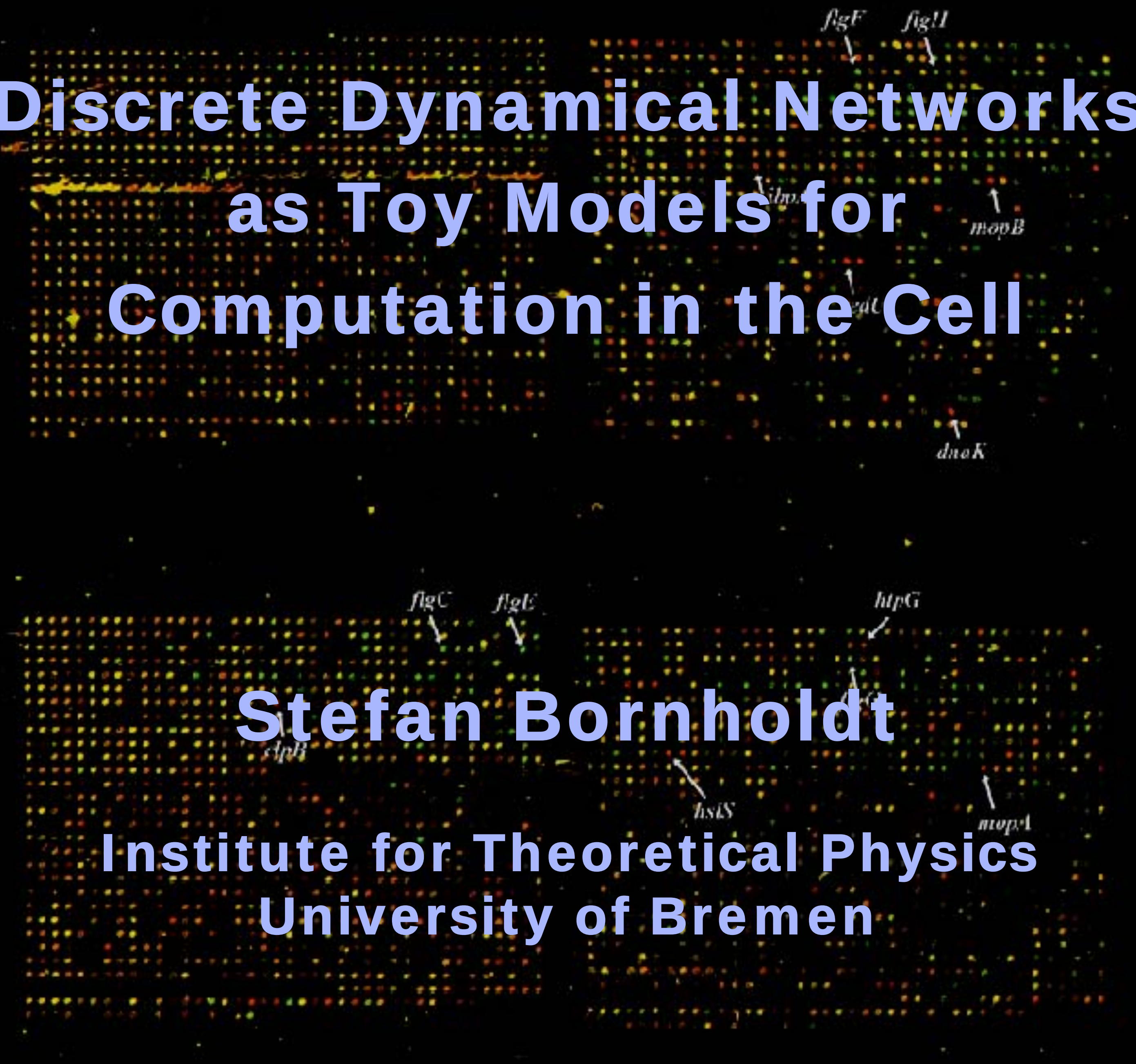

Discrete Dynamical Networks as Toy Models for Computation in the Cell

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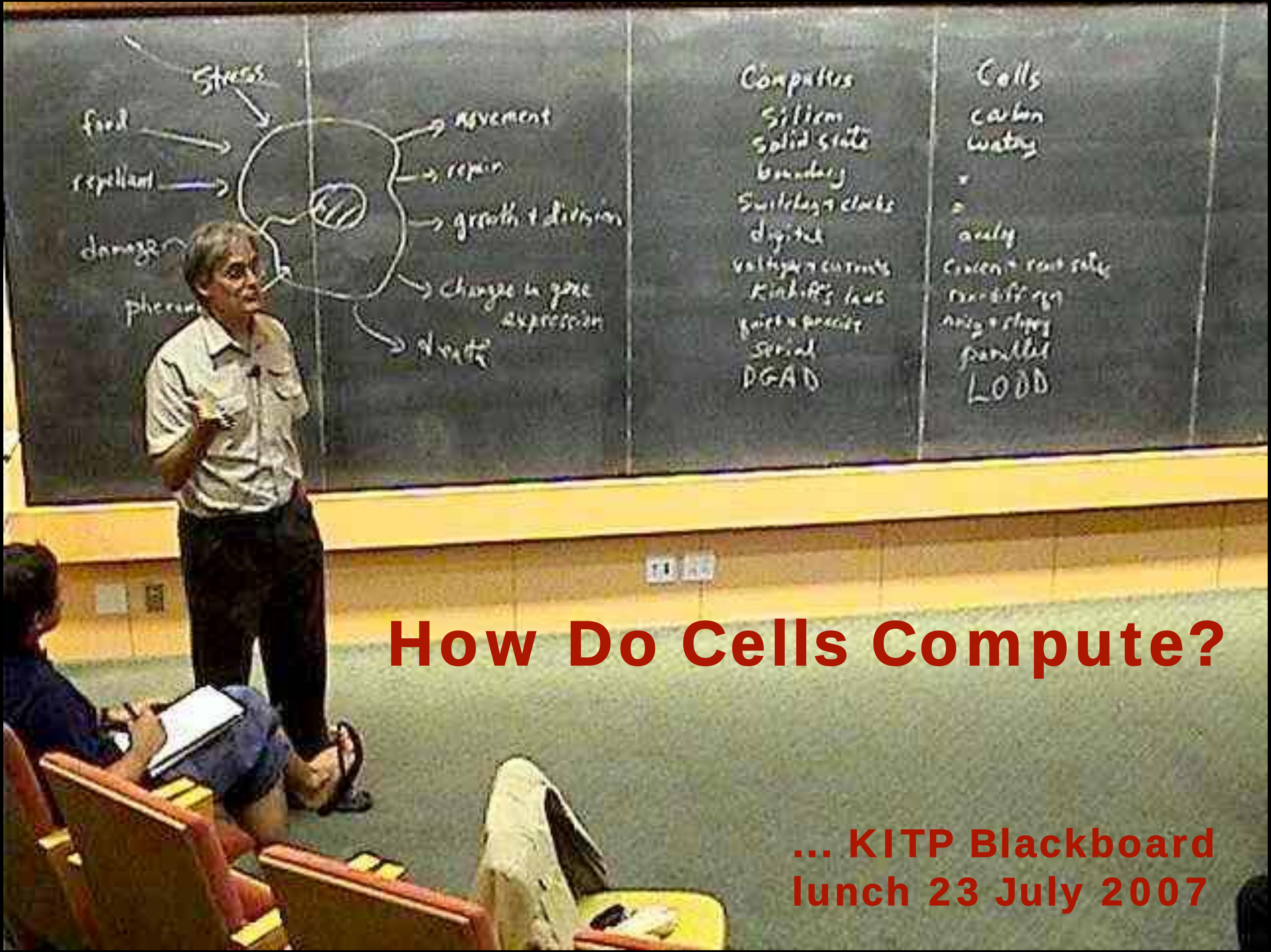


How Do Cells Compute?

... KITP Blackboard
lunch 23 July 2007

- Computers and the living cell

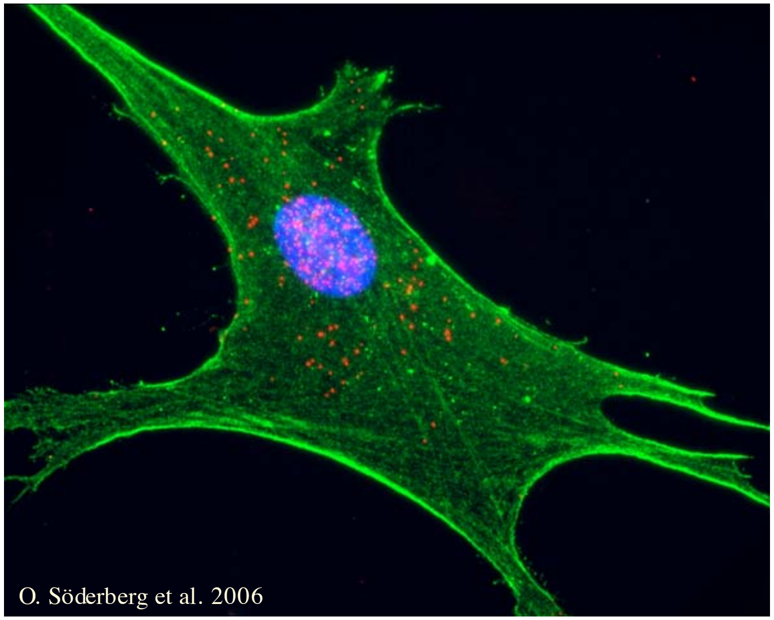
- Discrete networks as models for cellular computation

- A biological example: The yeast cell cycle

- Discrete network models and stochastic dynamics

- Applications and outlook

Computation in the Cell?

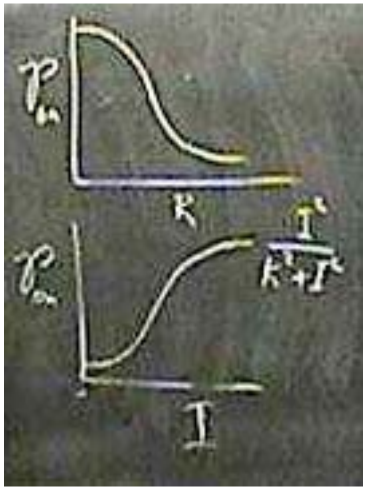


O. Söderberg et al. 2006

- Adapting and reacting to environment: **analog computation?**
- Controlling sequences of events, cell-cycle, multicellular development, etc.: **digital computation?**

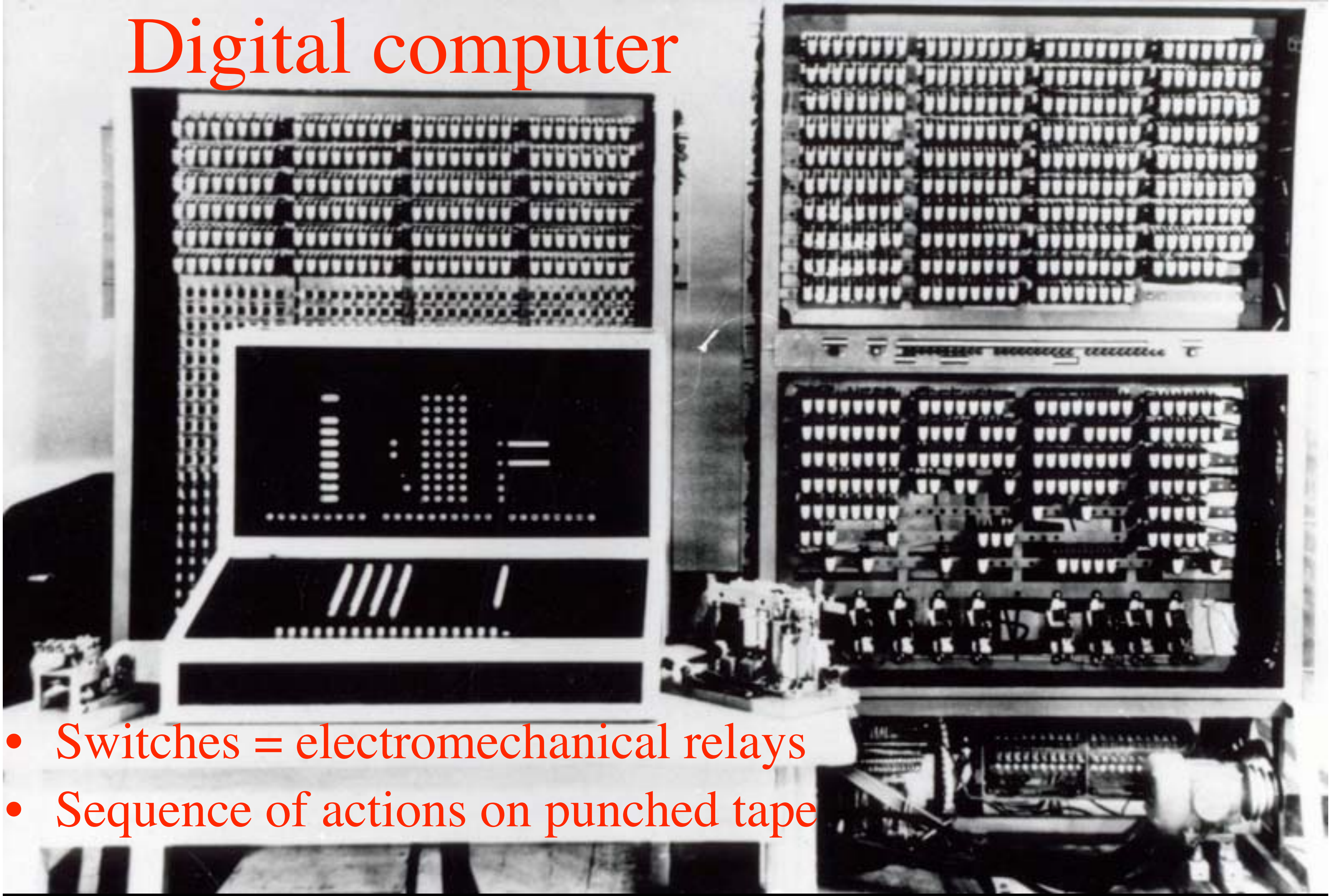
Computational elements in the cell

- This workshop: We‘ve seen many molecular regulatory elements with **binary** characteristics,
- and even **bistable** switches.



