Computational Modeling of Crosstalk in Cancer Signaling Networks

Jie Zheng[1], Rafal Zielinski[5], Pawel F Przytycki[3], David Zhang[4], Jacek Capala[5] and Teresa M Przytycka[2]

[1]School of Computer Engineering, Nanyang Technological University, Singapore, [2] National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health (NIH), USA,
[3] Columbia College Columbia University New York, NY, USA, [4] Department of Electrical & Computer Engineering, University of Maryland, College Park, USA, [5]National Cancer Institute, NIH, USA

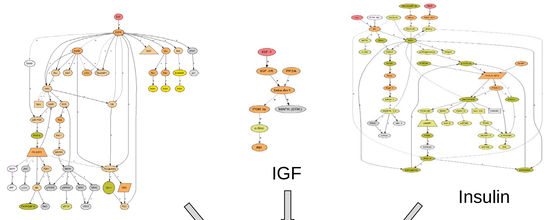
Background

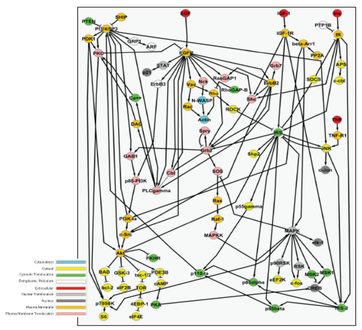
- Signaling pathways are not isolated information highways, but rather interact in a number of ways forming crosstalk
- Defects in signaling pathways are associated with cancer, understanding of the crosstalk between them is fundamental for designing molecularly targeted therapy
- Most models require kinetic parameters, which may not be available for newly discovered pathways; thus qualitative parameter-free models are needed

Our Contributions

- Propose a simple parameter-free model based on Boolean Network
- Two measures to prioritize molecules important for crosstalk
- Dynamic simulation to predict causal relations between signal receptors and downstream proteins
- Experimental verification of computational prediction

Step I: Building Network



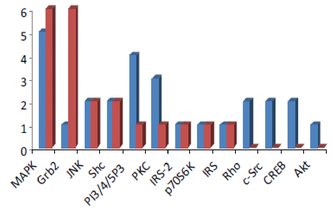


Signaling network combining EGF, IGF, and Insulin signaling pathways from STKE:
www.stke.sciencemag.org/cgi/collection/canonical_pathways

Step II: Static Analysis

Network crosstalk of a node is the difference in the degree of the node in the network containing all considered pathways and the maximum degree of this node in any one individual pathway. A high network crosstalk value implied that a node is a connecting node between two or more pathways.

Path crosstalk of a node is the difference between its signal-flow centrality for the entire network and its maximum signal-flow centrality in any one individual pathway. A high path crosstalk value implied that a node is more important in the combined network than it was in the individual pathways.



The network crosstalk (red) and path crosstalk (blue) values for all the signaling molecules in the network which have non-zero network crosstalk values.

Step III: Dynamic Simulation

Model of Boolean Network

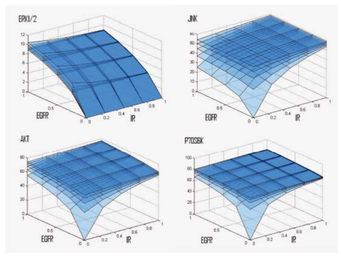
- A directed graph
- Nodes are elements (genes, proteins)
- Edges are interactions (phosphorylation)
- At each time, state of a node is determined by the states of upstream neighbors (activating or blocking) via a transfer logical function

Our Simulation Algorithm

- Edge weight between 0 and 1, representing efficiency of signal passing an edge
- Iteratively update state of a node *u* via:

$$X(t) = X(t-1) + [\,1 - \Pi(1 - Ai)\,] \times \Pi(1 - Bj) \times [1 - X(t-1)],$$

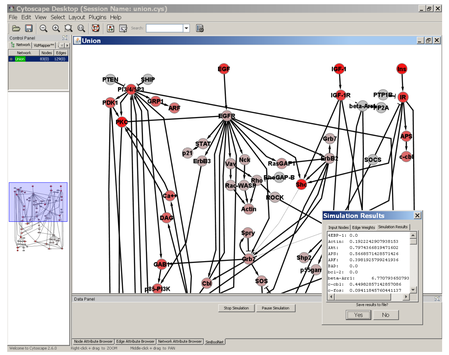
where $X(t)$ is the activities of *u* at time *t*, and Ai (Bj) are weighted signals from activating (blocking) upstream neighbors



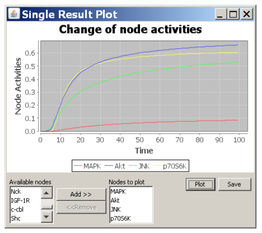
Results of dynamic simulations. X and Y axes are levels of EGF and IR; each layer on the graph is a different level of activation of IGF-1R, with top layers corresponding to higher IGF-1R activities. Z-axis is level of a downstream molecule.

SimBoolNet

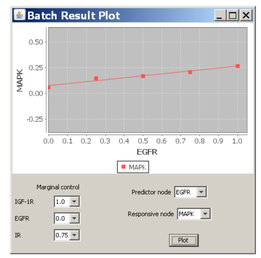
- An open source plugin of Cytoscape
- Single and batch-mode simulations (below)
- Results can be saved for further analysis
- Java source code & user manual freely available at:
http://www.ncbi.nlm.nih.gov/CBBresearch/Przytycka/SimBoolNet/



Single and Batch-mode Simulations

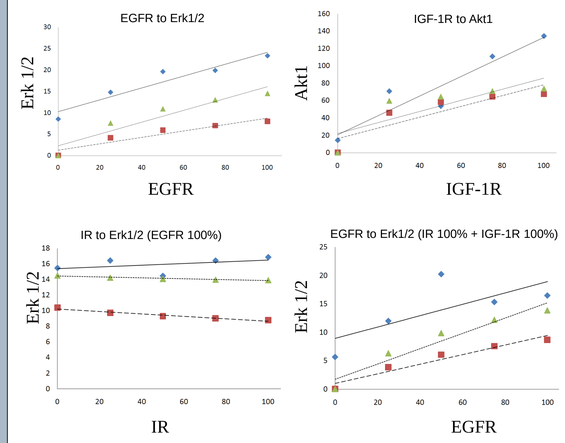


Single-mode:
- Users specify input activities to signal receptors
- Process of node changes is visualized by animated change of node colors
- Time series of node changes (left side)



Batch-mode:
- Multiple single-mode runs
- Different combinations of input nodes activities
- A scatter plot with a regression line between an input node and a downstream node, when activities of other input nodes are fixed
- Useful to study causal relation and crosstalk

Step IV: Experimental Verification



Comparison between experimental and simulated data. In each figure, blue diamonds represent real data; green triangles represent the results of simulation, where we set weights of both activation and blockage edges to 0.8; red squares represent the data of simulation, where we set weights of activation edges to 0.8 and blockage edges to 0.5.

Conclusions

- Simple qualitative models based on Boolean Network can be used to simulate the dynamics in signaling pathways with crosstalk
- SimBoolNet is a promising tool to facilitate experimental studies of signaling networks, and generating hypothesis of causal relations among signaling molecules

Acknowledgement

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