Dynamics

Given $f : \{0,1\}^n \to \{0,1\}^n$

State tranistion graph $S(f)$ of f

- vertex set $\{0,1\}^n$ (state space)
- edge set $\{(x, f(x)) \mid x \in \{0,1\}^n\}$ – synchronous update

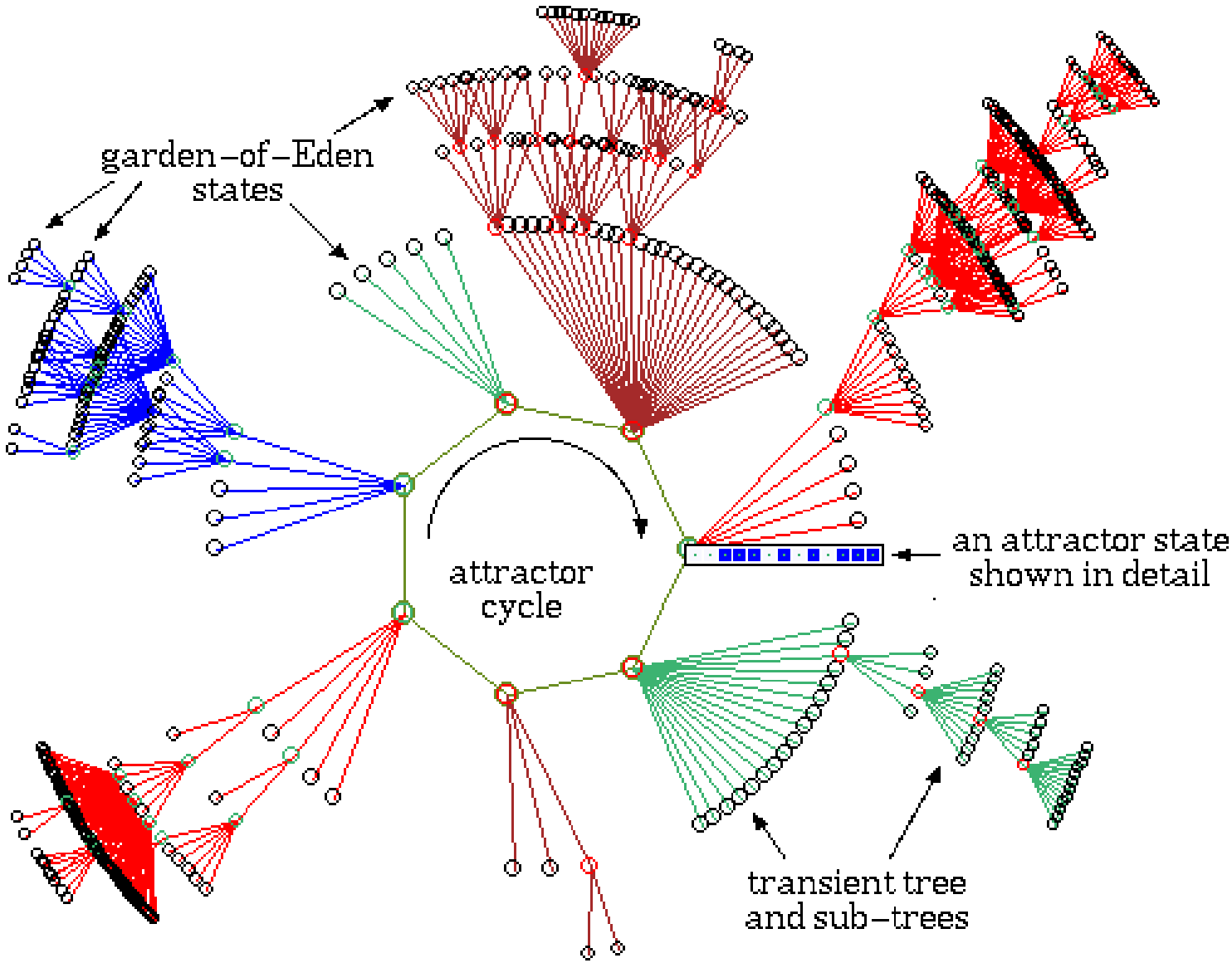
Trajectories: infinite paths $(x(0), x(1), \dots)$ in $S(f)$ (simulation)

Note: conceptual differences to ODE/PLDE description

- explicit description of trajectories
- trajectories can merge

Consequences of synchronous update and finite state space

- deterministic behavior
- each trajectory ends in a cycle
- components of $S(f)$ consist of single cycle and attached trees



Andy Wuensche, www.ddlab.com

Attractors

Given state transistion graph $S(f)$

Definition A set A of vertices (states) of $S(f)$ is called trap set, if no trajectory starting in A can leave A. If in addition A is strongly connected, then A is called attractor.