- Digital variables {0,1} can be represented:
- Elements for digital computation exist in the cell!
- So... is there any digital computation in the cell?

Digital computer

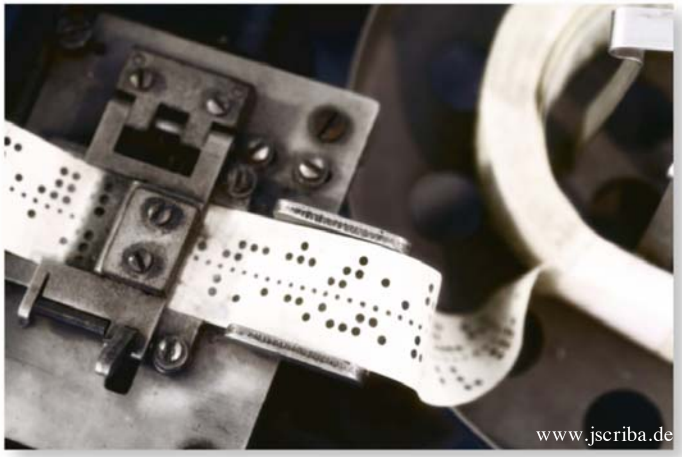


- Switches = electromechanical relays
- Sequence of actions on punched tape

(K. Zuse, 1941)

Sequence control options

- **Computer:** Desired sequence of actions is stored on the tape
- **Dynamical System:** Sequence emerges as dynamical trajectory of the system, determined by the circuitry of the system

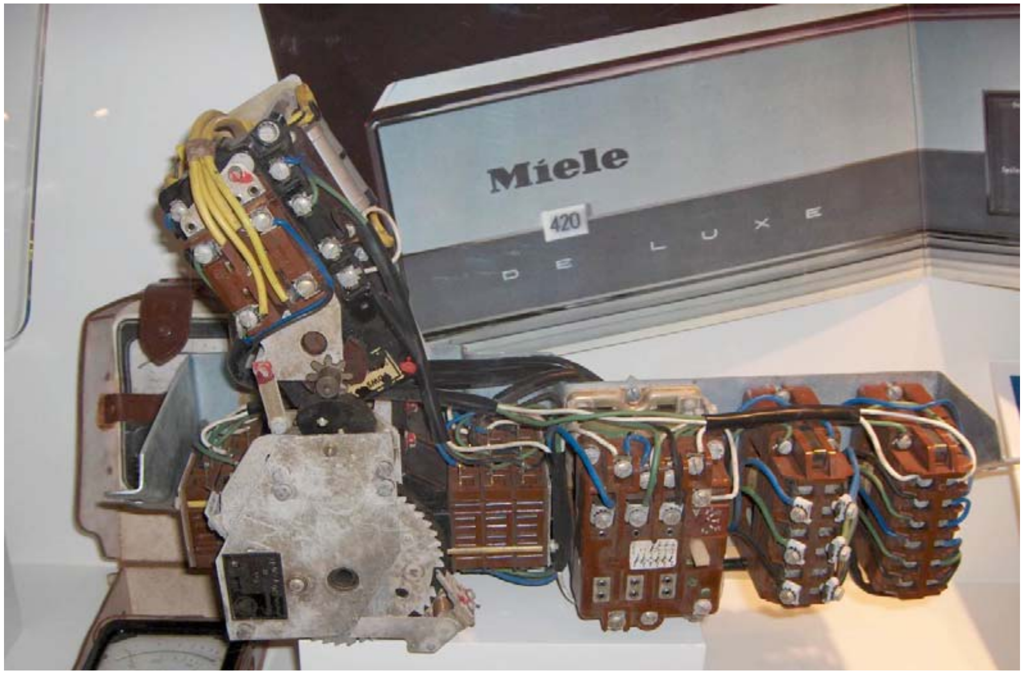


- If you had the choise: punched tape is easiest
- If all you have is squishy stuff (water, molecules, ...) and have to generate a sequence from that: There is the dynamical systems approach, only.
- Problem: How to reliably generate a sequence of actions from squishy building blocks?

Engineering example: Controlling a washing machine

- **Software:** Sequence of switching events, controlling pumps, valves, motors, heater...
- **Input:** Switches, temperature probes, water level ...
- **Output:** Sequence of events, in response to selected program, temperature, water level, etc.

- **Hardware:** Similar to punched tape computer
- Switching disks mounted on common axle, driven by a motor



Analogy:
Controlling the cell cycle

- **Software:** Desired **sequence** of Gene/Protein activation states
- **Input:** External signals, cell size, temperature, etc.
- **Output:** Sequence of molecular activation patterns in response to external and internal signals

- **Hardware:** Molecular network, analog, autonomous dynamics, continuously updated (no computer clock cycle), many elements with tendency to binary states.

Dynamics of networks of switches

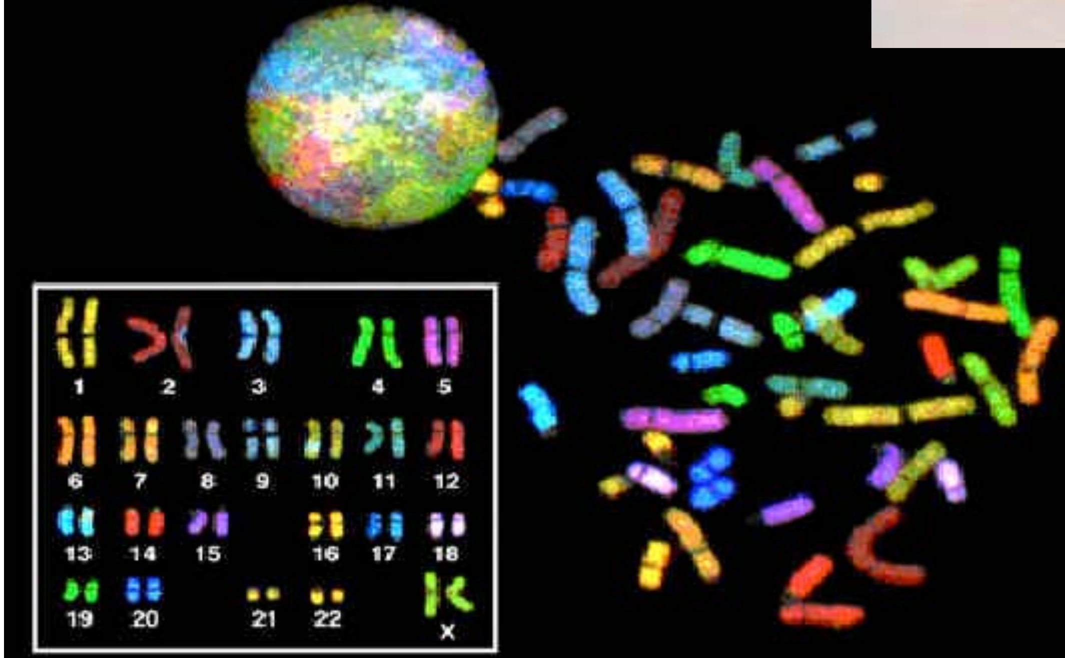
- **Massive simplification** of biochemical networks, what can we learn from it?

- **Idea:**
  - Drop prediction of **time.**
  - Keep the requirement to predict **ordered sequences of activation patterns.**

    This is the „**Software**“ in the analogy picture.

- Engineering knowledge applicable to this „software layer“?
- How can networks of unreliable elements work reliably?

Control on the systems level is very reliable!



?

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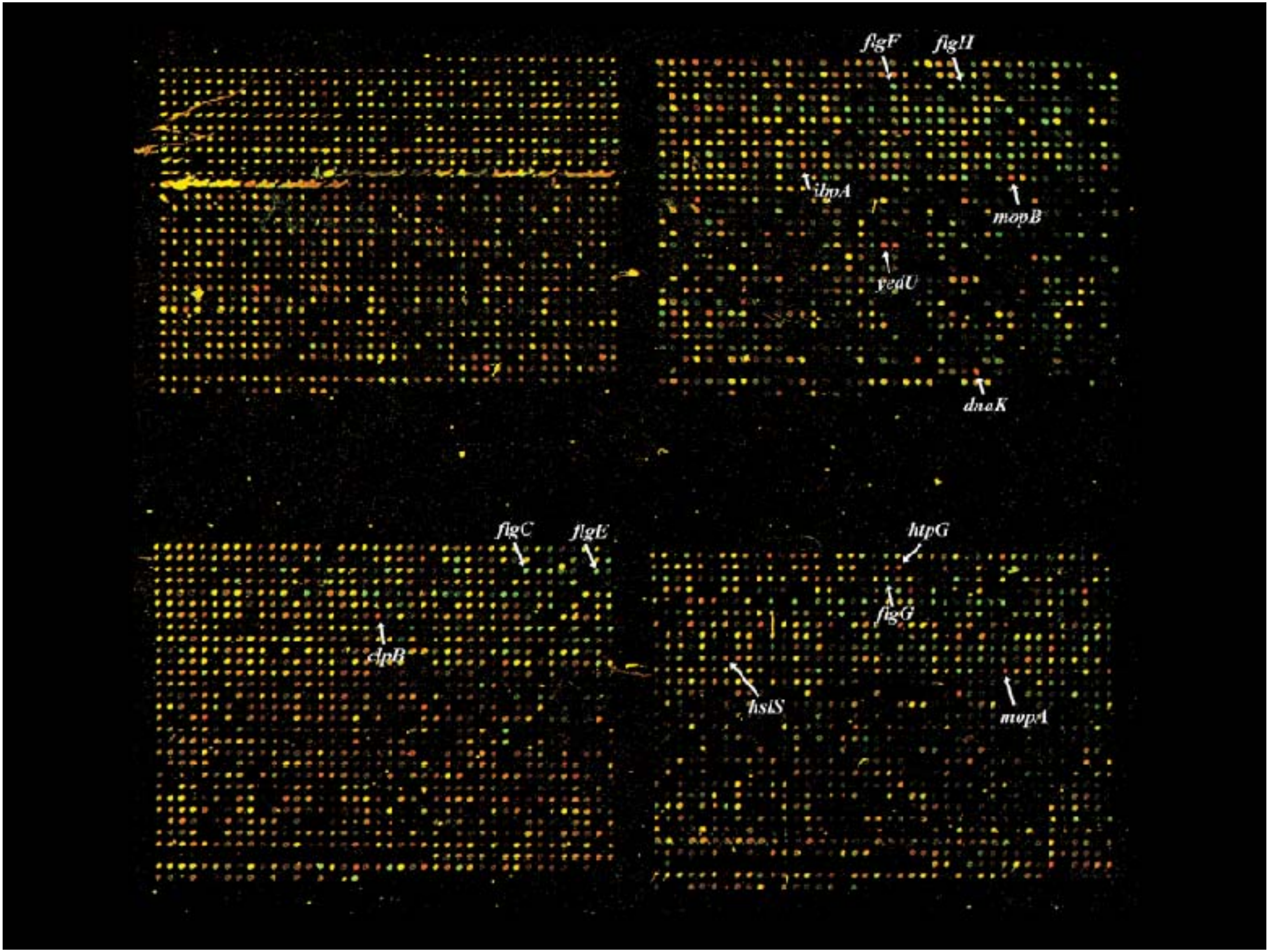
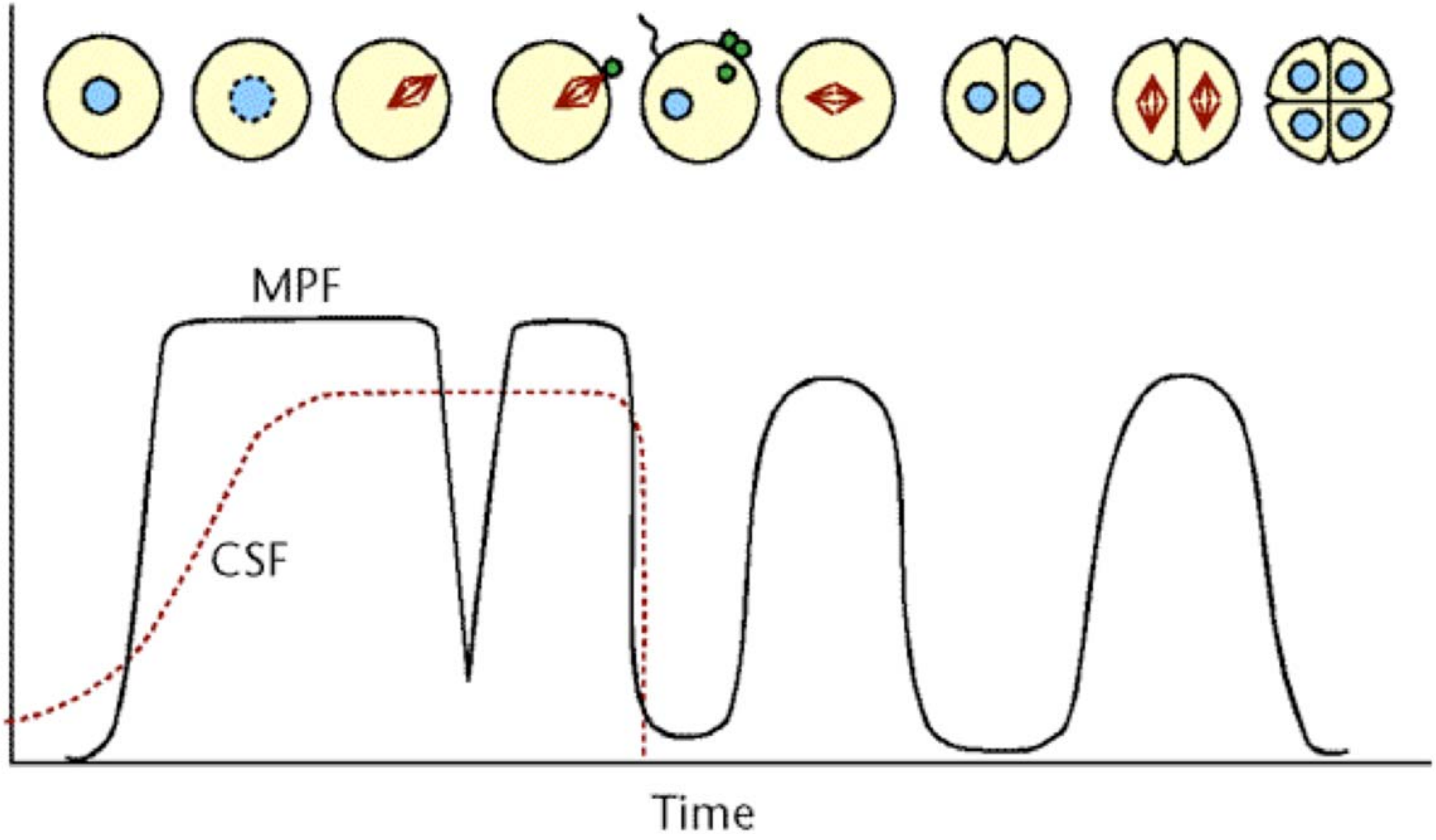


