Network Legos: Building Blocks of Cellular Wiring Diagrams

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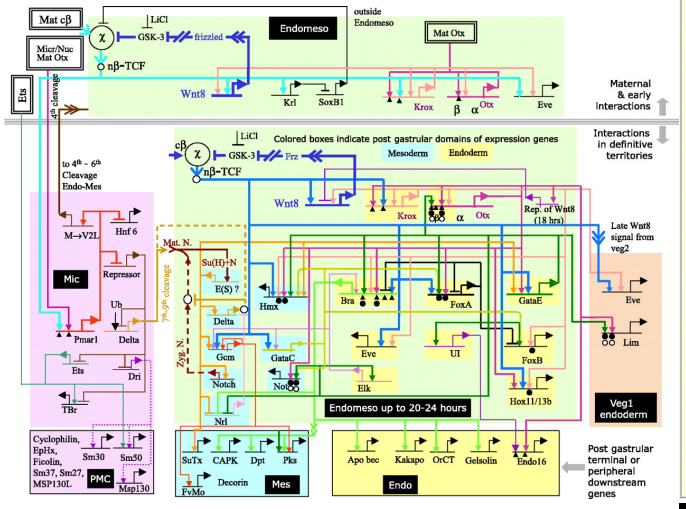
Goals of Systems Biology

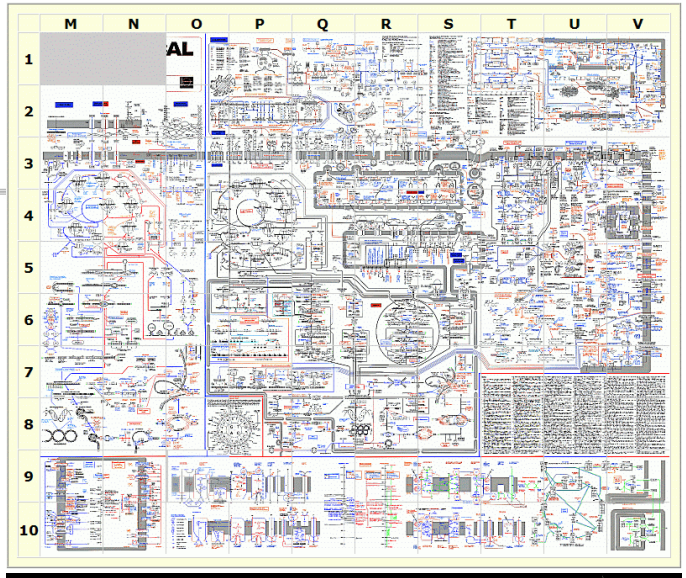
- Identify the building blocks of molecular interaction networks
- Interconnect the building blocks to build high level models of the cell
- Understand the interaction of the building blocks over time and under different conditions

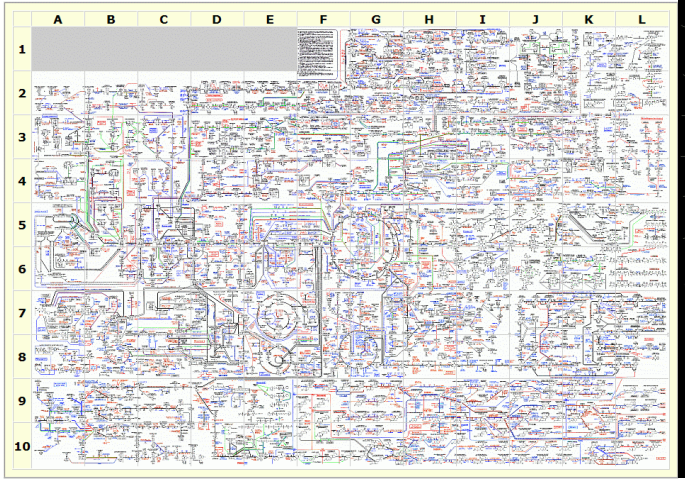
Goals of Systems Biology

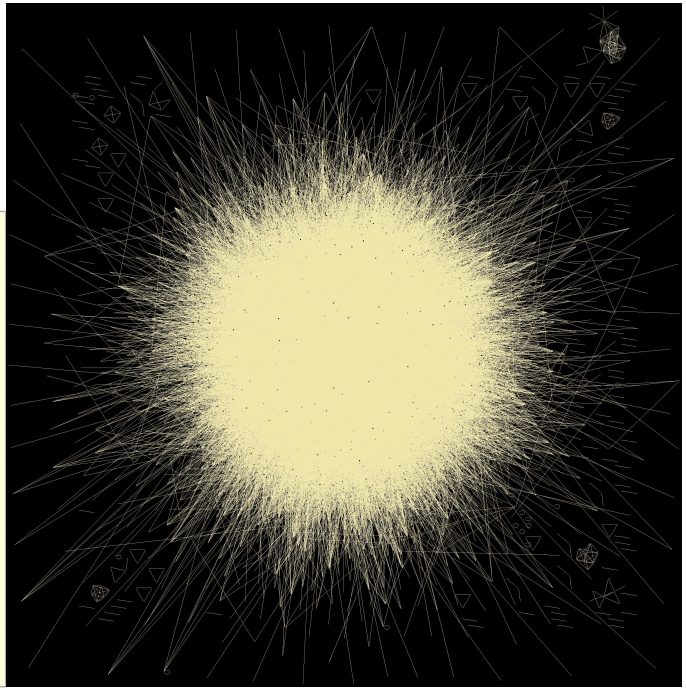
- Identify the building blocks of molecular interaction networks
- Interconnect the building blocks to build high level models of the cell
- Understand the interaction of the building blocks over time and under different conditions
- How do we automatically construct these building blocks?