- attractors are terminal strongly connected components
- attractors are fixed points and periodic points
- every trajectory leads to an attractor (basins of attraction)
- distinct attractors are disjoint
- asymptotical behavior (biological meaningful)

Perturbations

Minimal perturbation (noise): transiently flipping the value of a component

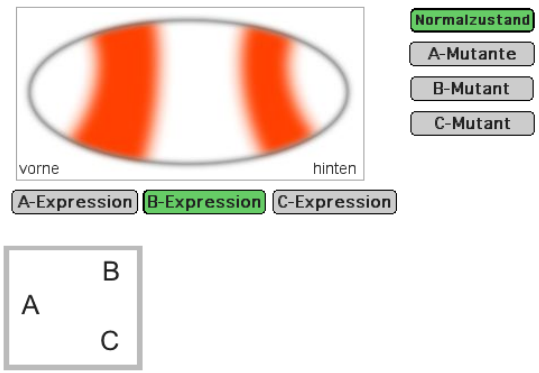
- comparison of different initial conditions
- how does the change cascade through the network?
- change in basin of attraction/attractor

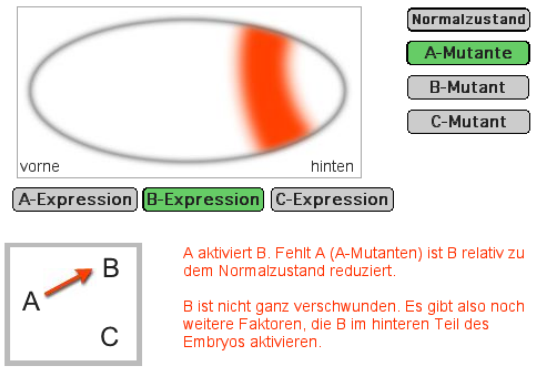
Structural perturbation (mutation): permanently changing a coordinate function f_i

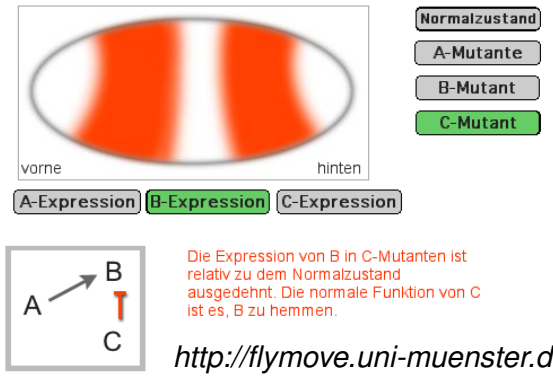
- comparison of two different networks
- attractors, basins of attraction, stability,...

Network Inference - Reverse Engineering

- analyzing binding sites and mutants







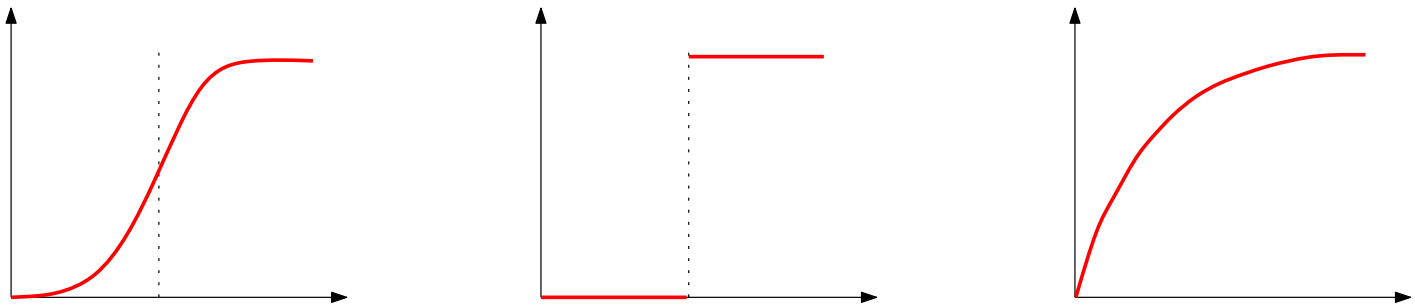
http://flymove.uni-muenster.de/

- time series data
  - data discretization
  - often many admissible models

Inferring interaction graphs: Given a function $f : \{0,1\}^n \longrightarrow \{0,1\}^n$, we can derive an interactions graph consisting of functional edges in agreement with the dynamics determined by f by using the previously introduced formulas describing functionality of edges and sign consistency.