flgF
flgH
ibpA
mopB
yedU
dnaK
flgC
flgE
clpB
htpG
flgG
hslS
mopA

Dynamics of genes (yeast)

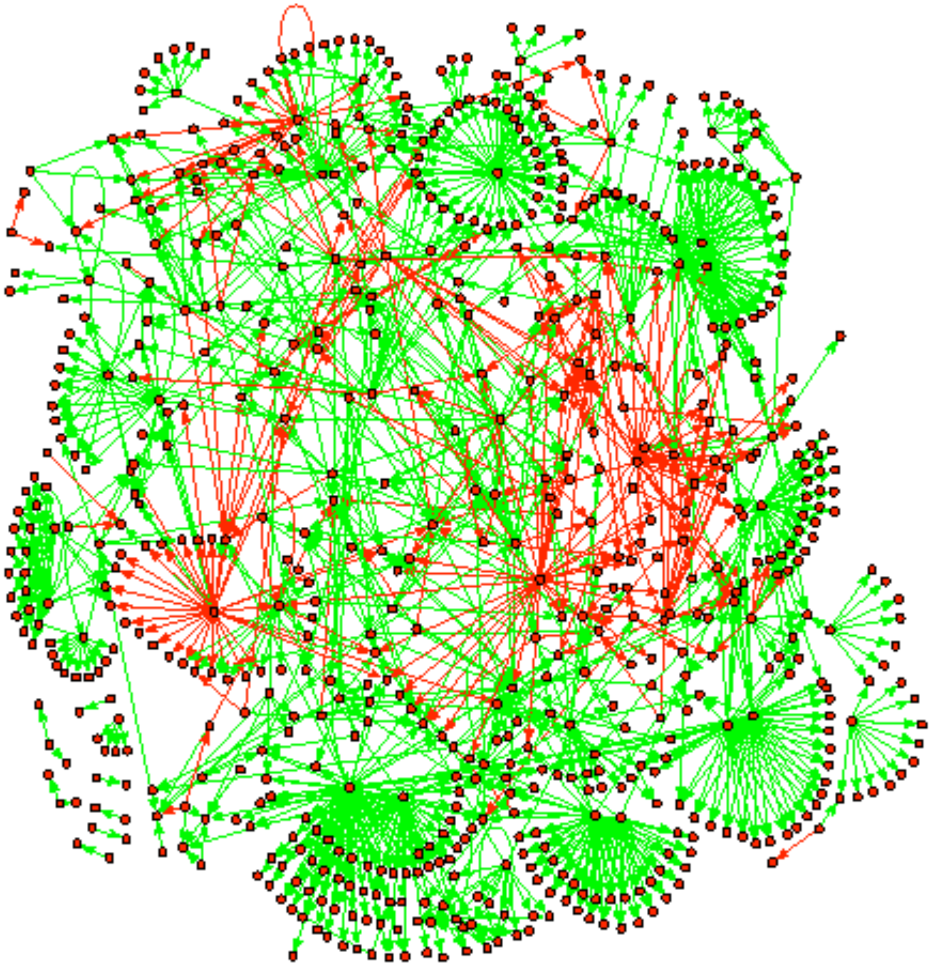


Remarkable: **steep flanks and plateaus**

Hypothesis: **Represent a gene by a switch-like dynamics**

Gene regulation network of yeast

Simplified levels of activation and inhibition:



[S. Maslov and K. Sneppen, 2003]

Discrete dynamical networks as models for gene regulation have been around: Boolean networks [Kauffman 1969]

Here: Threshold networks [S.B. & K. Sneppen 1998]

$$S_i(t+1) = \operatorname{sgn} \sum_{j=1}^{N} J_{ij} S_j(t) \qquad S_i \in \{-1,+1\} \qquad J_{ij} \in \{-1,0,+1\}$$

asymmetric!

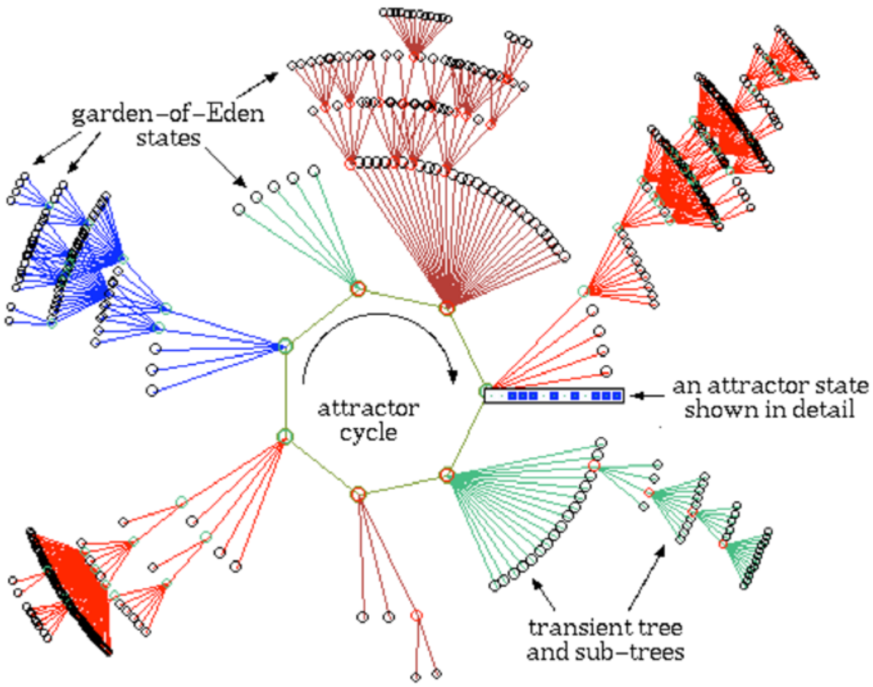
Dynamics:

Transients, attractors with lengths scaling with system size as $t \sim e^N$ for overcritical connectivity $K > K_c \sim 2$

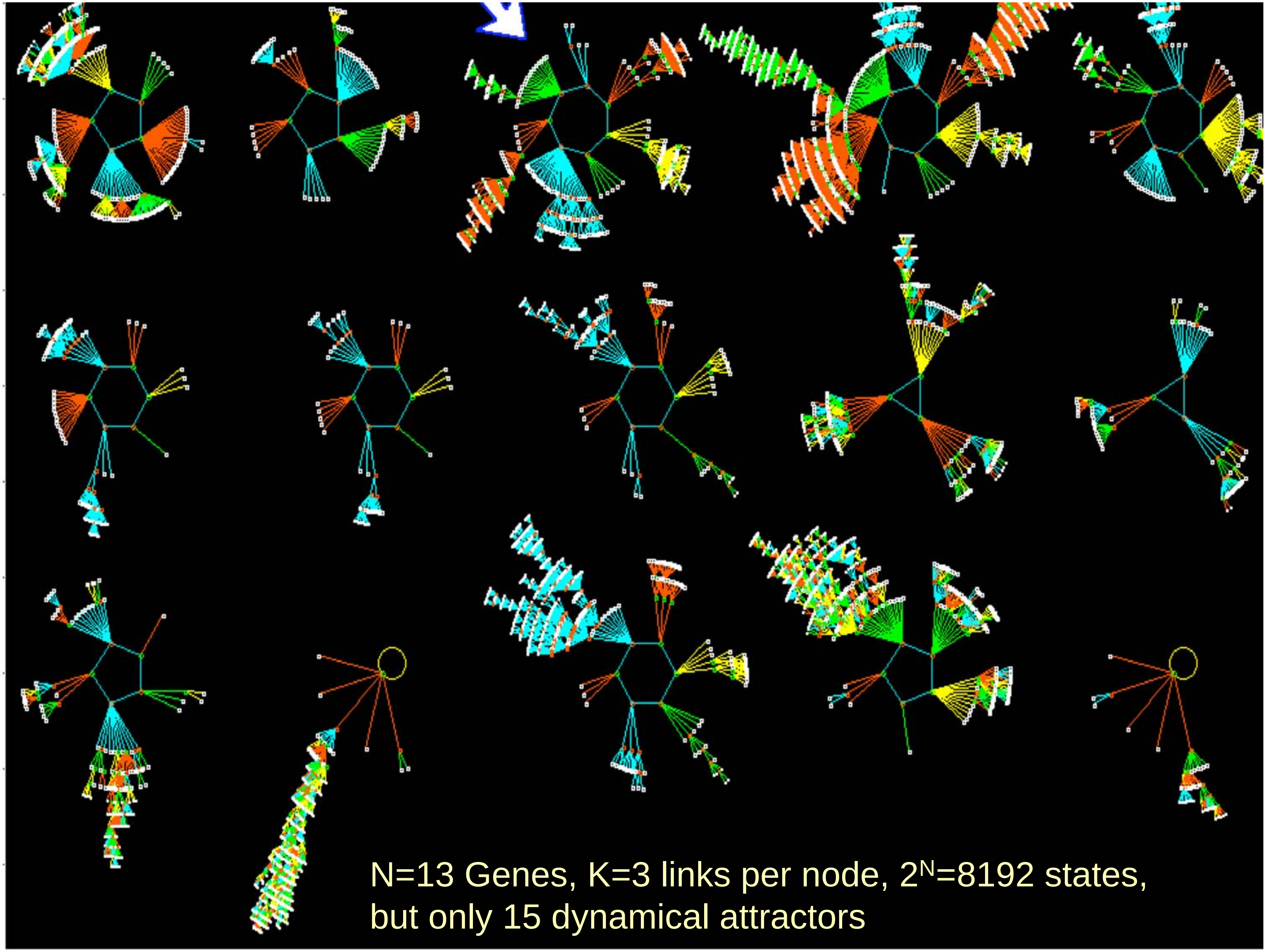
Few attractors:

fixed points, limit cycles.

Large basins of attraction.

