Protein networks: from topology to logic

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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
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 $(s_1, t_1), \ldots, (s_k, t_k)$.
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• Goal: compute an orientation in which the number of connected pairs is maximized.

Si $\rightarrow \ldots \rightarrow t_i$
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
  \[ c(s,t) \leq O(x,y) \text{ for all edges in the path from } s \text{ to } t \]

- **Objective:** \[ \max \sum c(s,t) \]
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 $G_i = T_1 \cup \ldots \cup T_i$ 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.
The SHORTEST approach (application)

- Yeast: similar accuracy, 8-fold more coverage!
The SHORTEST approach (application)

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

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

- **F-measure**: mixed 0.13, shortest 0.61
Subnetwork inference
Identifying process-specific proteins

Terminals: affected proteins

Anchor: causal proteins

Genome-wide screen

Literature/inference
From components to a map

**Goal:** Infer the underlying subnetwork

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**Terminals:** affected proteins

**Anchor:** causal proteins

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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

Terminals: Differentially spliced events

Anchor: TF
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
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)
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!

<table>
<thead>
<tr>
<th>Original function</th>
<th>Proposed modification</th>
<th>Reconstructed function</th>
</tr>
</thead>
<tbody>
<tr>
<td>erb11 AND (pip3 OR pi34p2) → vav2</td>
<td>erb11 → vav2 REMOVE</td>
<td>erb11 → vav2 REMOVE</td>
</tr>
<tr>
<td>sos1eps8e3b1 → raccdc42</td>
<td>REMOVE</td>
<td>sos1eps8e3b1 → raccdc42 REMOVE</td>
</tr>
<tr>
<td>erb11 AND csr6 → stat3</td>
<td>REMOVE</td>
<td></td>
</tr>
<tr>
<td>mk2 → hsp27</td>
<td>REMOVE</td>
<td></td>
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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)
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Orientation
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