Being Aware of the Level of Abstraction

- omitting components, simplifying processes
- logical idealization of regulatory interactions



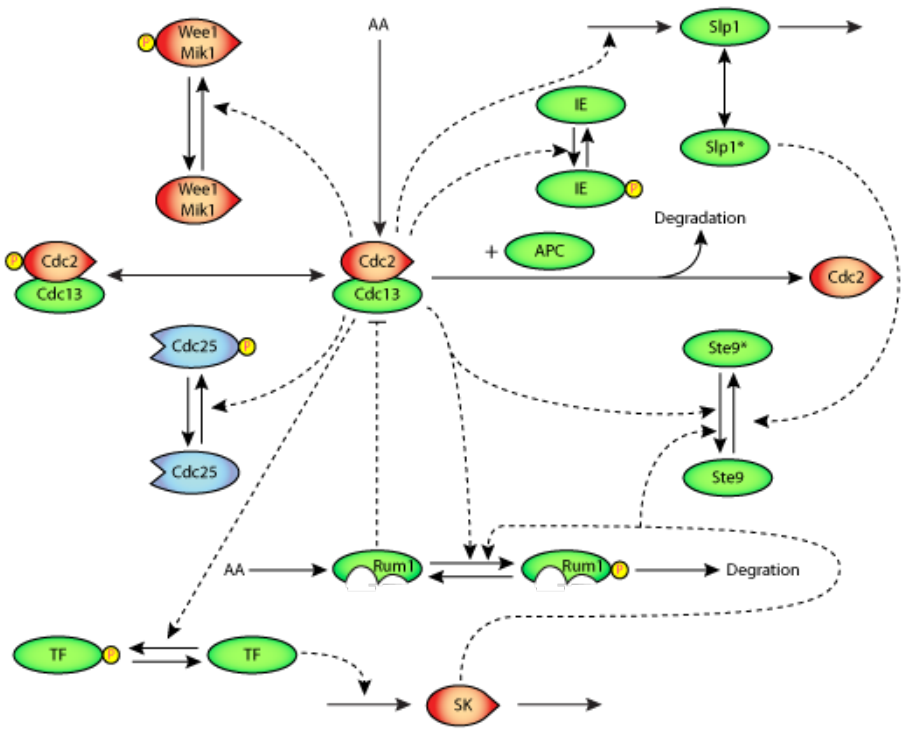
- all or nothing functionality
- ignoring spatial and temporal data

Cell cycle of fission yeast

M. Davidich, S. Bornholdt, *Boolean network model predicts cell cycle sequence of fission yeast*, PLoS ONE 3(2): e1672, 2008

Aim: recover cell cycle sequence of *S. pombe* from Boolean model based only on known biochemical interaction topology

$\Rightarrow$ functional robustness of the topology



Structure

vertices: components (Rum1, Ste9, Slp1, PP, Cdc25), groups of components (Wee1/Mik1, SK), complexes in different states (Cdc2/Cdc13, Cdc2/Cdc13*), indicator of cell mass (Start)