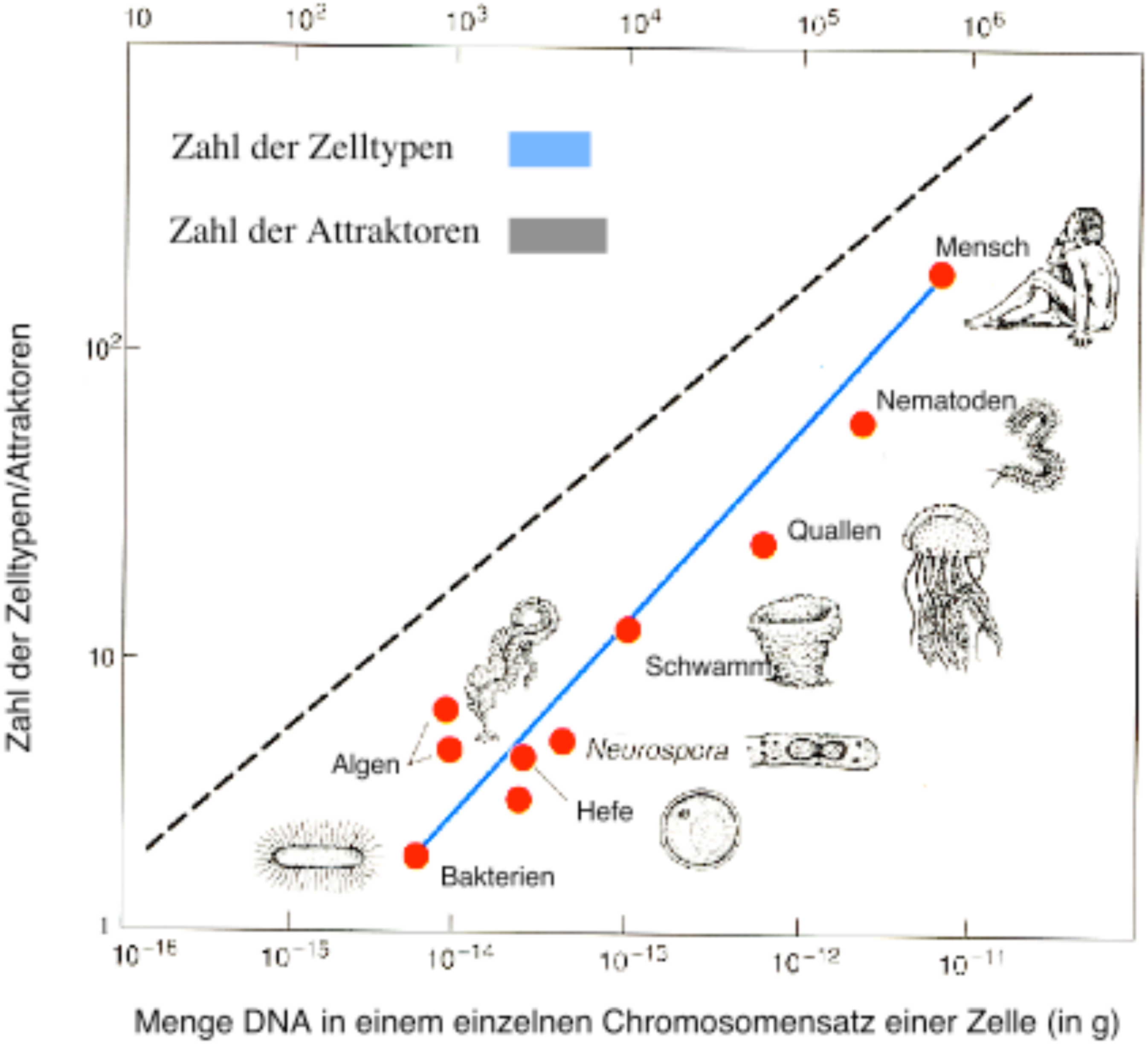

garden-of-Eden states
attractor cycle
an attractor state shown in detail
transient tree and sub-trees

After A. Wuensche (1998)



N=13 Genes, K=3 links per node, 2^N=8192 states, but only 15 dynamical attractors

Kauffman‘s Attractor Hypothesis (1969):
„Attractors of gene networks determine cell types“



Boolean models for regulatory networks

„more than anecdotal“ only very recently:

- R. Albert & H. Othmer: The topology of the regulatory interactions predicts the expression pattern of the **Drosophila segment polarity genes**, J Theor Biol 223 (2003) 1.

- F. Li, T. Long, Y. Lu, Q. Ouyang & C. Tang: The **yeast cell cycle network** is robustly designed, PNAS 101 (2004) 4781.

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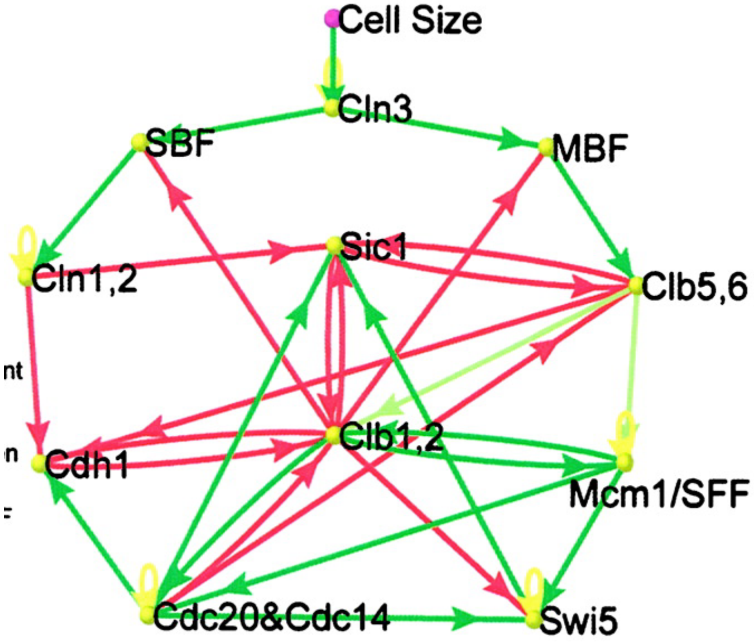
Dynamical model of the yeast cell cycle

[Li et al., PNAS 2004]

- Threshold network:



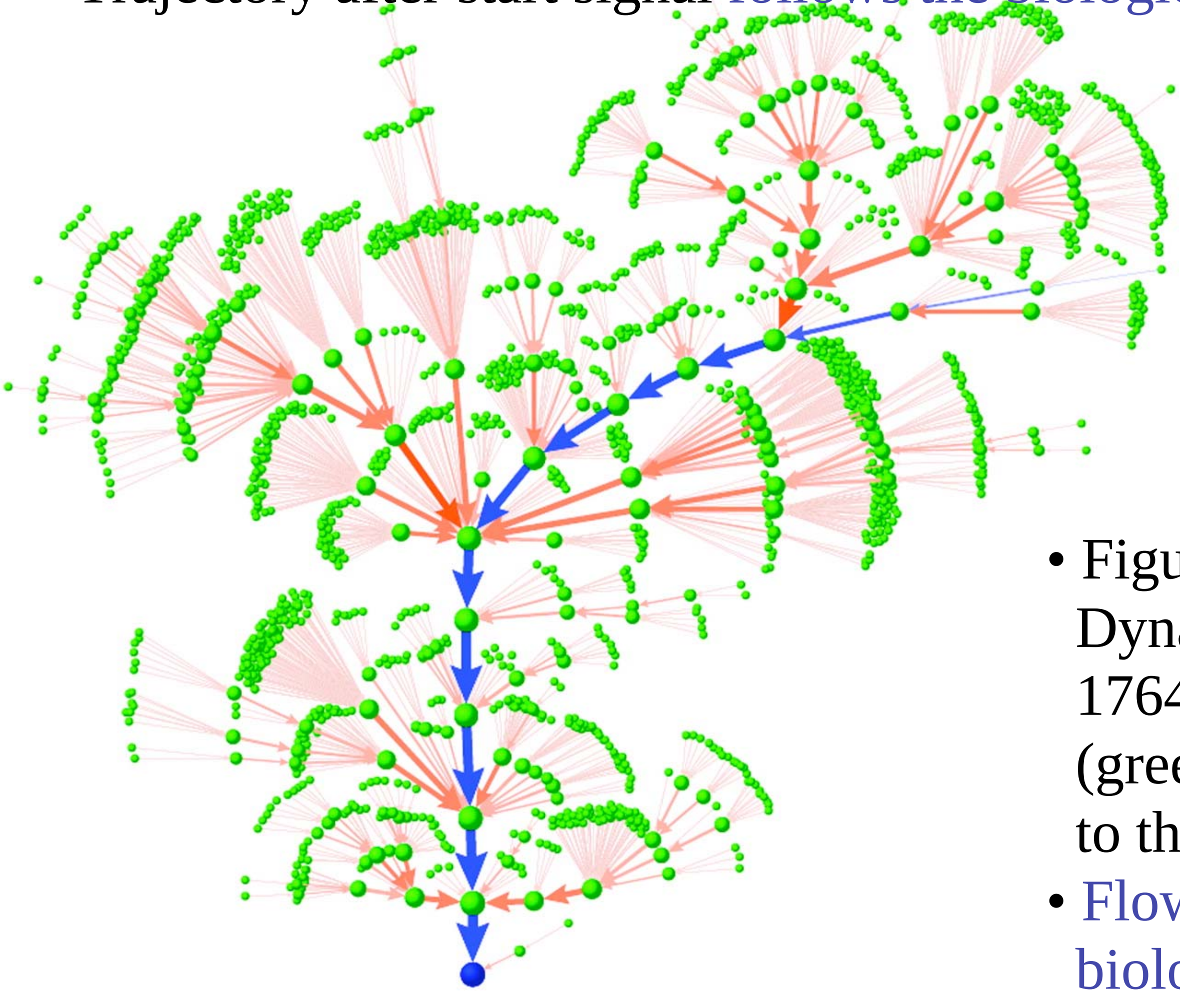
$$S_i(t+1) = \begin{cases} 1, & \sum_j a_{ij} S_j(t) > 0 \\ 0, & \sum_j a_{ij} S_j(t) < 0 \\ S_i(t), & \sum_j a_{ij} S_j(t) = 0 \end{cases}$$

- Couplings activating/inhibitory $a_{ij}=1$/ $a_{ij}=-1$
- Degradation $S_i(t+1) = 0$ if no input for more than 1 time step
- Synchronous dynamics for all genes

Largest attractor in state space

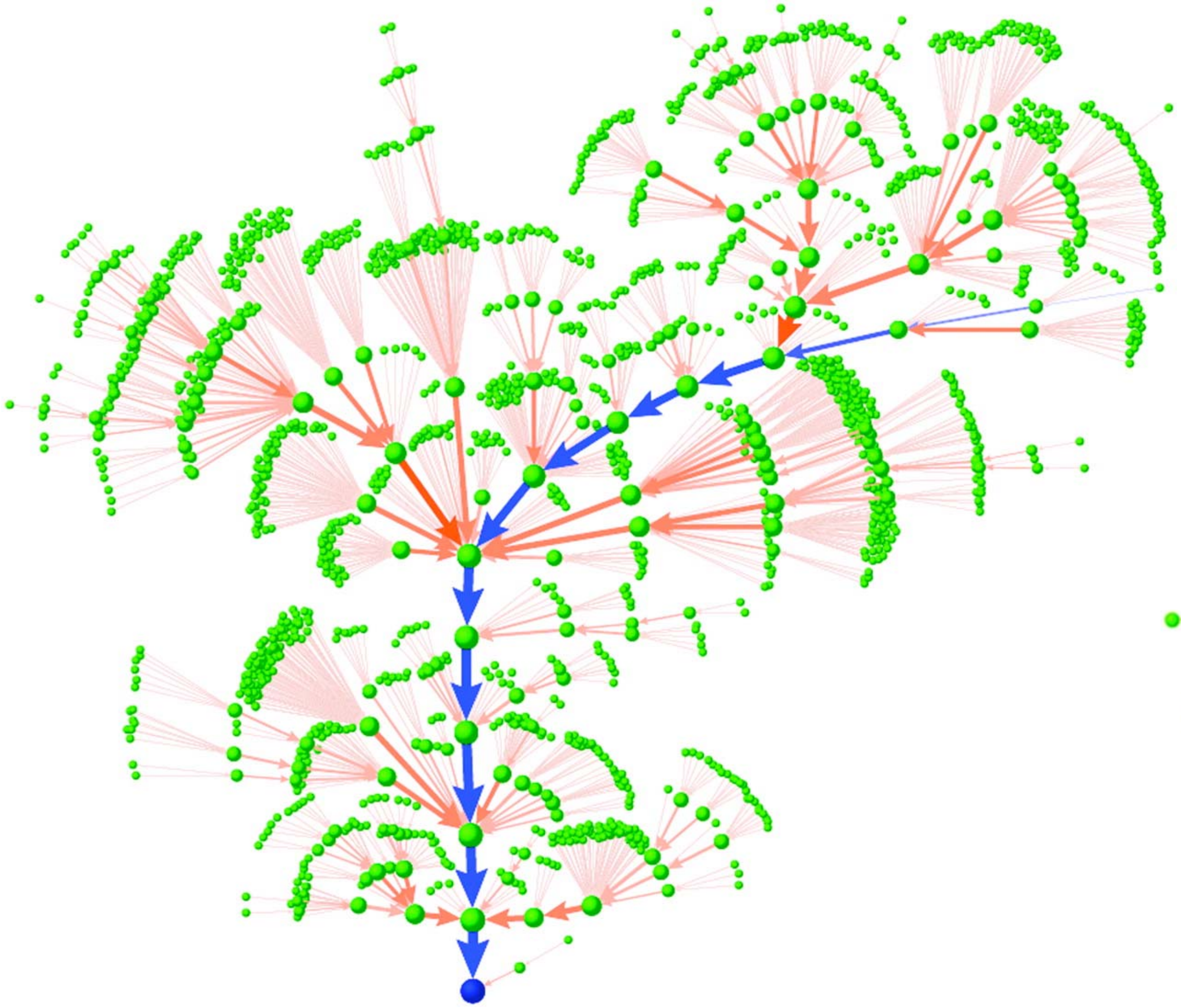
State space: 2^{11}=2048 states, 7 attractors (fixed points)