Cellular Wiring Diagrams

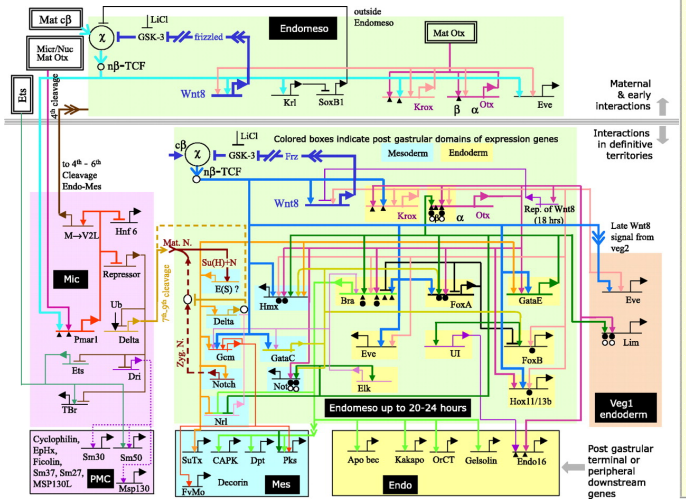


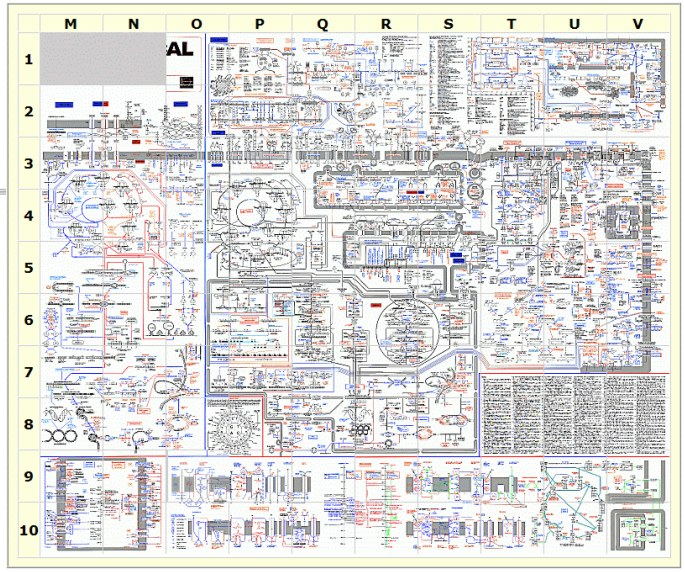


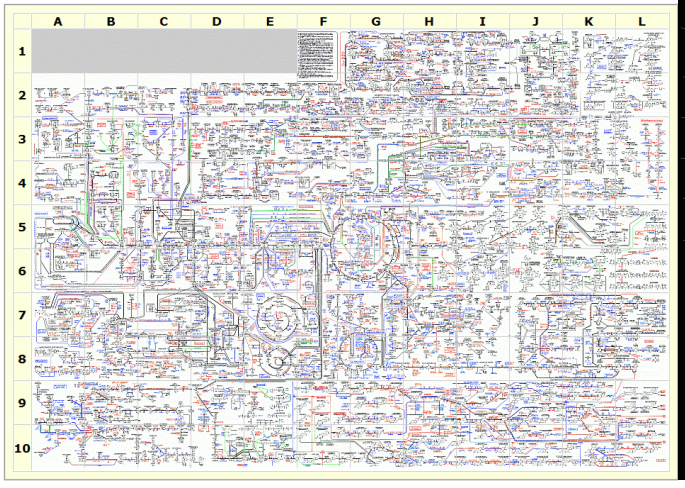


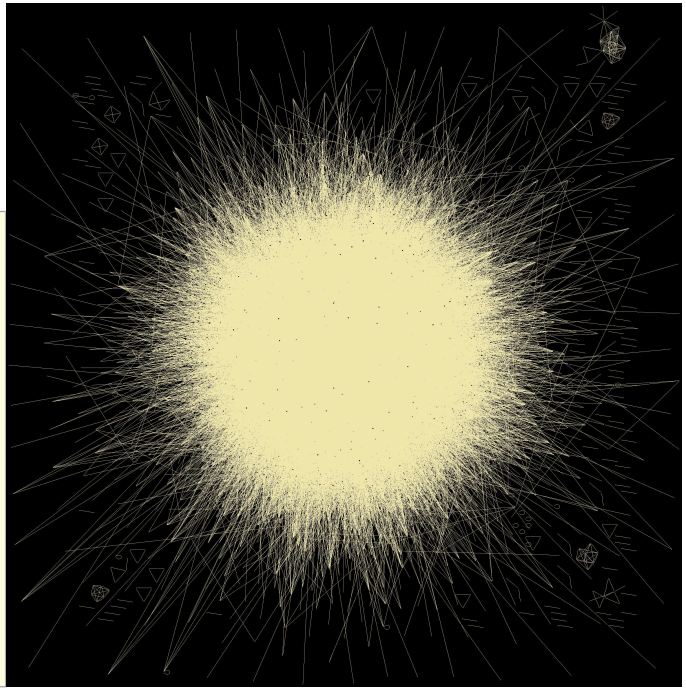


Cellular Wiring Diagrams









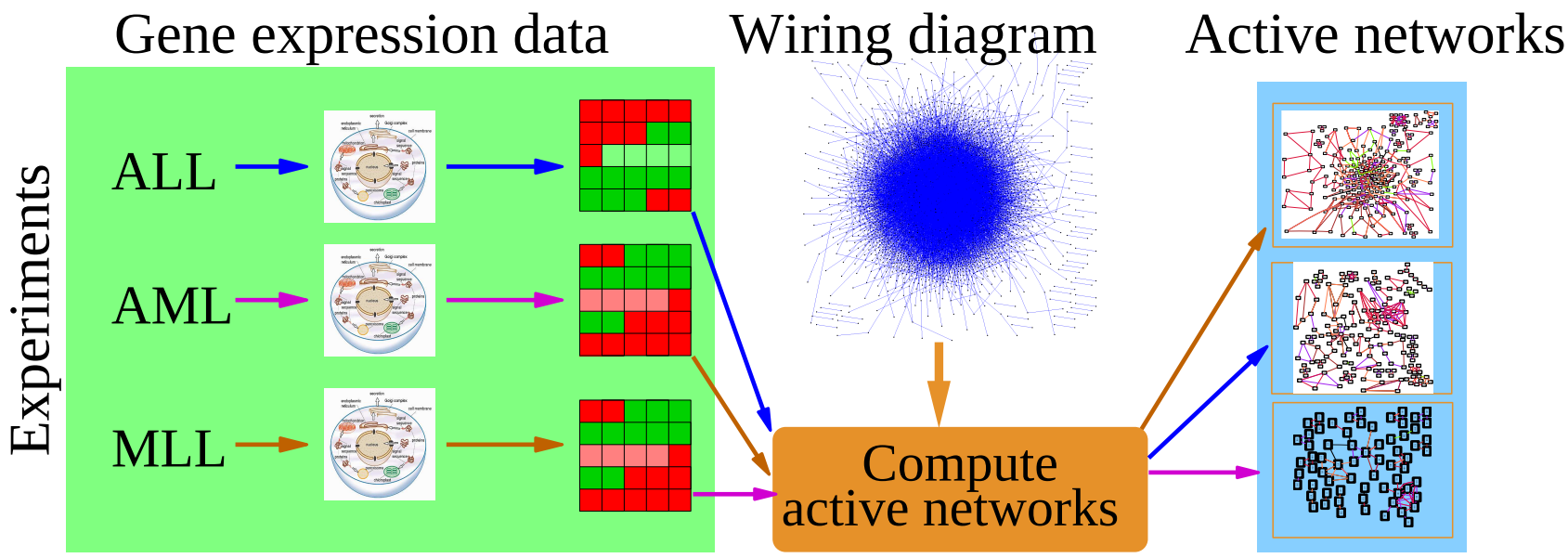
- These wiring diagrams are static.

Cell State is Dynamic

- Active molecular interactions change with time, external signals, and perturbations.
- We need to integrate wiring diagram with other types of data to compute the cell's response to different conditions.

