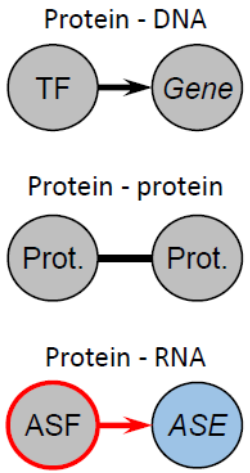
Yosef et al., Science Signaling'11
Atias et al., MBS'13

Application to alternative splicing events in cancer



Anchor: TF

Terminals:
Differentially spliced events

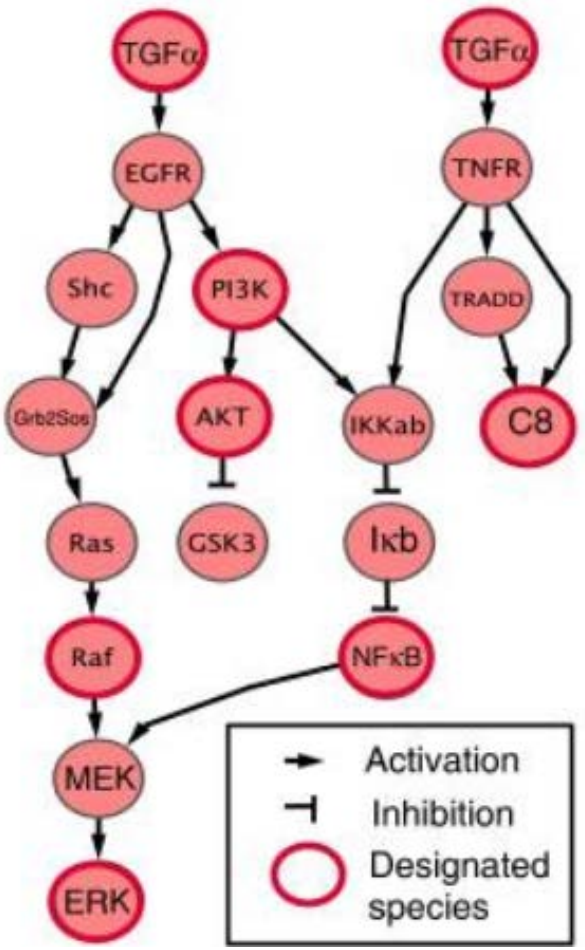


Dror Hollander, Gil Ast

Logical model learning

The Boolean model

- Each node=protein/ligand can be active (1) or inactive (0).
- The activity of a node is a *Boolean function* of the activities of its predecessors in the network.



The computational problem

Input: (i) Directed network

(ii) Protein activity readouts following different perturbations

Goal: learn the Boolean functions so as to minimize disagreements with experimental data

Stimuli							
TGFα	+	−	+	+	+	+	Design
TNF	−	+	+	−	+	−	
Inhibitors							
PI3K	−	−	−	+	+	−	
Raf	−	−	−	−	−	+	
Readouts							
NFκB	0	0	1	0	0	0	Measured
ERK	1	0	1	1	1	0	
C8	0	1	1	0	1	0	
AKT	1	0	1	0	0	1	