- Largest attractor (1764 states) = biologically stable final state
- Trajectory after start signal follows the biological time sequence

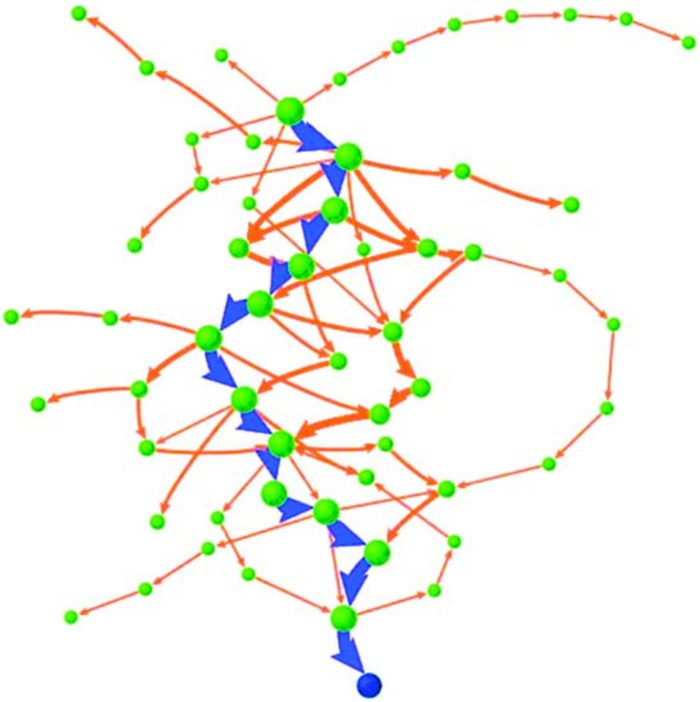


- Figure:
  Dynamical trajectories of the
  1764 protein states
  (green nodes), that flow
  to the largest fixed point (G1)
- Flow converges to the
  biological path (blue)

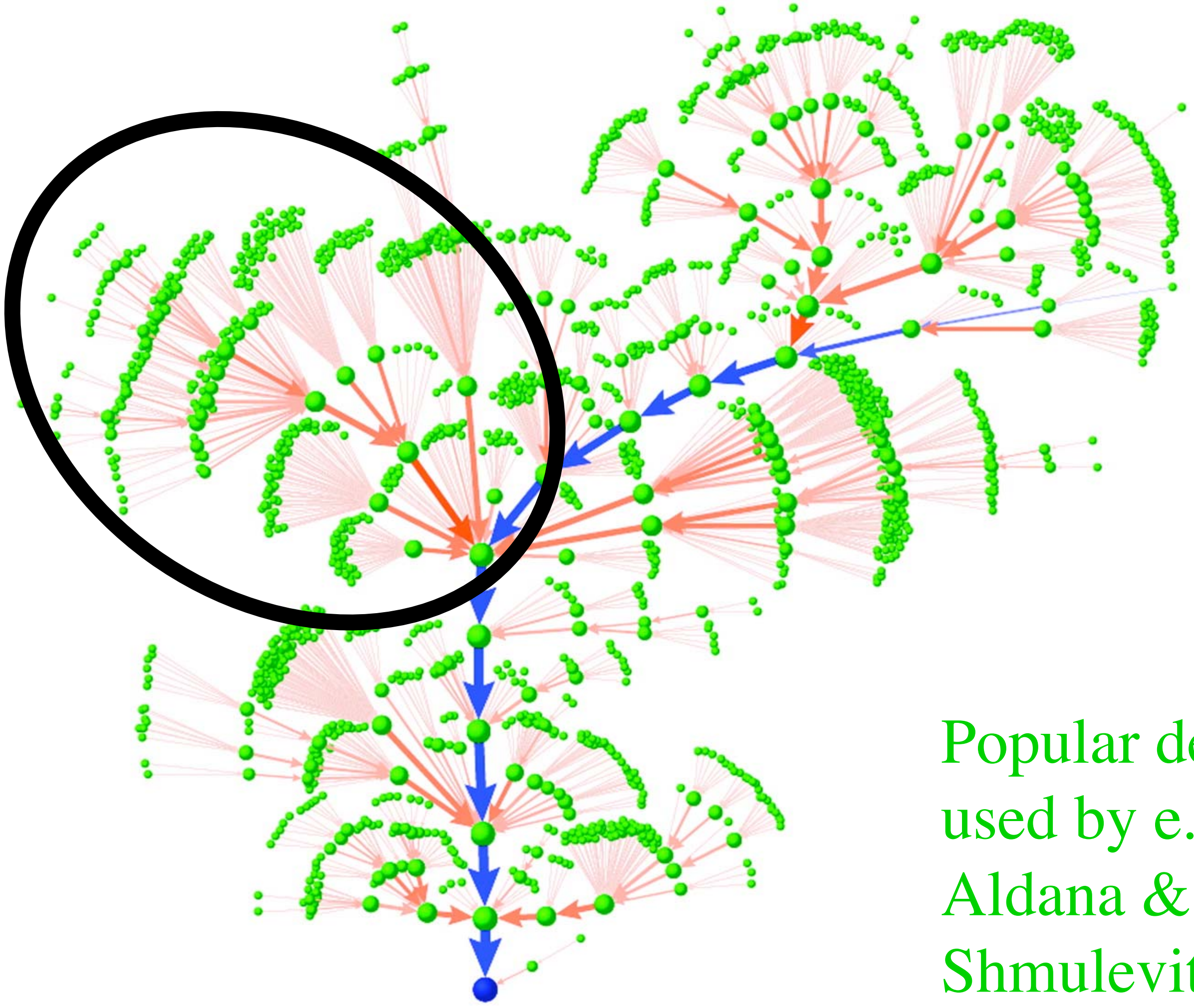
Robustness I: Network mutations



50% of mutations keep biological path:



Robustness II: Damage spreading after “spin flip”



Popular definition of Robustness used by e.g.

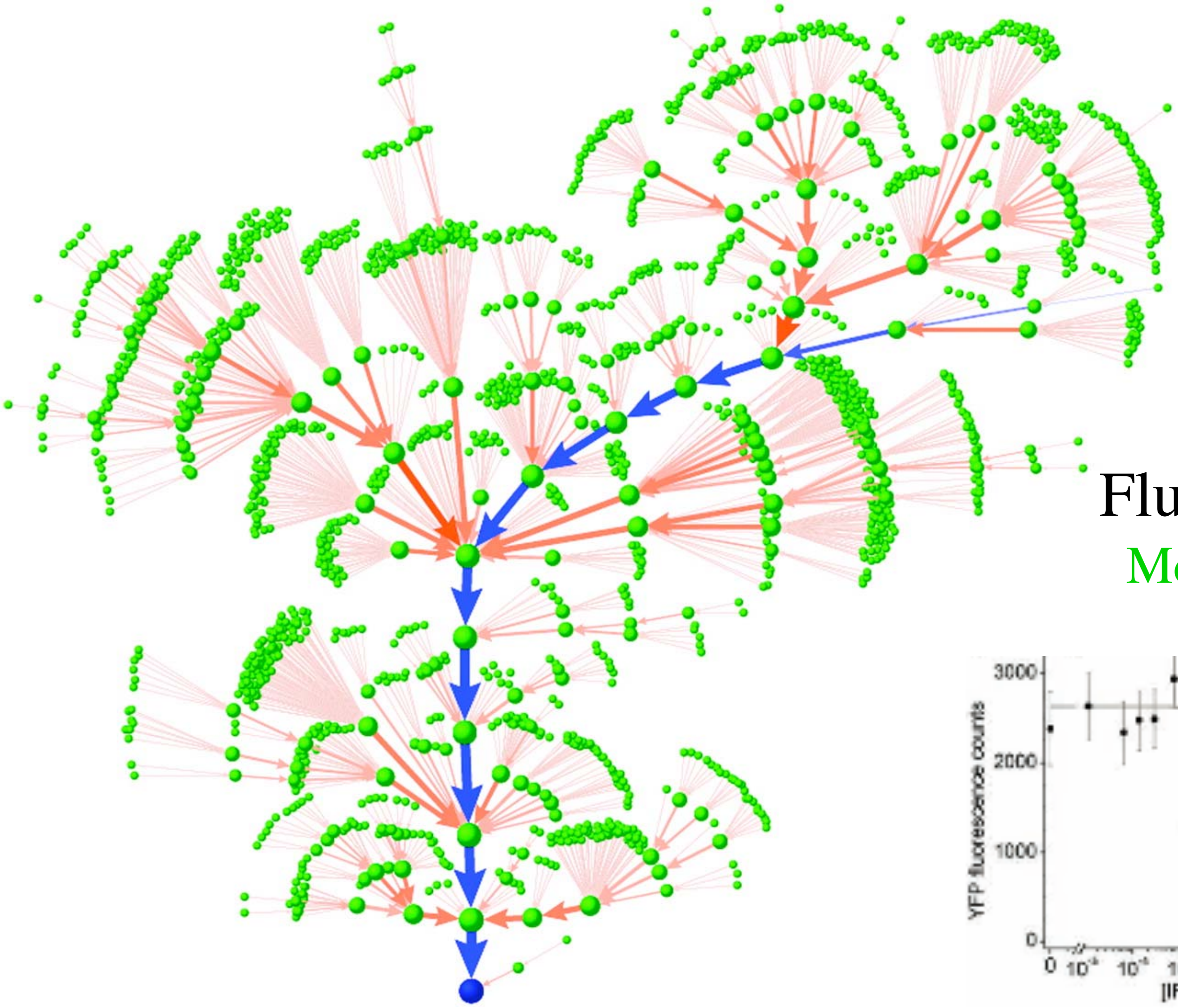
Aldana & Cluzel, PNAS 2003

Shmulevith et al., PNAS 2003

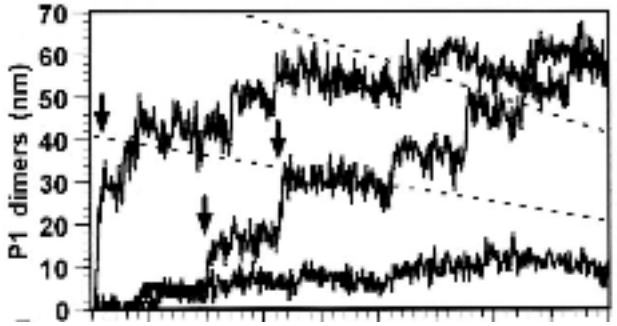
Kauffman et al., PNAS 2003

Kauffman et al., PNAS 2004

Robustness III: Biochemical stochasticity

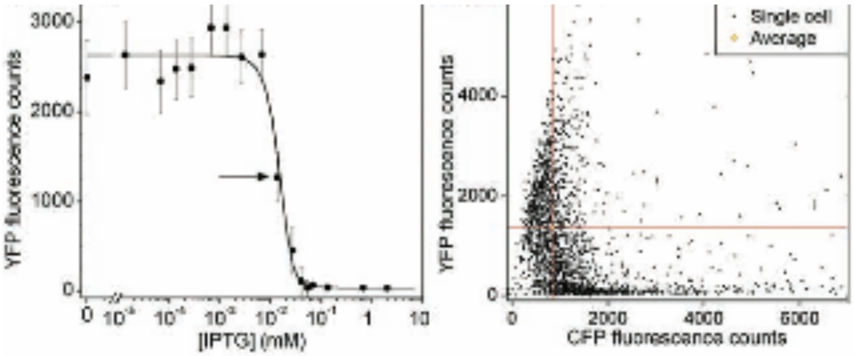


Genes are noisy:



Fluctuating switching times

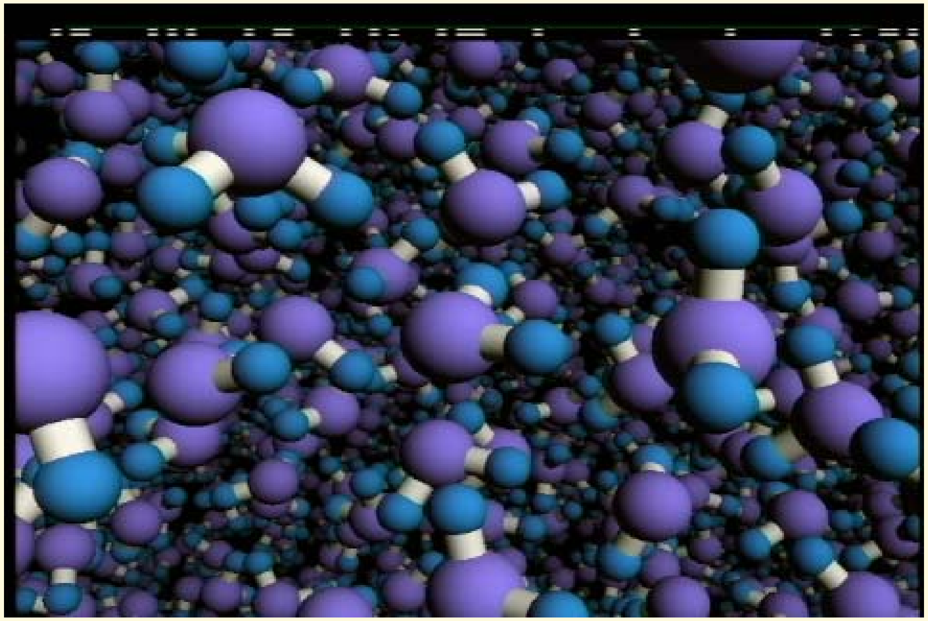
McAdams & Arkin PNAS 1997



Fluctuating gene activity

Pedraza & Oudenaarden Science 05

How does the cell achieve a clockwork-like reliability from molecular building blocks?



