Aspects of analysis

Focus on size of attractors and basins of attraction, number of attractors, stability

Impact of K (averaged)

$K = N$:
- ▷ network is complete graph, successor states chosen at random
- ▷ attractors can be very large (exponential in N), number of attractors of order N, maximal sensitivity to intial conditions (chaotic)

$K = 1$:
- ▷ structure decomposes into simpe cycles with tails, behavior determined by constant functions and cycles (product of subsystems)
- ▷ attractor number exponential in N, attractor size of order N, limited effect of perturbations (ordered)

$K = 2$:
- ▷ variability in structure, canalyzing functions
- ▷ attractor number and size increases superpolynomial with N, good stability properties (critical)

Understanding RBNs yields insights into more complex real world networks

Reasons for order

Frozen core: set of "dynamically inactive" elements dividing the system into functionally isolated modules

- fixed value for large part of the dynamical behavior
- decision taking subnetworks
- combinatorial dynamics (attractors)
  - modularity allows for short cycle lengths ($K = 1$)
  - "walls of constancy" absorb perturbations ($K = 1$), restrict attractors reachable by mutations/noise
  - moderate number of attractors w.r.t. N due to big number of frozen elements

Observation: large connected frozen structure percolates spontaneously if $K = 2$

Canalyzing functions

Definition $f : \{0,1\}^n \to \{0,1\}$ is called *canalyzing (in i)*, if there is $i \in \{1,\ldots,n\}$ and $c, c' \in \{0,1\}$ such that $f(x) = c'$ for all $x \in \{0,1\}^n$ with $x_i = c$.
The input value c is called *canalyzing value*, and the output c' is called *canalyzed value*.

- elements regulated by canalyzing functions are insensitive to other regulator inputs in the presence of canalyzing value
- *forcing structures* can percolate through the network if canalyzing functions of several elements interlock:
  $A \to B$ with A, B regulated by canalyzing functions, and canalyzed value of A is canalyzing value of B (*forcing connection*)
- concepts of frozen core and canalyzing functions can be generalized for multi-valued functions.
- many biological functions are canalyzing

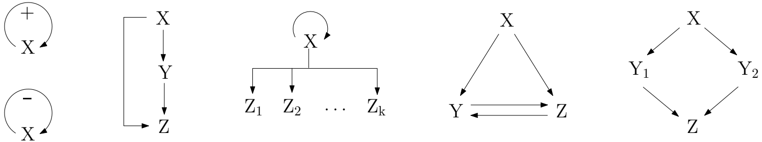
Structural modularity

Consider interaction graph $G(f) = (V, E)$ representing the network structure

- find modules based on graph theoretical criteria, shared expression pattern ...

▷ include statistical significance [U. Alon et al., Science, 2002]

  - recurring patterns of interconnections with significantly higher occurrence than in random networks (motifs)
  - sets of motifs of distinct networks may differ considerably
  - similar motifs in networks with similar function
    $\Rightarrow$ homologies, classification, comparison



Significance of motifs

- evaluating structural significance
  - pairwise disconnectivity index: importance of subgraph M for sustaining network connectivity [B. Goemann et al., 2009]:

    compare number of connected ordered pairs in G with number in $G \setminus M$

    check all (sets of) subgraphs of given size (motifs, anti-motifs)
    - ⋆ no correlation between abundance of pattern and topological significance
    - ⋆ topological role of substructures mainly determined by location/embedding

- evaluating functional significance
  - analyzing behavior of isolated motifs
    - ⋆ biological meaningful behavior (differentiation, oscillation, pulse, coordinated expression,...)
    - ⋆ not necessarily retrievable in complex system

Compositional dynamics

Consider disjoint modules

$G^1, \ldots, G^k$ interaction graphs associated with discrete functions $f^1, \ldots, f^k$ and state space X^i, $G := \bigcup_{i=1}^k G^k$, f derived from $f^1, \ldots, f^k$

- all attractors of (G, f) can be derived from products of attractors of (G^i, f^i), $i \in \{1, \ldots, k\}$
- asynchronous update
  - # attractors of (G, f) is the product of # attractors of (G^i, f^i)
  - cardinality of compositional attractor A is the product of the cardinalities of the component attractors
- synchronous update
  - # attractors of (G, f) depends on # of attractors of (G^i, f^i) as well as least common multiple and greatest common divisor of the component attractor lengths
  - maximal length of a compositional attractor is the maximum of the least common multiple of attractor lengths of component attractors

Non-isolated modules

Interacting modules

consider network (G, f) with associated state space $X = X_1 \times \cdots \times X_n$

- module attractors generally not preserved
- dynamics of the isolated module is not necessarily imprinted on network dynamics