NFκB	0	0	0	0	0	0
ERK	1	0	1	1	1	0
C8	0	1	1	0	1	0
AKT	1	0	1	0	0	1

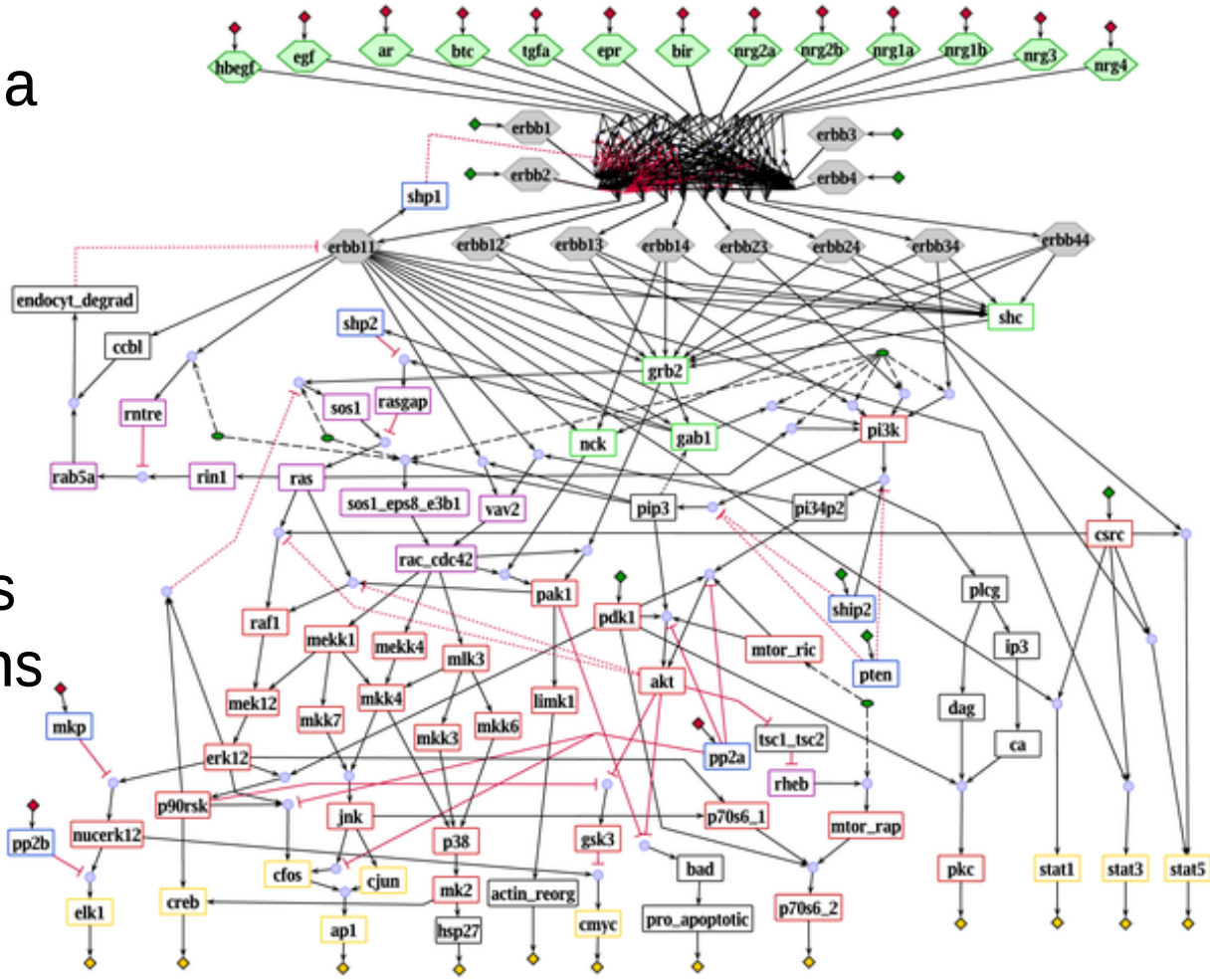
Algorithmic results

- *ILP* formulation, solved to *optimality*
- *Activation/repression effects* are automatically learned as part of the logic
- Particularly efficient solution for *threshold* functions (generalize AND & OR)

Sharan & Karp, JCB 2013

Application to EGFR signaling

- Detailed model by Oda et al. and Samaga et al. contains:
  - 112 nodes
  - 157 non-I/O reactions
- Readouts: 11 proteins under 34 perturbations
- **76%** fit to data



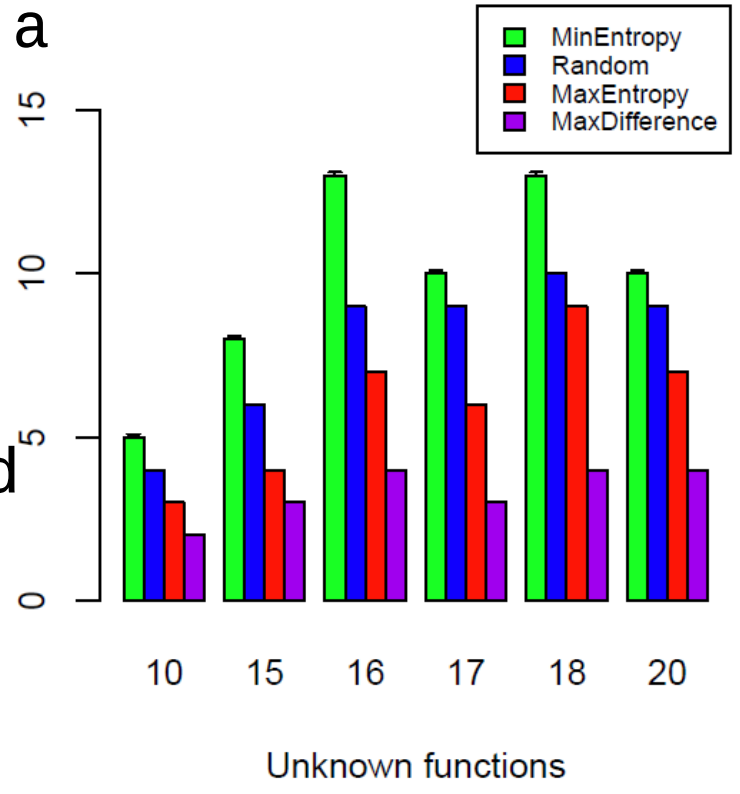
Improving the fit

- Focus on 16 uncertain gates (2^33 possible models), for 4 of which modifications were manually proposed
- 11 of 12 reconstructed functions matched the curated description
- 3 of 4 proposed changes were predicted correctly, the fourth rejected.
- The learned model achieved the same **90%** fit as the manual model!

Original function	Proposed modification	Reconstructed function
erb11 AND (pip3 OR pi34p2) → vav2	erb11 → vav2	**erb11 → vav2**
sos1eps8e3b1 → raccdc42	REMOVE	sos1eps8e3b1 → raccdc42
erb11 AND csrc → stat3	REMOVE	**REMOVE**
mk2 → hsp27	REMOVE	**REMOVE**

Challenges ahead

- Integrate the three phases (orientation, inference, logic) into a coherent pipeline
- Deal with multiple solutions:
  - Confidence computation
  - Experimental design
  - Rank via biologically-motivated secondary criteria
- Advance from static (acyclic) to dynamic models



Atias et al., Bioinformatics'14 (ECCB)

Acknowledgments

Orientation
Dana Silverbush
Michael Elberfeld
Danny Segev…

Logic
Richard Karp
Nir Atias…

Inference
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Nir Atias
Assaf Gottlieb
Gil Ast
Dror Hollander
Martin Kupiec
Eytan Ruppin…