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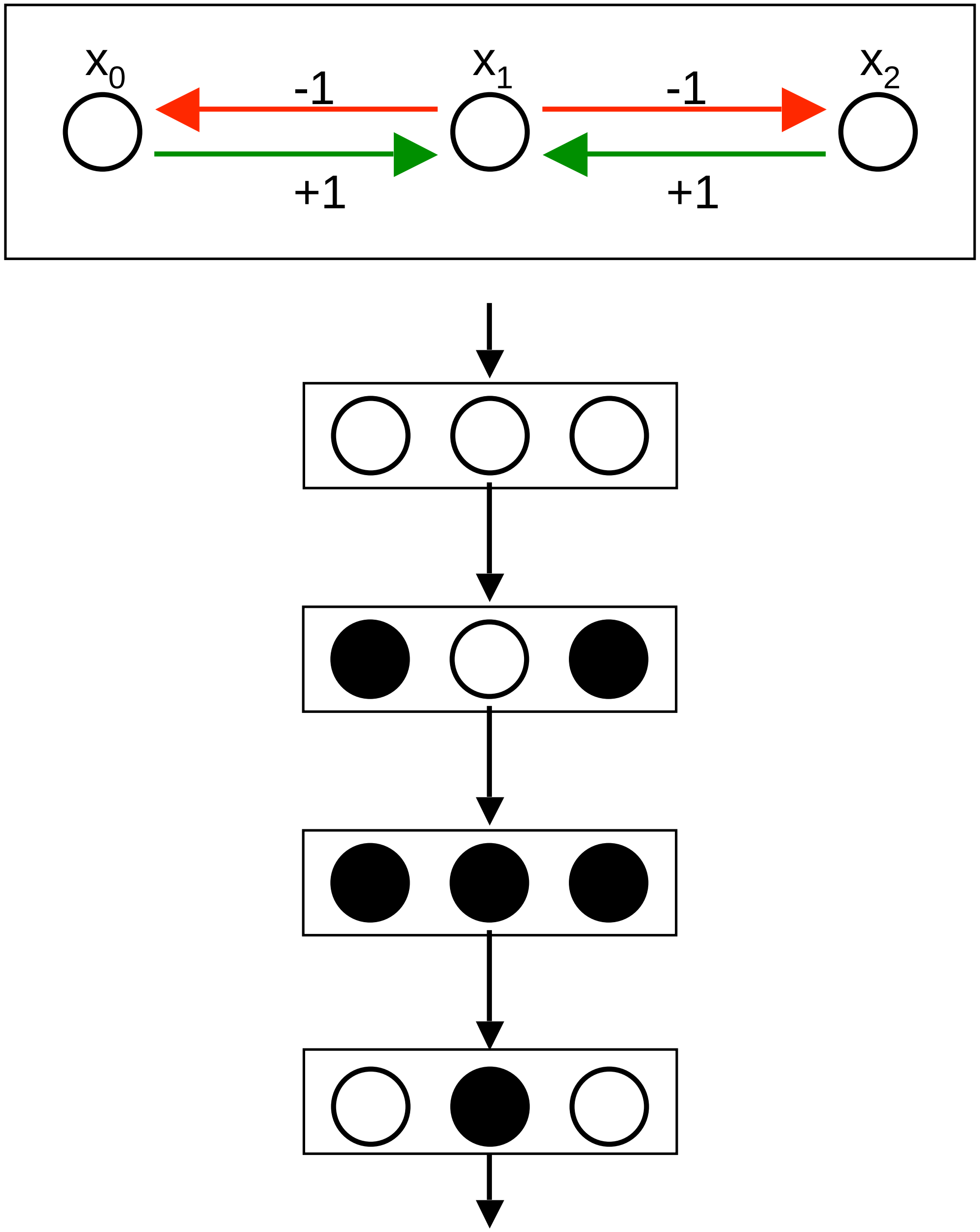
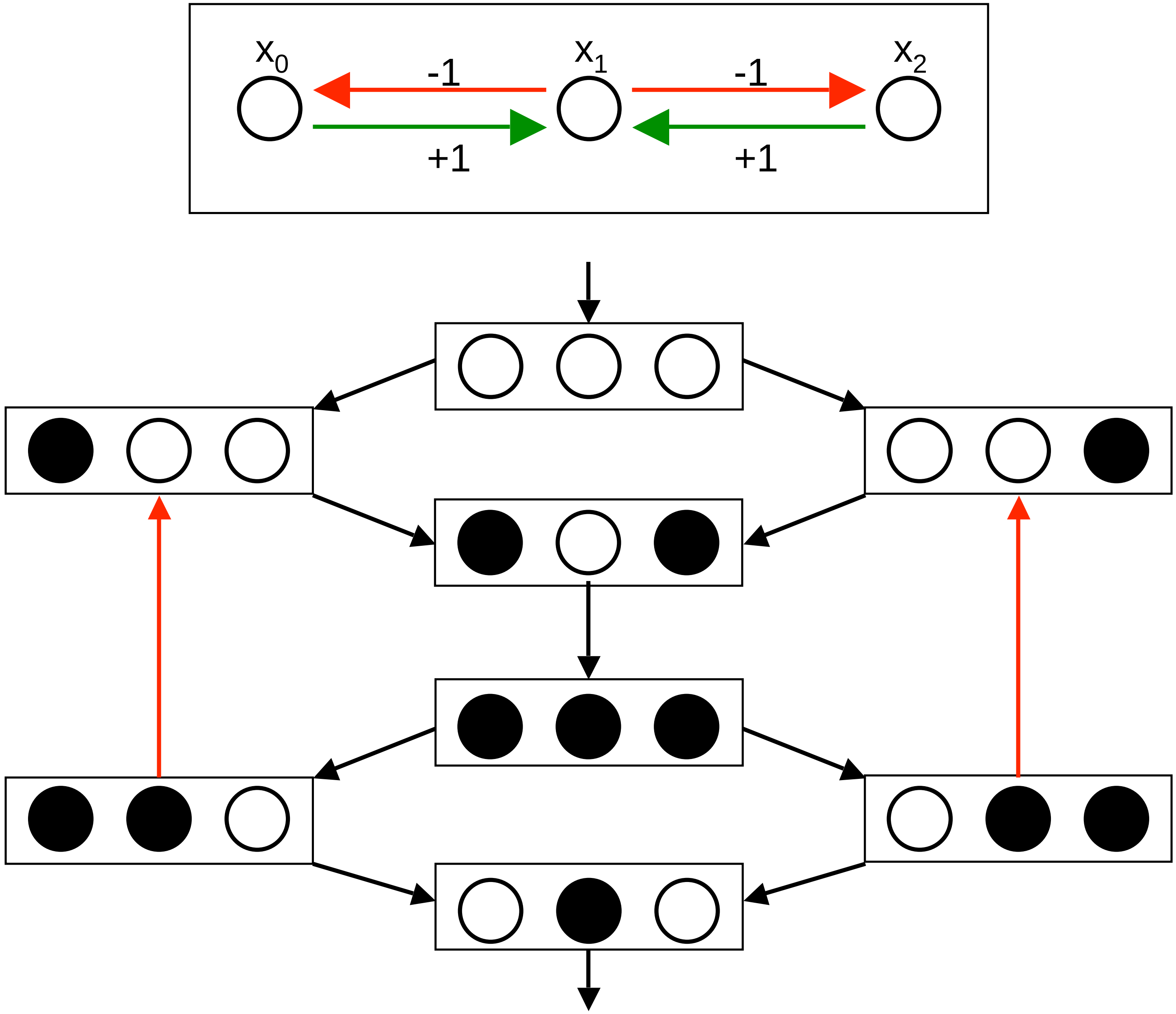
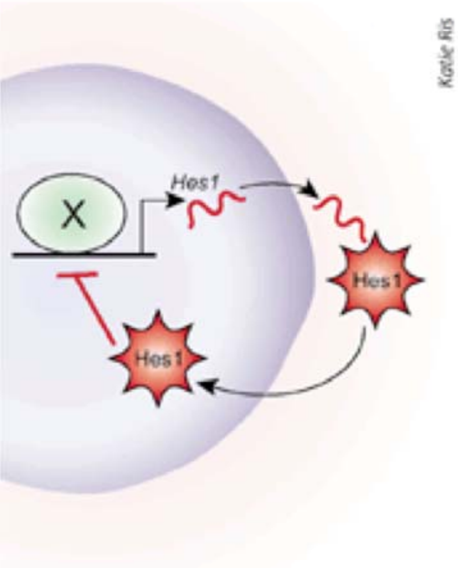
Synchronous update (no noise)

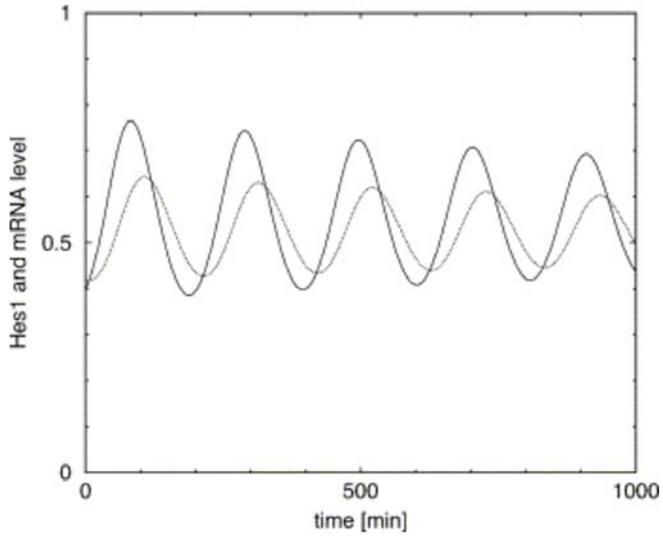


Asynchronous update (noisy)



Simplest genetic circuit: Self-regulating switch Hes1





$$\frac{d[mRNA]}{dt} = \frac{\alpha k^h}{k^h + [Hes1(t-\tau)]} - \frac{[mRNA(t)]}{\tau_{RNA}}$$

$$\frac{d[Hes1]}{dt} = \beta[mRNA(t)] - \frac{[Hes1(t)]}{\tau_{Hes1}}$$

[M.H. Jensen, K. Sneppen, G. Tiana 2003]

Simplest model that keeps timing info

- Keep delay and one low pass filter, difference equation for RNA concentration c:

$$\Delta c_i = \alpha\left[f\left(S_i(t-\tau)\right) - c_i(t)\right]\Delta t$$

- Let threshold sum now drive the concentration gradient:

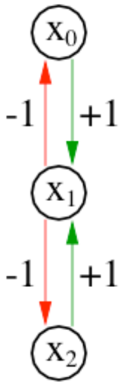
$$\Delta c_i = \varepsilon \cdot \operatorname{sgn}\left(\sum_j J_{ij} S_j(t-\tau) - \vartheta_i\right)$$