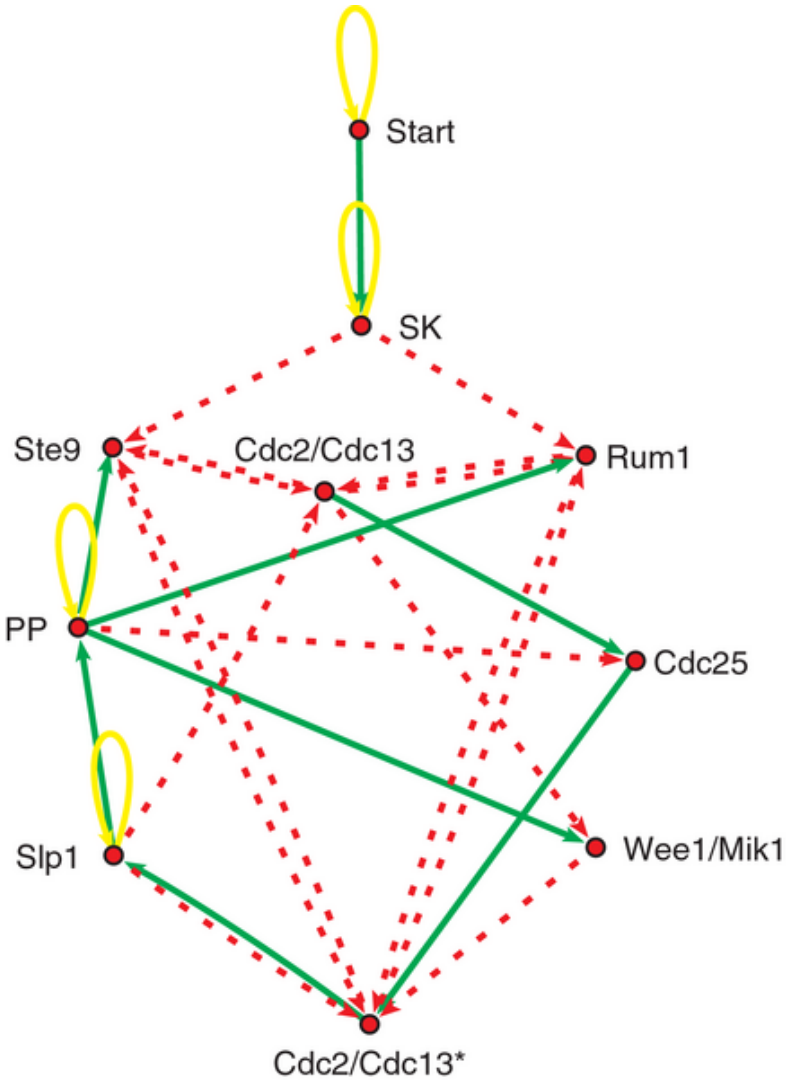
edges: (de)phosphorylation, complex formation, degradation,...

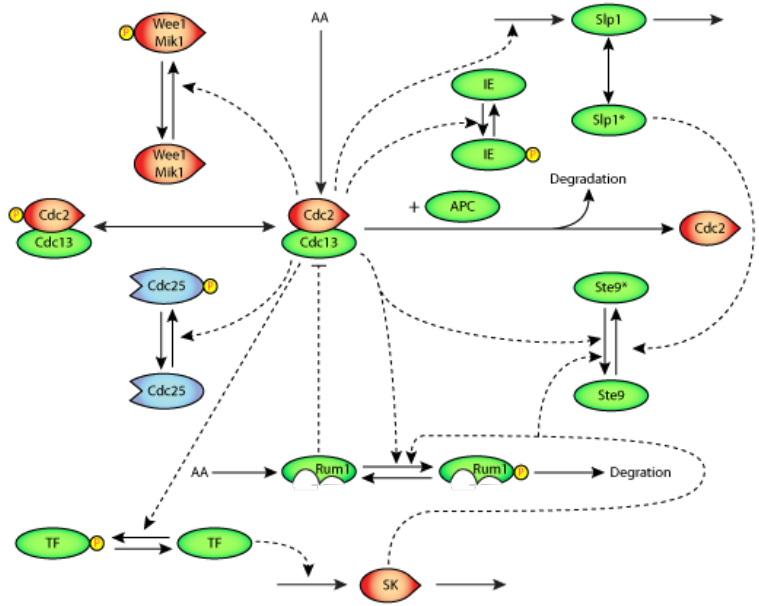
Network components and interactions

Table 1. The rules of interaction of the main elements involved in the fission yeast cell cycle regulation.