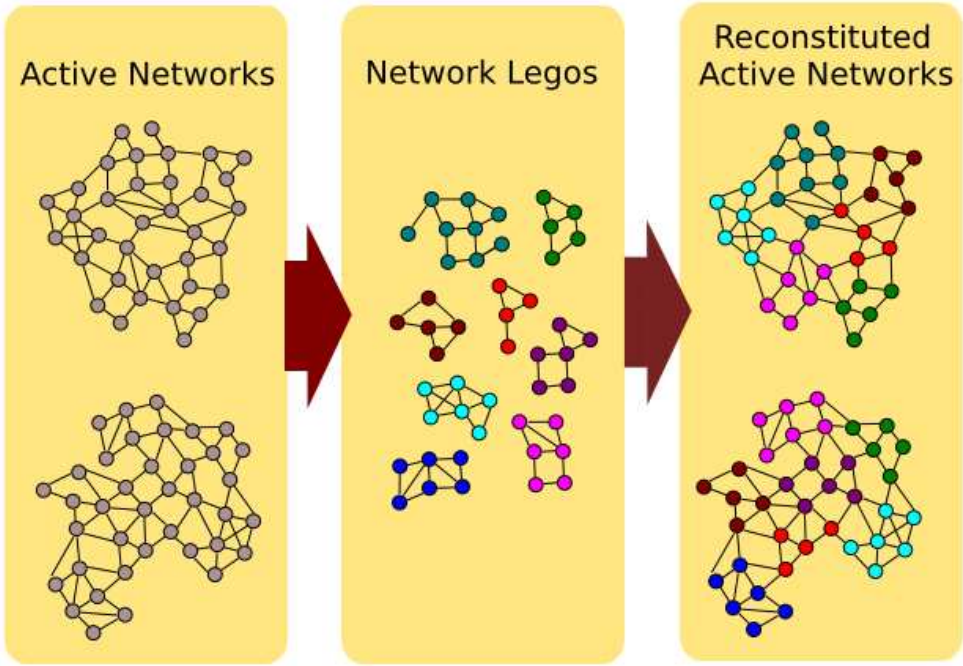
Active Networks

- Transcriptional regulatory measurements provide dynamic snapshots of cellular activity.
- *Active networks*: Molecular interactions activated by the cell in response to a stimulus.
- Methods to integrate wiring diagram with transcriptional measurements to compute response networks:
  - Ideker et al., Bioinformatics 2002
  - Luscombe et al., Nature 2004
  - Han et al., Nature 2004
  - Ulitsky and Shamir, BMC Sys Bio 2007