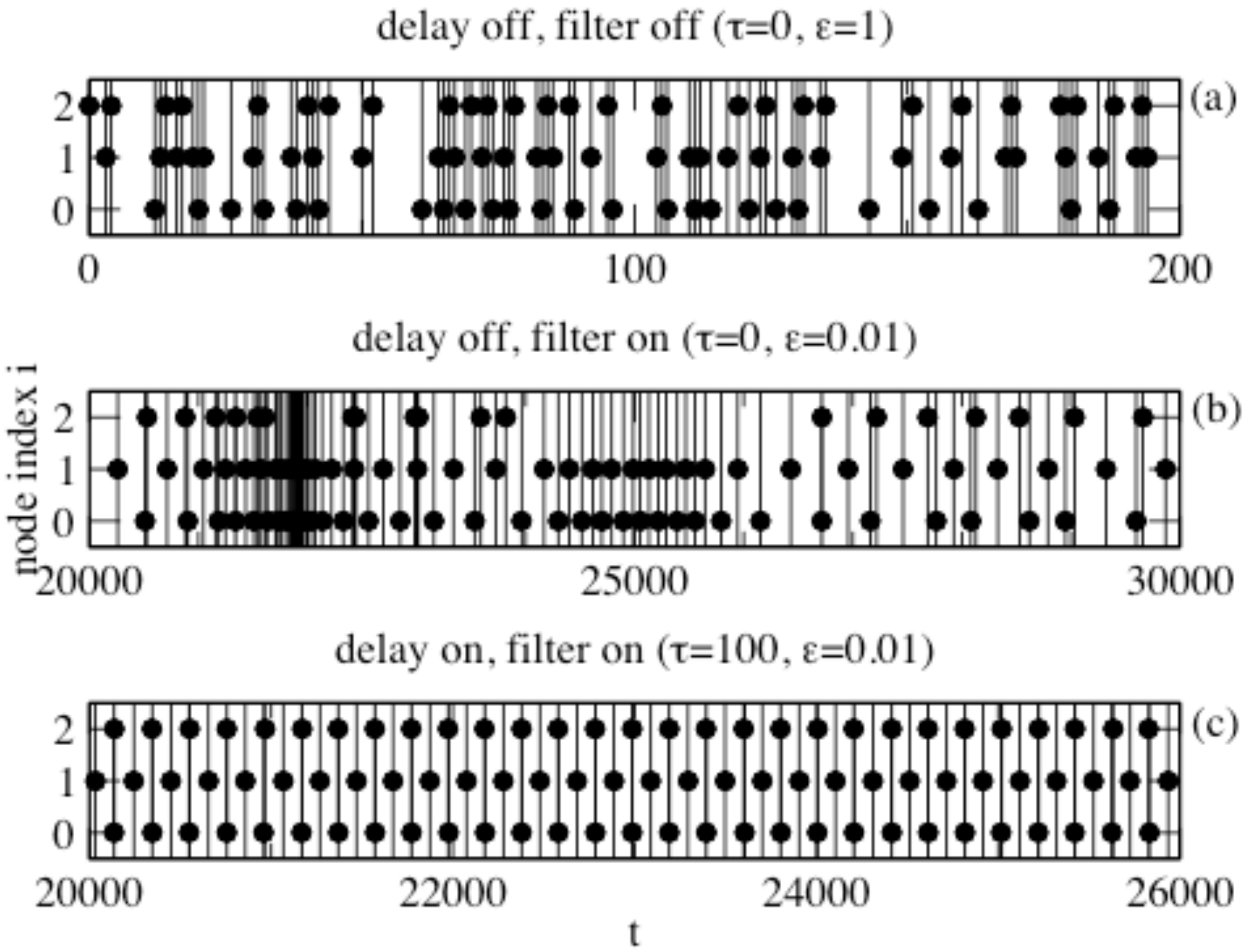
$$\varepsilon = \alpha\Delta t \qquad S_j = \theta\left(c_j - 1/2\right) \qquad c_i \in [0,1]$$

- Stochastic numerical integration: random sequential update

[K. Klemm & S.B., q-bio/0309013]

Switching pattern of nodes with filter and delay




delay off, filter off (τ=0, ε=1)

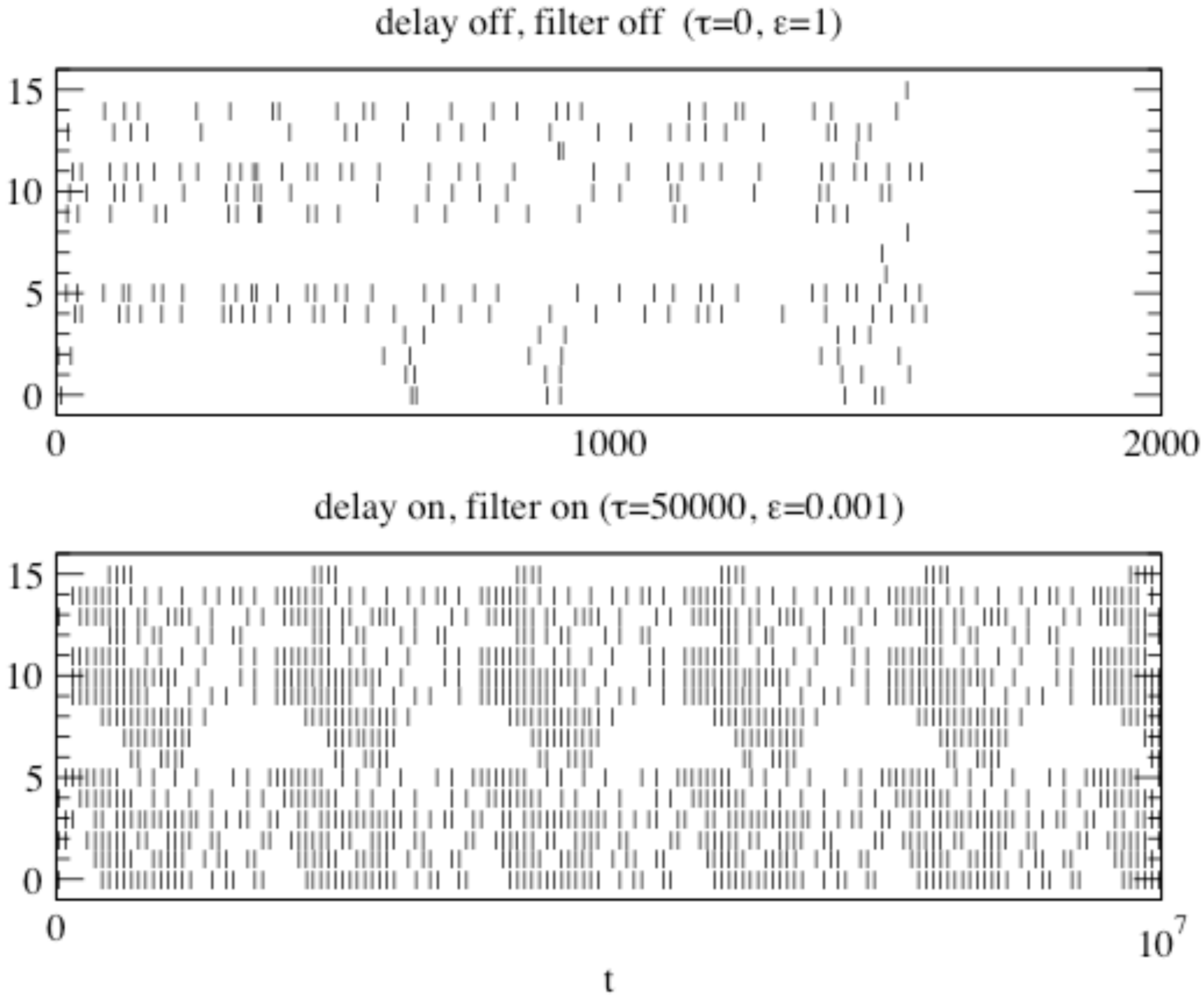
delay off, filter on (τ=0, ε=0.01)

delay on, filter on (τ=100, ε=0.01)

- Stable quasi-deterministic dynamics under asynchronous (random single spin) updates!

Dynamics on a random network

N=16, K=3, random single spin updates



delay off, filter off (τ=0, ε=1)

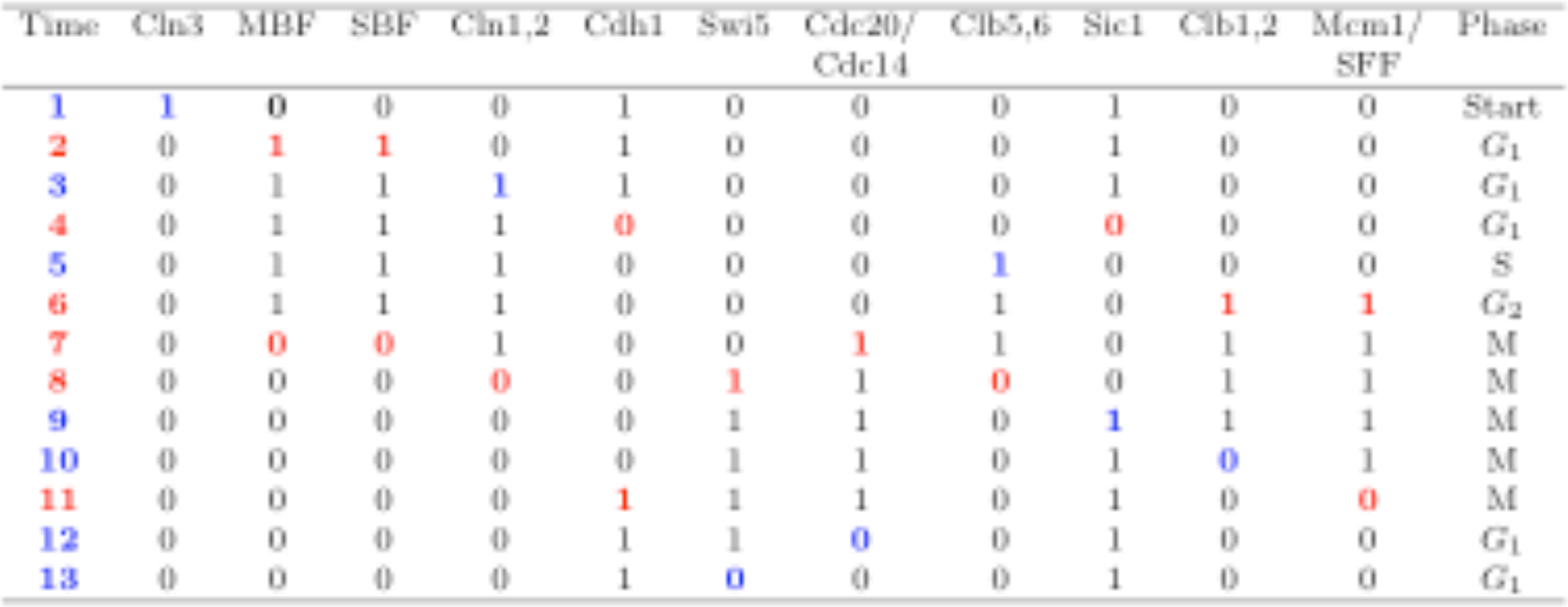
delay on, filter on (τ=50000, ε=0.001)

Parallel-update dynamics recovered under asynchronous dynamics!

[K. Klemm & S.B., q-bio/0309013]

The yeast cell cycle network revisited:
How does it deal with noise?

Multi-switch events can in principle de-synchronize:



Time	Cln3	MBF	SBF	Cln1,2	Cdh1	Swi5	Cdc20/ Cdc14	Clb5,6	Sic1	Clb1,2	Mcm1/ SFF	Phase
1	1	0	0	0	1	0	0	0	1	0	0	Start
2	0	1	1	0	1	0	0	0	1	0	0	G_1
3	0	1	1	1	1	0	0	0	1	0	0	G_1
4	0	1	1	1	0	0	0	0	0	0	0	G_1
5	0	1	1	1	0	0	0	1	0	0	0	S
6	0	1	1	1	0	0	0	1	0	1	1	G_2
7	0	0	0	1	0	0	1	1	0	1	1	M
8	0	0	0	0	0	1	1	0	0	1	1	M
9	0	0	0	0	0	1	1	0	1	1	1	M
10	0	0	0	0	0	1	1	0	1	0	1	M
11	0	0	0	0	1	1	1	0	1	0	0	M
12	0	0	0	0	1	1	0	0	1	0	0	G_1
13	0	0	0	0	1	0	0	0	1	0	0	G_1

[asynchronous modeling strategy e.g: M Chaves,
R Albert, ED Sontag, J Theor Biol 235 (2005) 431]

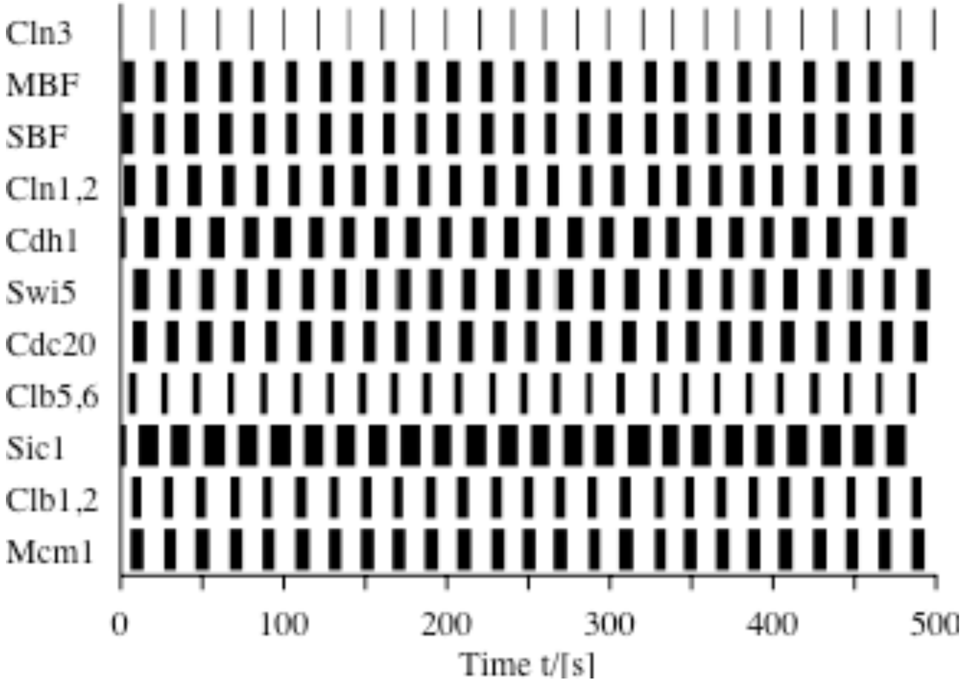
A stochastic model of the yeast cell cycle network

Delay differential equation: $\dfrac{dc_i(t)}{dt} = f_i(t,t_d) - \dfrac{c_i(t)}{\tau}$

$$f_i(t,t_d) = \begin{cases} 1, \sum_j a_{ij} S_j(t-t_d) > 0 \\ 0, \sum_j a_{ij} S_j(t-t_d) < 0 \end{cases}$$

$$S_i(t) = \begin{cases} 1, c_i(t) > 0.5 \\ 0, c_i(t) < 0.5 \end{cases}$$

Fluctuating delay t_d:



Order of switching events stable against timing fluctuations ---> Yeast cell cycle is stable

[S. Braunewell & S.Bornholdt, J. Theor. Biol. 245 (2007) 638]
[other stochastic yeast model: Zhang et al., Physica D 219 (2006) 35]

Are we just lucky?