Parent node	Daughter node	Rule of activation (comments)	Rule of inhibition (comments)
Start node	Starter Kinases (SK): Cdc2/Cig1, Cdc2/Cig2, Cdc2/Puc1	Start node works as an indicator of mass of the cell and activates Start Kinases (SK) Cdc2/Cig1, Cdc2/Cig2, Cdc2/Puc1, +1[9]	
SK	Ste9, Rum1		Phosphorylate, thereby inactivate, −1 [9,25]
Cdc2/Cdc13	Cdc25	Cdc25 is phosphorylated thereby activated, +1 [9].	
Wee1, Mik1	Cdc2/Cdc13*		Phosphorylate, inactivating, −1 [9]
Rum1	Cdc2/Cdc13, Cdc2/Cdc13*		Binds and inhibits activity, −1 [9].
Cdc2/Cdc13	Rum1		Phosphorylates and thereby targets Rum1 for degradation. −1 [9,25]
Ste9	Cdc2/Cdc13, Cdc2/Cdc13*		Labels Cdc13 for degradation [25,9], −1.
Cdc2/Cdc13*	Slp1	Highly activated Cdc2/Cdc13* activates Slp1, [24,9] +1.	
Slp1	Cdc2/Cdc13, Cdc2/Cdc13*		Promotes degradation of Cdc13, thereby the activity of Cdc2/Cdc13 drops −1 [9]
Slp1	PP	Activates, +1 [9]	
PP (Unknown phosphatase)	Ste9, Rum1, Wee1, Mik1	Activates Rum1, Ste9, and the tyrosine-modifying enzymes (Wee1, Mik1) [9], +1	
Cdc25	Cdc2/Cdc13*	Cdc25 reverses phosphorylation of Cdc2, thereby Cdc2/Cdc13* becomes active, +1 [9,24]	
Cdc2/Cdc13	Ste9		inhibits −1 [24]
PP	Cdc25		inhibits −1 [9]
Cdc2/Cdc13	Wee1, Mik1		inhibits −1 [24]
Cdc2/Cdc13*	Rum1, Ste9		Inhibits −1 [24]

Interaction graph





- Cdc2/Cdc13* represents Cdc2/Cdc13 in its highly activated form
- positive/negative interactions according to preceding table
- add degradation (yellow loops) to nodes without negative regulation
  why not to all nodes?

Boolean function

Define $f = (f_1, \ldots, f_{10}) : \{0,1\}^{10} \to \{0,1\}^{10}$,

$$f_i(x) := \begin{cases} 1 & , \quad \sum_j \varepsilon_{ji} x_j > \theta_i \\ 0 & , \quad \sum_j \varepsilon_{ji} x_j < \theta_i \\ x_i & , \quad \sum_j \varepsilon_{ji} x_j = \theta_i \end{cases},$$

with $\varepsilon_{ji} \in \{-1, 0, +1\}$ according to the sign of $j \to i$, and i-th component activation threshold $\theta_i = 0$ with two exceptions:

- Cdc2/Cdc13* threshold =1
  needs to be actively maintained by positive regulation
- Cdc2/Cdc13 threshold =-1
  no positive regulators, constant synthesis of Cdc13, stable concentration of Cdc2

Derive synchronous state transition graph from f

- no quantification of interaction strengths
- no distinction between different time scales

  no parameters, no temporal assumptions?