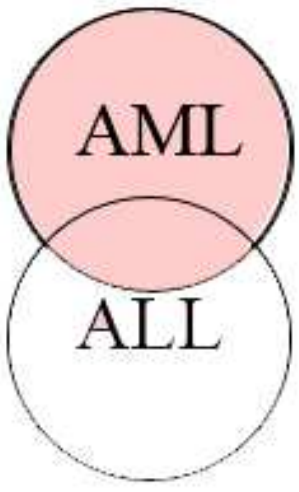


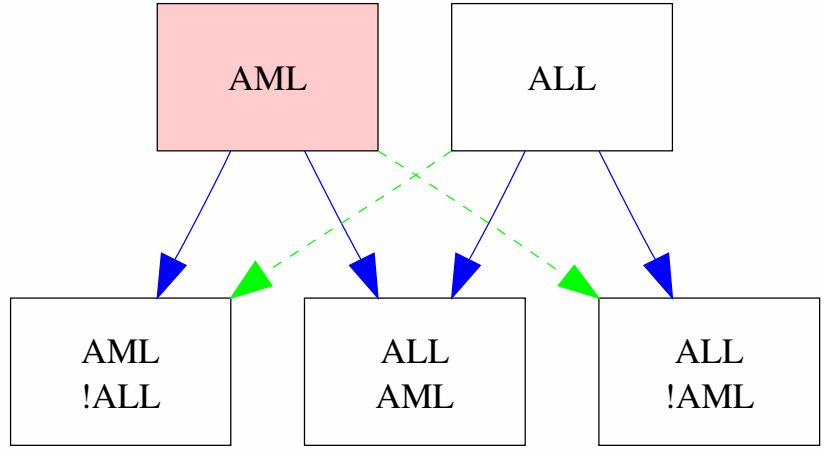
Goals of the Network Lego Approach

- What are the similarities and differences between active networks?
- Can we identify building blocks or network legos that constitute each of the active networks?



Comparing Two Active Networks





AML

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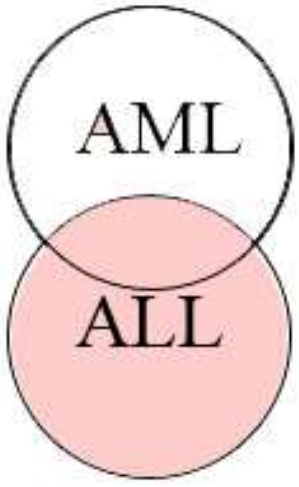

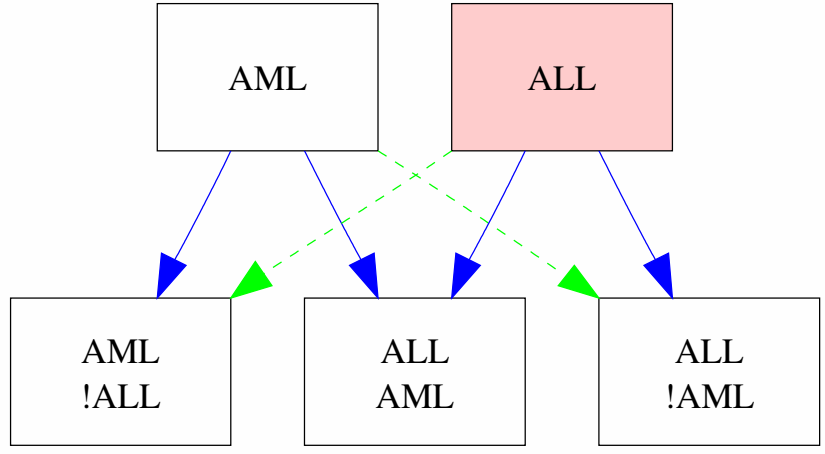

ALL

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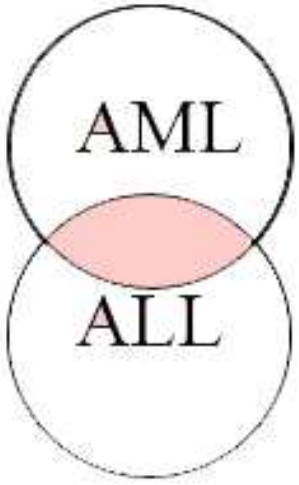

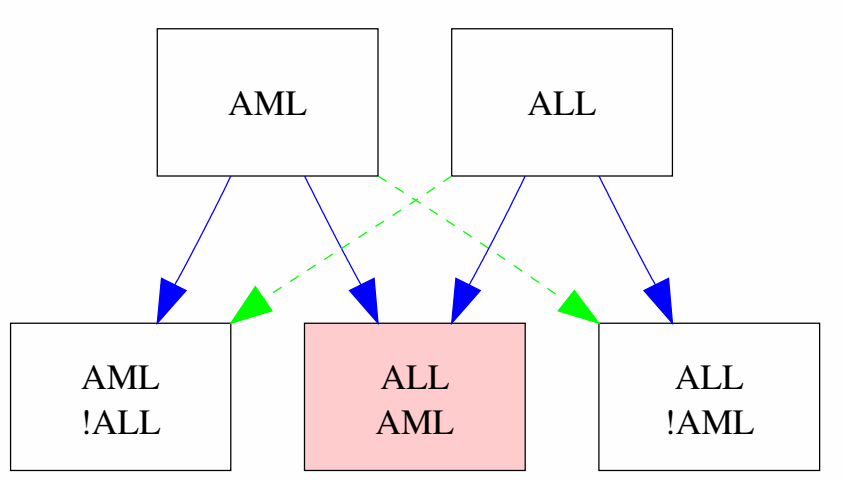

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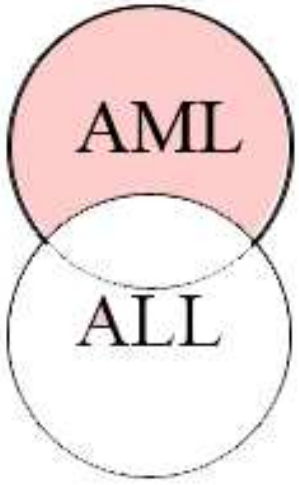