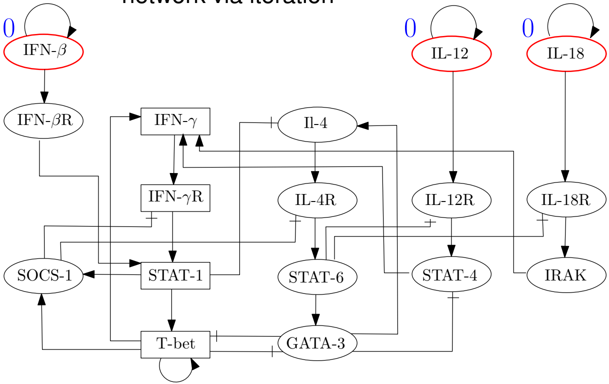
Recover isolation

- find partial fixed points, i. e. find $I \subset \{1, \ldots, n\}$ and $x_i \in X_i$ s. t. $f_i(y) = x_i$ for $i \in I \subset \{1, \ldots, n\}$ and all $y \in X$ with $y_i = x_i$ for all $i \in I$ (*frozen core*)
- consider part of state space $X[I, x_i] := \{y \in X \mid \forall i \in I : y_i = x_i\}$
- consider graph components $Z^1, \ldots, Z^k$ of the subgraph of G derived from the vertices $j \notin I$, and associated functions f^j derived by projection of $f|_{X[I,x_i]}$

$\Rightarrow$ all attractors in $X[I, x_i]$ can be derived from attractors of (Z_j, f^j)

Network analysis using modules – Th cell differentiation

- easy calculation of partial fixed points for networks with input layer
  - fix input values
  - constraint percolation through network via iteration



Complexity reduction

input $(0, 0, 0)$

- state space sizes: 82944 / 2592

[L. Mendoza, Biosystems 84(2), 2006]

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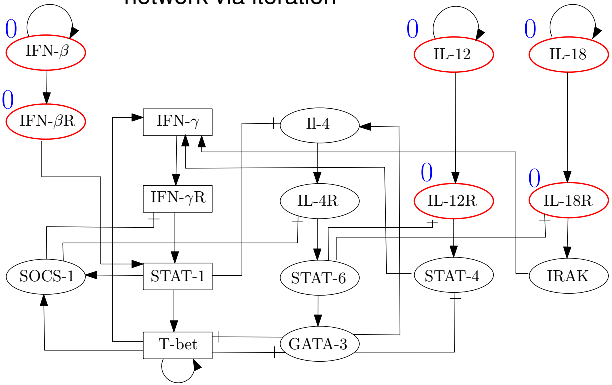

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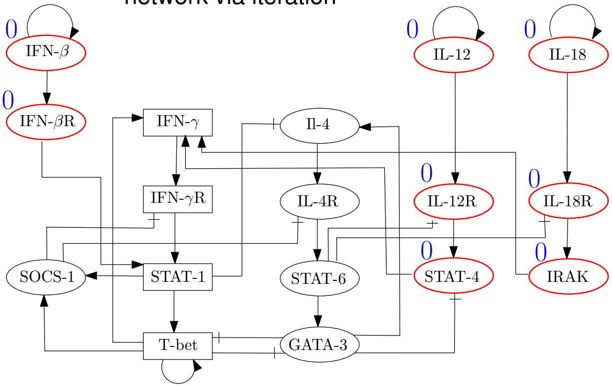

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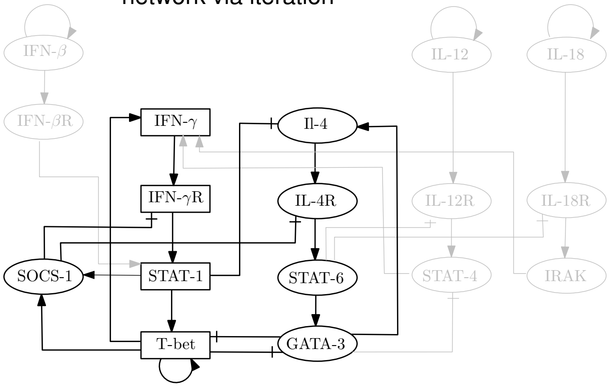

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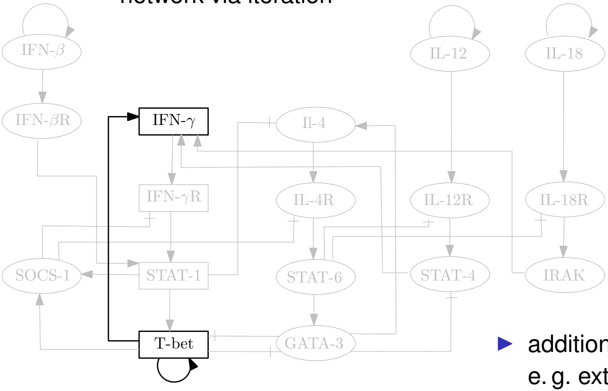

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Complexity reduction

input $(0, 0, 0)$

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input $(1, 0, 0)$

- state space sizes: 82944 / 4

- additional information, e. g. extent of crosstalk, linking structural and dynamical aspects

Transfer of characteristics

- isolated modules may imprint qualitative characteristics on the network
- isolation in parts of state space may be sufficient
- example: positive and negative circuits
  - isolated circuits show distinct behavior:
    $\star$ positive circuits induce multiple attractors
    $\star$ negative circuits induce cyclic attractors (cardinality >1)
    note differences for synchronous and asynchronous update
  - check characteristics for complex networks containing circuits
    $\Rightarrow$ characteristics are conserved for circuits in "conditional" isolation (compositional properties)

Exploiting modularity

- reduce network complexity
- understand design principles