Dynamics - simulation

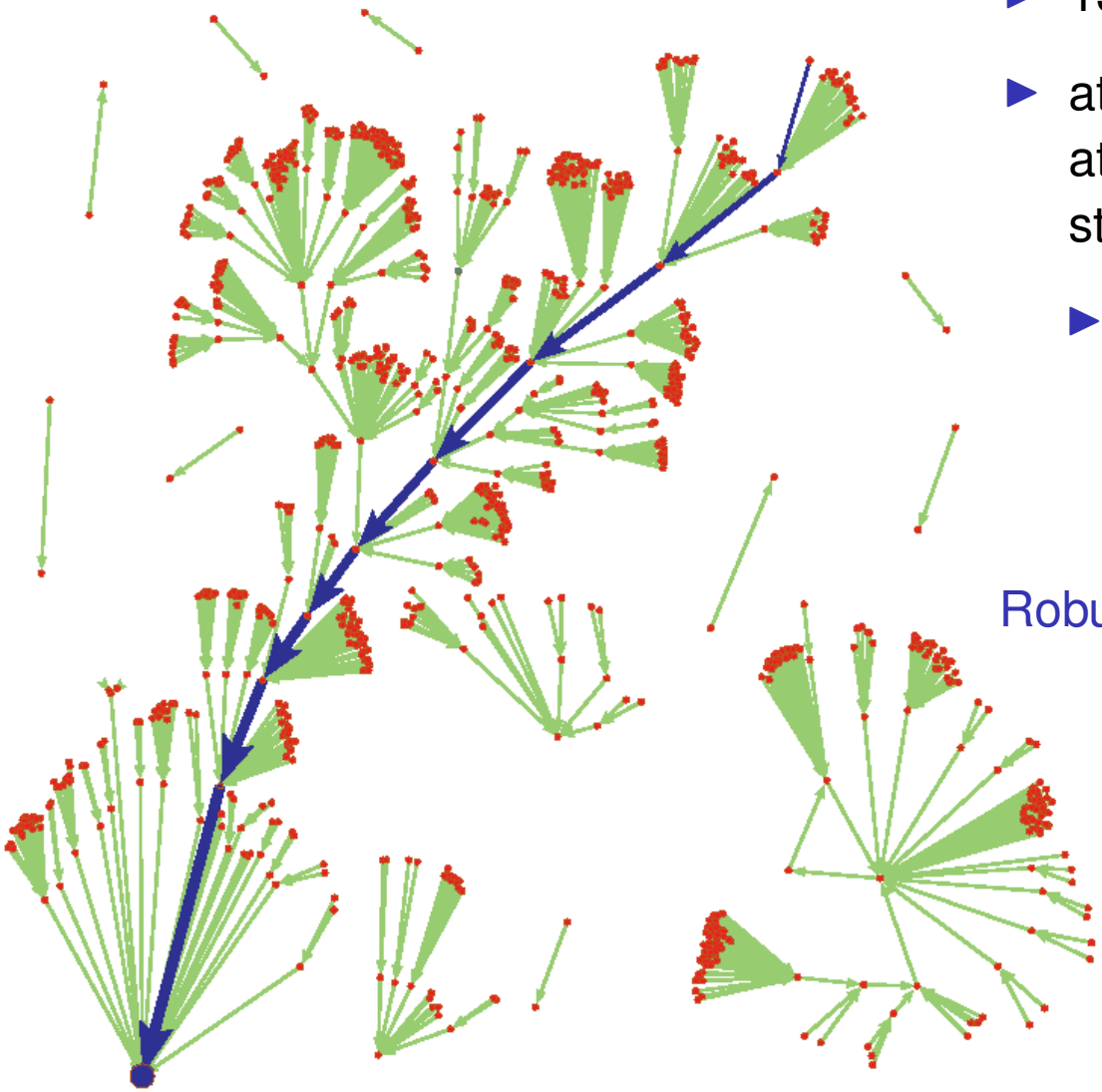
Initial state: excite G1 stationary state with cell size signal (Start=1)

Time Step	Start	SK	Cdc2/Cdc13	Ste9	Rum1	Slp1	Cdc2/Cdc13*	Wee1 Mik1	Cdc25	PP	Phase	comments
1	1	0	0	1	1	0	0	1	0	0	START	Cdc2/Cdc13 dimers are inhibited, antagonists are active.
2	0	1	0	1	1	0	0	1	0	0	G1	SK are becoming active
3	0	0	0	0	0	0	0	1	0	0	G1/S	When Cdc2/Cdc13 and SK dimers switch off Rum1 and Ste9/APC, the cell passes 'Start' and DNA replication takes place, Cdc2/Cdc13 starts to accumulate
4	0	0	1	0	0	0	0	1	0	0	G2	Activity of Cdc2/Cdc13 achieves moderate level, which is enough for entering G2 phase but not mitosis, since Wee1/Mik1 inhibits the activity of residue Tyr-15 of Cdc2 (Cdc2/Cdc13* is not active)
5	0	0	1	0	0	0	0	0	1	0	G2	Moderate activity Cdc2/Cdc13 activates Cdc25
6	0	0	1	0	0	0	1	0	1	0	G2/M	Cdc25 reverses phosphorylation, removing the inhibiting phosphate group and activating Cdc2/Cdc13*
7	0	0	1	0	0	1	1	0	1	0	G2/M	Cdc2/Cdc13* reaches high activity level sufficient to activate Slp1/APC mitosis
8	0	0	0	0	0	1	0	0	1	1	M	Slp1 degradates Cdc13, that is inhibits complex Cdc2/Cdc13 and Cdc2/Cdc13*.
9	0	0	0	1	1	0	0	1	0	1	M	Antagonists of Cdc2/Cdc13 are reset.
10	0	0	0	1	1	0	0	1	0	0	G1	Cell reaches G1 stationary state (PP is inactive)

doi:10.1371/journal.pone.0001672.t002

- sequence returns to G1
- sequence matches cell cycle

State transition graph



- 13 attractors (12 fixed points, 1 cycle)
- attractor corresponding to G1 with attraction basin containing 73% of states
  - 81% of states return to G1 after minimal perturbation in biological sequence (states of blue path)

Robustness due to network structure?