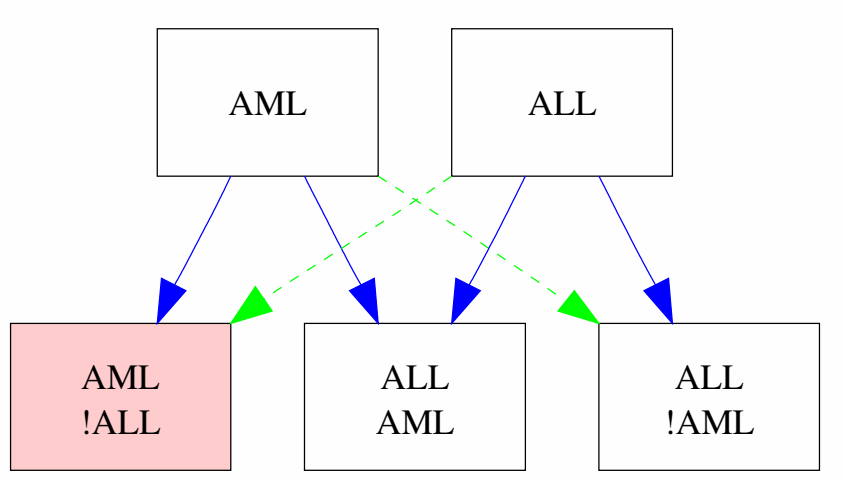

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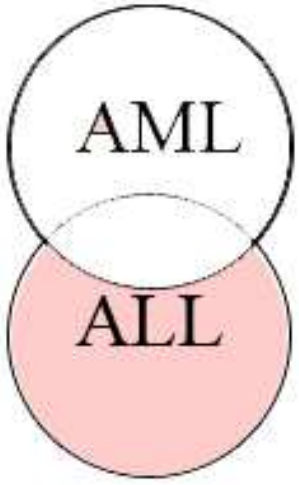

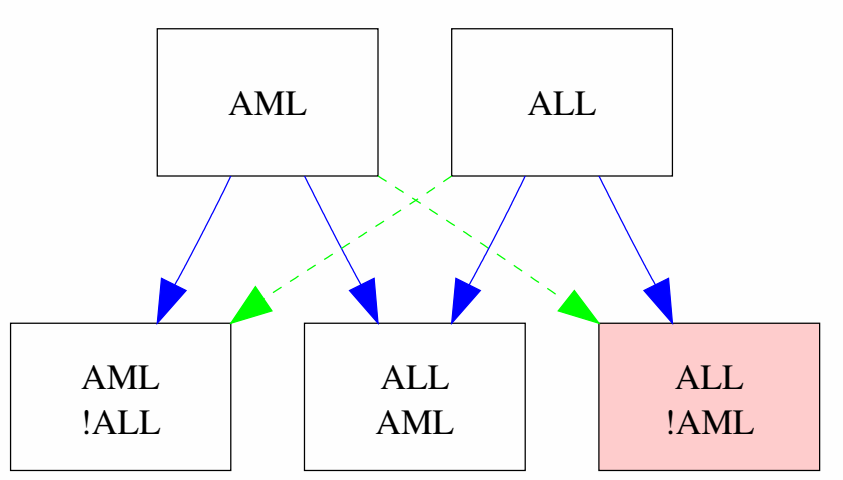

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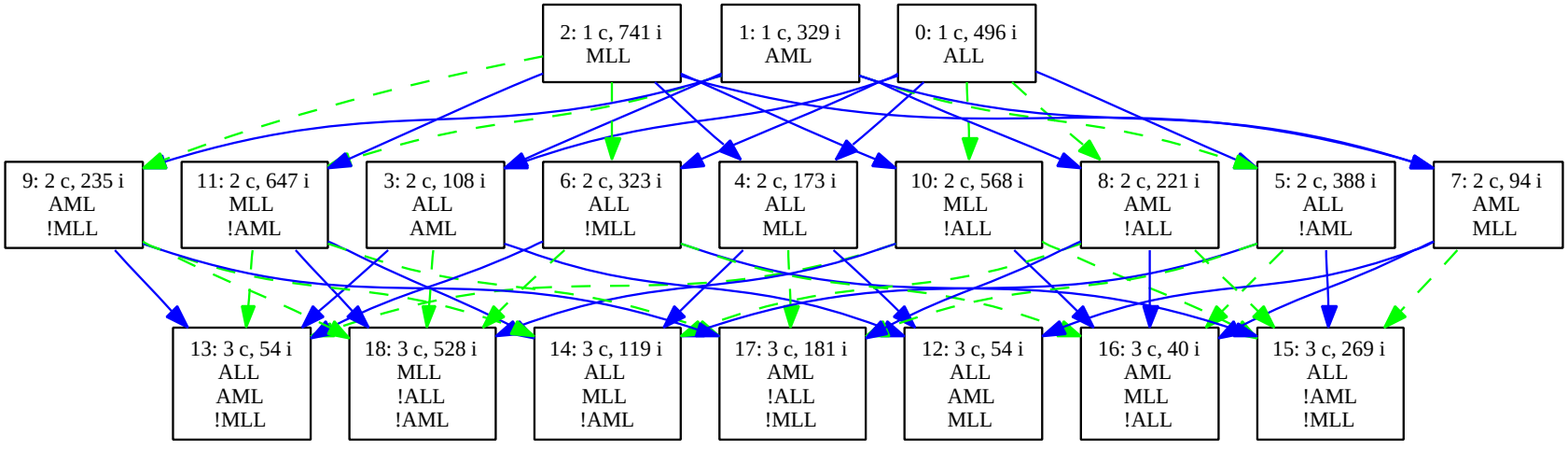
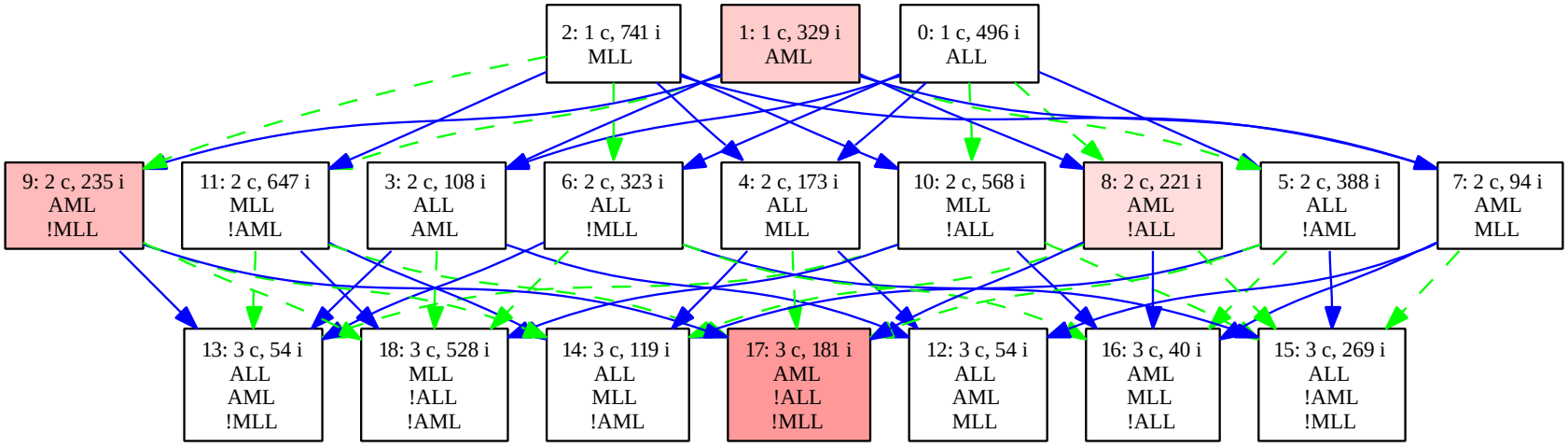
Comparing Three Active Networks

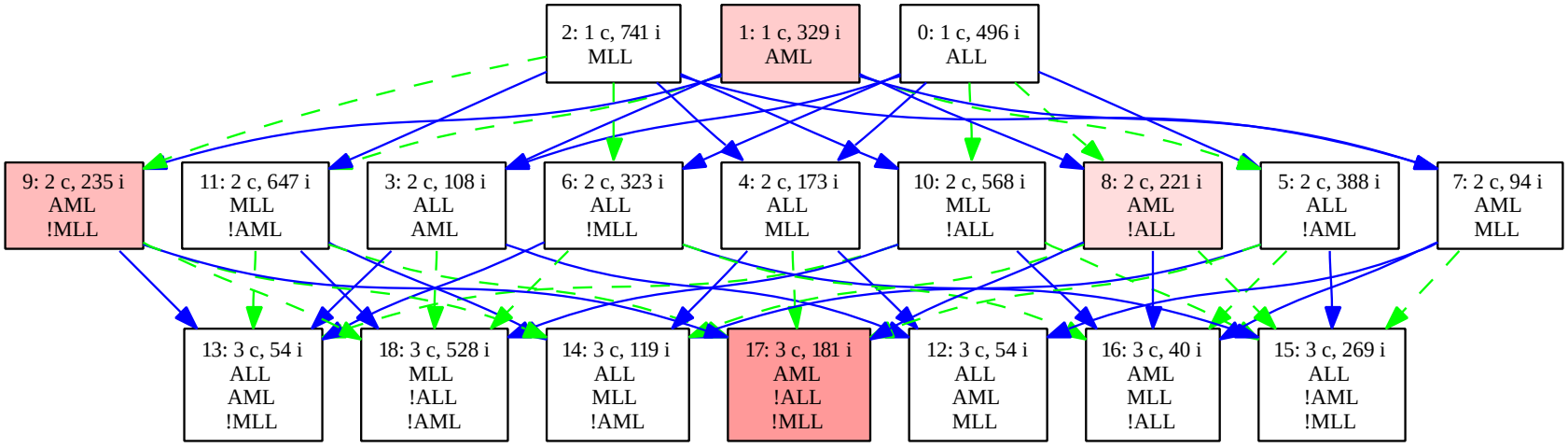


Differential Activation of the Kit Receptor Pathway in AML



- AML: p-value 2×10^{-4}
- AML $\cap$!ALL: p-value 1×10^{-3}
- AML $\cap$!MLL: p-value 6.7×10^{-5}
- AML $\cap$!ALL $\cap$!MLL: p-value 3.5×10^{-7}