- comparison with random networks (keep nodes, # activating/inhibiting links, # self-activation/degradation, activation thresholds)
  - mean size of biggest attractor basins about 40% of all states

network topology optimized for robustness?

Discussion

- generic choice of f
- simplification of time evolution
- importance of network topology (only basis of the model?)
- coarse modeling predicts biologically relevant dynamical features

Discussion

- generic choice of f
  assumptions about underlying logic
- simplification of time evolution
  strong assumption about time delays
- importance of network topology (only basis of the model?)
  analyze all compatible functions and all possible time delay constraints for assessment of topology importance
- coarse modeling predicts biologically relevant dynamical features

Discussion

- generic choice of f
  assumptions about underlying logic
- simplification of time evolution
  strong assumption about time delays
- importance of network topology (only basis of the model?)
  analyze all compatible functions and all possible time delay constraints for assessment of topology importance
- coarse modeling predicts biologically relevant dynamical features

Useful refinements of the modeling framework

- multi-valued instead of Boolean variables
- less rigorous assumptions on temporal evolution

Multi-value formalism

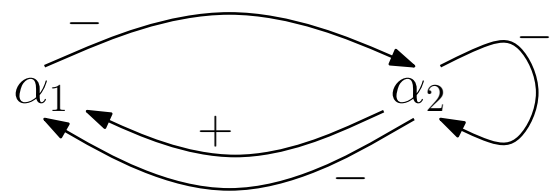
Allow for arbitrary number of activity levels for each component

- component α_i takes values in $X_i := \{0, \ldots, p_i\}$ with $p_i \in \mathbb{N}$
- state space $X := X_1 \times \cdots \times X_n$
- discrete function $f = (f_1, \ldots, f_n) : X \to X$ captures behavioral rules

$\Rightarrow$ quantification of interaction strength possible (parameters!)

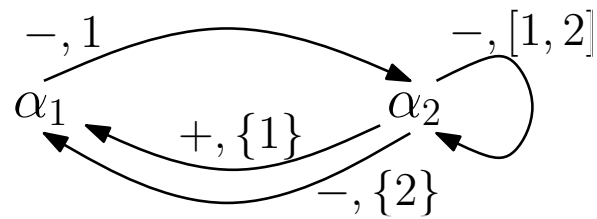
Structure (Interaction graph)

- signed directed (multi-)graph
  as in the Boolean case



or

- signed directed (multi-)graph
  additionally labeled with activity levels
  - many different notations:
    sets (most general), intervals, thresholds,...



Functional topology

Again, make sure f is consistent with the interaction graph

- $f_i(x)$ only depends on x_j if α_j is predecessor of α_i
- functionality of edges, sign and (if applicable) label consistency
- avoid dynamically superfluous activity values:
  $p_i \leq$ # successors of α_i, unless modeling meaningful "output"

Remark: for precise representation use parallel edges of same sign (and different activity level label) to indicate different interaction strengths

Functional topology

Again, make sure f is consistent with the interaction graph

- $f_i(x)$ only depends on x_j if α_j is predecessor of α_i
- functionality of edges, sign and (if applicable) label consistency
- avoid dynamically superfluous activity values:
  $p_i \leq$ # successors of α_i, unless modeling meaningful "output"

Remark: for precise representation use parallel edges of same sign (and different activity level label) to indicate different interaction strengths

Definition Let $x \in X$. By $G(x)$ we denote the directed signed (multi-)graph with vertex set $\{\alpha_1, \ldots, \alpha_n\}$ and edge set $E(x) \subseteq V \times V \times \{+,-\}$, where an edge (i,j,ε) belongs to $E(x)$ iff there exists $c_i \in \{-1,+1\}$ such that $x_i + c_i \in X_i$ and

$$\operatorname{sgn} \frac{f_j((x_1, \ldots, x_{i-1}, x_i + c_i, x_{i+1}, \ldots, x_n)) - f_j(x)}{c_i} = \varepsilon .$$

We call $G(x)$ the *local interaction graph of f in x* and We call $G(f) := \bigcup_{x \in \{0,1\}^n} G(x)$ *global interaction graph of f*.