Differential Activation of the Kit Receptor Pathway in AML



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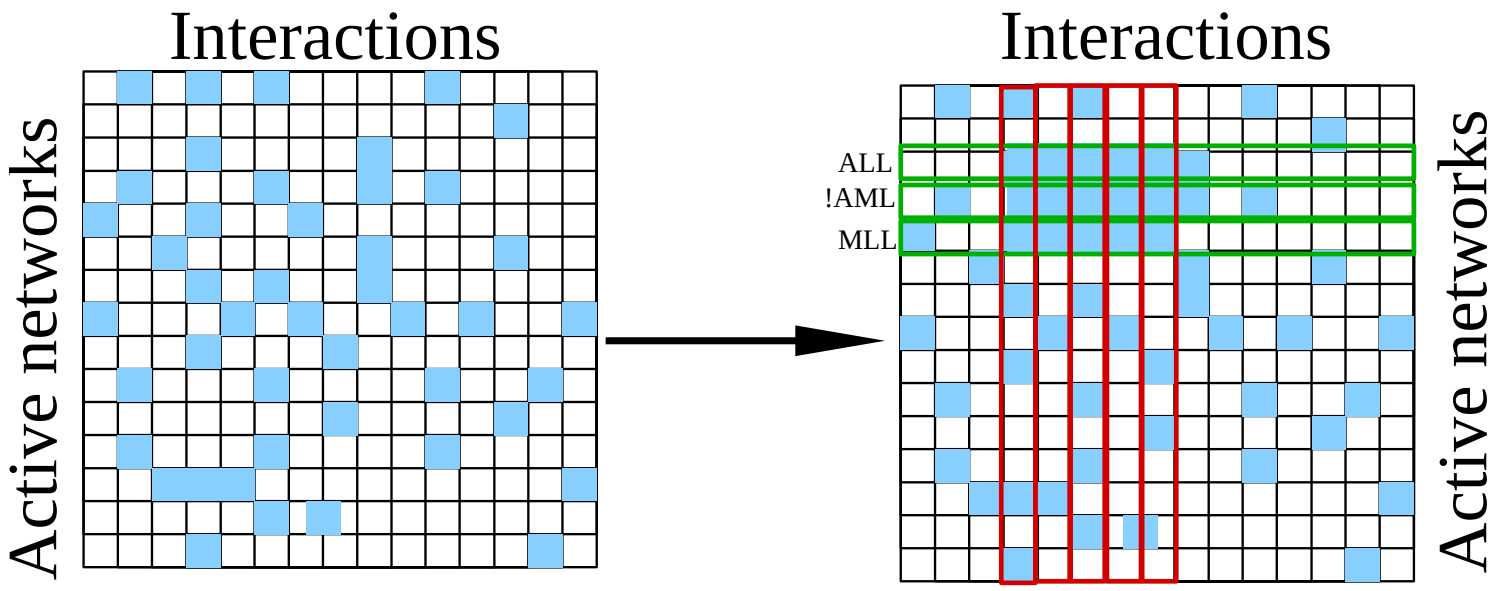
- c-KIT receptor is activated in almost all subtypes of AML but not in ALL (Reuss-Borst et al., *Leukemia*, 1994, Bene et al., *Blood*, 1998, Schwartz et al., *Leuk Lymphoma.*, 1999).

Challenges in Comparing Arbitrary Numbers of Active Networks

- How to do we efficiently compute all combinations?
- Which combinations are the network legos?
- How do we demonstrate that we have found network legos?

How to do we efficiently compute all combinations?

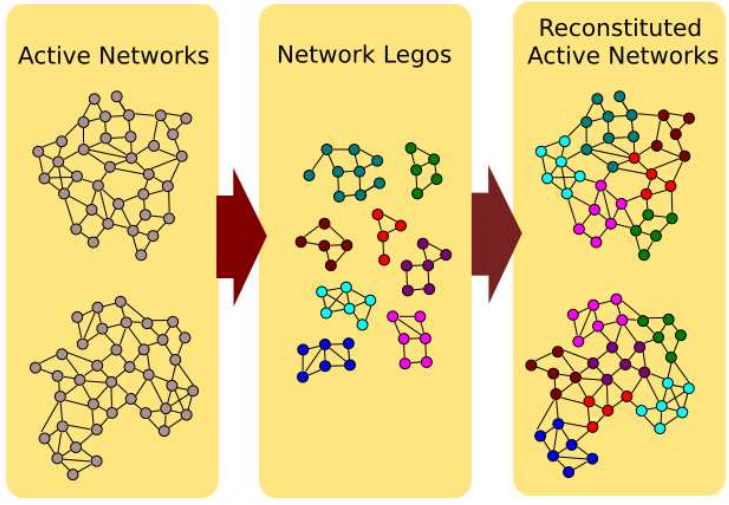


- Construct a binary matrix M whose columns are interactions.
- Represent each active network and its complement in M's rows.
- Compute all closed biclusters in M.
- Connect biclusters in a DAG.

Which combinations are the network legos?

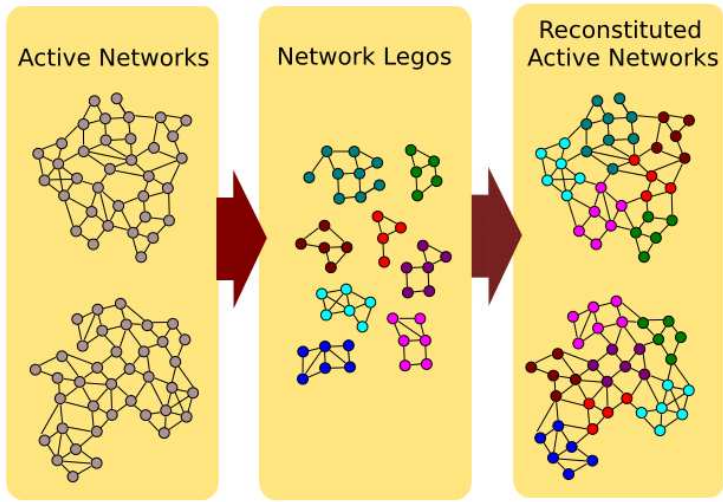
- For each bicluster B with n non-complemented and c complemented active networks
  1. Pick n non-complemented and c complemented active networks repeatedly at random, compute the number of interactions induced by this combination, and build a distribution of the number of interactions.
  2. Set the p-value of B to be the fraction of random biclusters with more interactions than B.
- B is a *network lego* if it is more significant than any of its ancestors or descendants in the DAG.

How do we demonstrate that we have found network legos?



- Stability
  - Sequentially remove each active network from the input and recompute network legos.
  - For each original network lego, compute the fraction of leave one out datasets for which the network lego occurs with at least 95% fidelity.

How do we demonstrate that we have found network legos?



- Stability
  - Sequentially remove each active network from the input and recompute network legos.
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- Recoverability
  - Compute the union of network legos.
  - Measure the size of the intersection of each active network with this union.

Analysis of Human Stress Data

- 13 distinct stresses applied to human cells (Murray et al., Mol. Bio. Cell, 2004).
- Stress conditions include heat shock, oxidative stress, cell cycle arrest, and crowding.
- Two cell types: WI38 Fibroblasts and Hela.
- Murray et al. note that each stress elucidated a unique response.

Human Stress Results

- 13 stresses and their active networks yielded 444201 closed biclusters.
- 143 biclusters are network legos.
- The network legos contained between 165 and 1148 proteins.
- The network legos have 95% stability.
- The network legos provide better than 86% recoverability for all active networks.
- We recovered 11 active networks at 100%.

#conditions	5	6	7	8	9	10	11	12
#legos	1	6	10	36	34	20	28	8

Human Stress Results without Cell Cycle Arrest Treatment

- The response networks for cell cycle arrest treatments contain interactions that are distinct compared to the interaction from other treatments.
- 11 stresses yielded only 15 network legos.
- The network legos provide better than 71% recoverability for all active networks.
- We recovered five active networks at 100%.
- Each formula contained at least 7 active networks

WI38 Menadione and WI38 DTT Network Lego

- One network lego contained endoplasmic reticulum stress and oxidative stress to fibroblasts in non-complemented form.
- All other stresses appeared in complemented form.
- This network lego is the only one enriched in functions related to the cell cycle and targets of the E2F1 transcription factor.
- Fibroblasts respond differently from HeLa cells to these two stresses.

Our Contributions

- Combined representation of biological processes using formulae and network legos.
- A formula relates different cellular states or perturbations by explicitly denoting their participation via intersections and complements.
- Each network lego corresponds to a functional module of coherently interacting genes in the universal network.
- Network legos serve as building blocks of active networks.

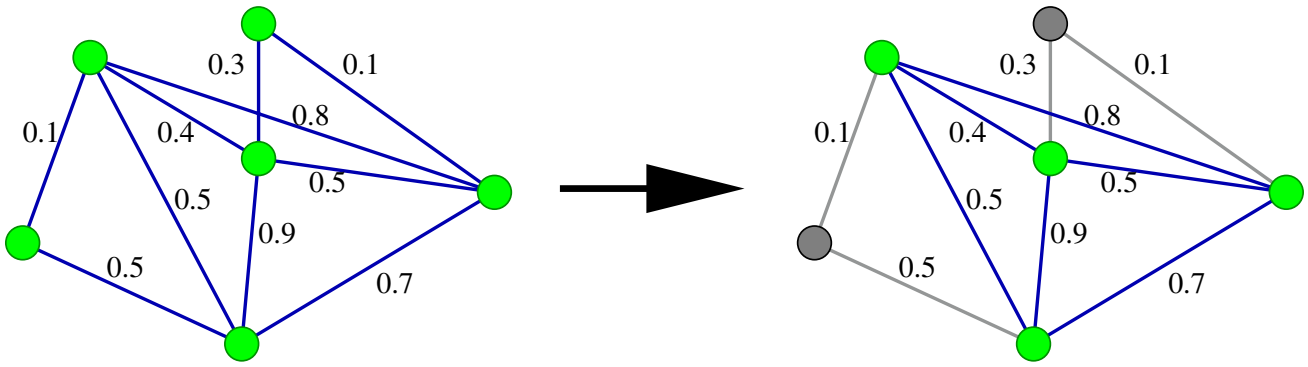
Future Work

- Explore network legos in the context of a larger compendium of cellular stresses.
- Develop an algorithm to directly compute network legos without searching the space of all active network combinations.
- Determine rules and grammar for combining network legos into active networks.

Algorithmic Ingredients: Active Networks

(i) Assign Pearson's correlation
as the interaction weight

(ii) Compute dense subgraphs



- Compute the Pearson's correlation coefficient of the expression profiles of the interacting genes.
- Search for pockets of concerted activity using an algorithm for finding dense subgraphs.