In fact most attractors in discrete dynamical networks are artifacts of the synchronous update mode (!) and disappear in the presence of noise...

[F. Greil & B. Drossel, Phys. Rev. Lett. 95 (2005) 048701; K. Klemm & S. Bornholdt, Phys. Rev. E 72 (2005) 055101(R)]

Independence of temporal order of flips requires:

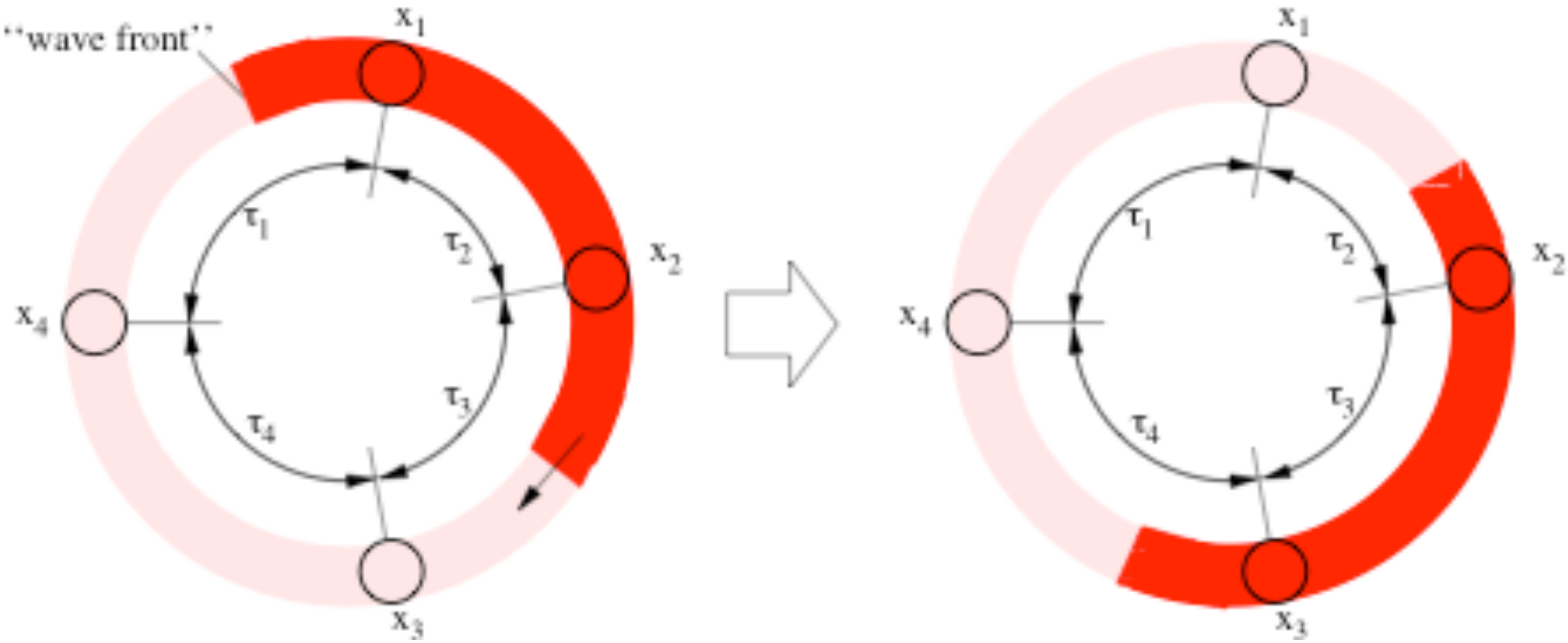
1. Nodes must have stable (non-fluctuating) input when they are required to flip.
2. Nodes that flip in the same macro time step must not influence each other.

...these are the same rules as in electrical engineering!

[K. Klemm & S.Bornholdt, PNAS 102 (2005) 18414]

Requirement for robustness against noise poses constraints on network topology

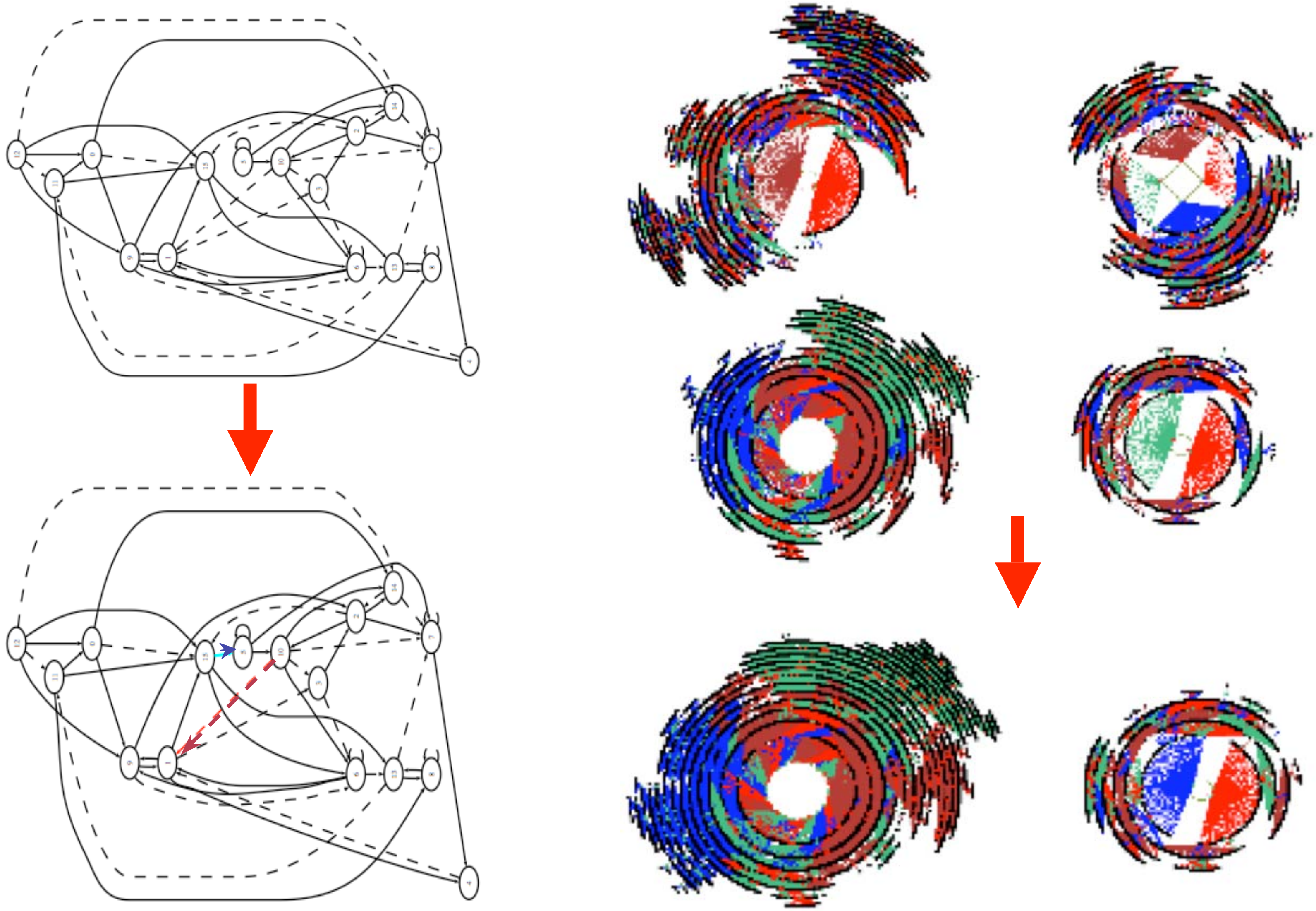
Why the 4-node Repressilator is unstable....



Phase not conserved for loops with even # of inhibitory links

[K. Klemm & S.Bornholdt, PNAS 102 (2005) 18414]

Reliable networks are evolvable



Single Mutations can stabilize a given attractor!

[S. Braunewell & S.Bornholdt (2007) arxiv.org/abs/0707.1407]

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Case study: Cell cycle control of fission yeast

Existing model: Differential equations with 40+ free parameters

$$\frac{d[\mathrm{Cdc13}_T]}{dt}=k_1M-(k_2'+k_2''[\mathrm{Ste9}]+k_2'''[\mathrm{Slp1}])[\mathrm{Cdc13}_T], \tag{1}$$

$$\frac{d[\mathrm{preMPF}]}{dt}=k_{\mathrm{wee}}([\mathrm{Cdc13}_T]-[\mathrm{preMPF}])-k_{25}[\mathrm{preMPF}]-(k_2' +k_2''[\mathrm{Ste9}]+k_2'''[\mathrm{Slp1}])[\mathrm{preMPF}], \tag{2}$$

$$\frac{d[\mathrm{Ste9}]}{dt}=(k_3'+k_3''[\mathrm{Slp1}])\frac{1-[\mathrm{Ste9}]}{J_3+1-[\mathrm{Ste9}]}-(k_4'[\mathrm{SK}] +k_4[\mathrm{MPF}])\frac{[\mathrm{Ste9}]}{J_4+[\mathrm{Ste9}]}, \tag{3}$$

$$\frac{d[\mathrm{Slp1}_T]}{dt}=k_5'+k_5''\frac{[\mathrm{MPF}]^4}{J_5^4+[\mathrm{MPF}]^4}-k_6[\mathrm{Slp1}_T], \tag{4}$$

$$\frac{d[\mathrm{Slp1}]}{dt}=k_7[\mathrm{IEP}]\frac{[\mathrm{Slp1}_T]-[\mathrm{Slp1}]}{J_7+[\mathrm{Slp1}_T]-[\mathrm{Slp1}]} -k_8\frac{[\mathrm{Slp1}]}{J_8+[\mathrm{Slp1}]}-k_6[\mathrm{Slp1}], \tag{5}$$

$$\frac{d[\mathrm{IEP}]}{dt}=k_9[\mathrm{MPF}]\frac{1-[\mathrm{IEP}]}{J_9+1-[\mathrm{IEP}]}-k_{10}\frac{[\mathrm{IEP}]}{J_{10}+[\mathrm{IEP}]}, \tag{6}$$

$$\frac{d[\mathrm{Rum1}_T]}{dt}=k_{11}-(k_{12}+k_{12}'[\mathrm{SK}]+k_{12}''[\mathrm{MPF}])[\mathrm{Rum1}_T], \tag{7}$$

$$\frac{d[\mathrm{SK}]}{dt}=k_{13}[\mathrm{TF}]-k_{14}[\mathrm{SK}], \tag{8}$$

$$\frac{dM}{dt}=\mu M, \tag{9}$$

$$[\mathrm{Trimer}]=\frac{2[\mathrm{Cdc13}_T][\mathrm{Rum1}_T]}{\Sigma+\sqrt{\Sigma^2-4[\mathrm{Cdc13}_T][\mathrm{Rum1}_T]}}, \tag{10}$$

$$[\mathrm{MPF}]=\frac{([\mathrm{Cdc13}_T]-[\mathrm{preMPF}])([\mathrm{Cdc13}_T]-[\mathrm{Trimer}])}{[\mathrm{Cdc13}_T]}, \tag{11}$$

$$[\mathrm{TF}]=G(k_{15}M,k_{16}'+k_{16}''[\mathrm{MPF}],J_{15},J_{16}), \tag{12}$$

where

$$k_{\mathrm{wee}}=k_{\mathrm{wee}}'+(k_{\mathrm{wee}}''-k_{\mathrm{wee}}')G(V_{a\mathrm{wee}},V_{i\mathrm{wee}}[\mathrm{MPF}],J_{a\mathrm{wee}},J_{i\mathrm{wee}}),$$

$$k_{25}=k_{25}'+(k_{25}''-k_{25}')G(V_{a25}[\mathrm{MPF}],V_{i25},J_{a25},J_{i25}),$$

$$\Sigma=[\mathrm{Cdc13}_T]+[\mathrm{Rum1}_T]+K_{\mathrm{diss}},$$

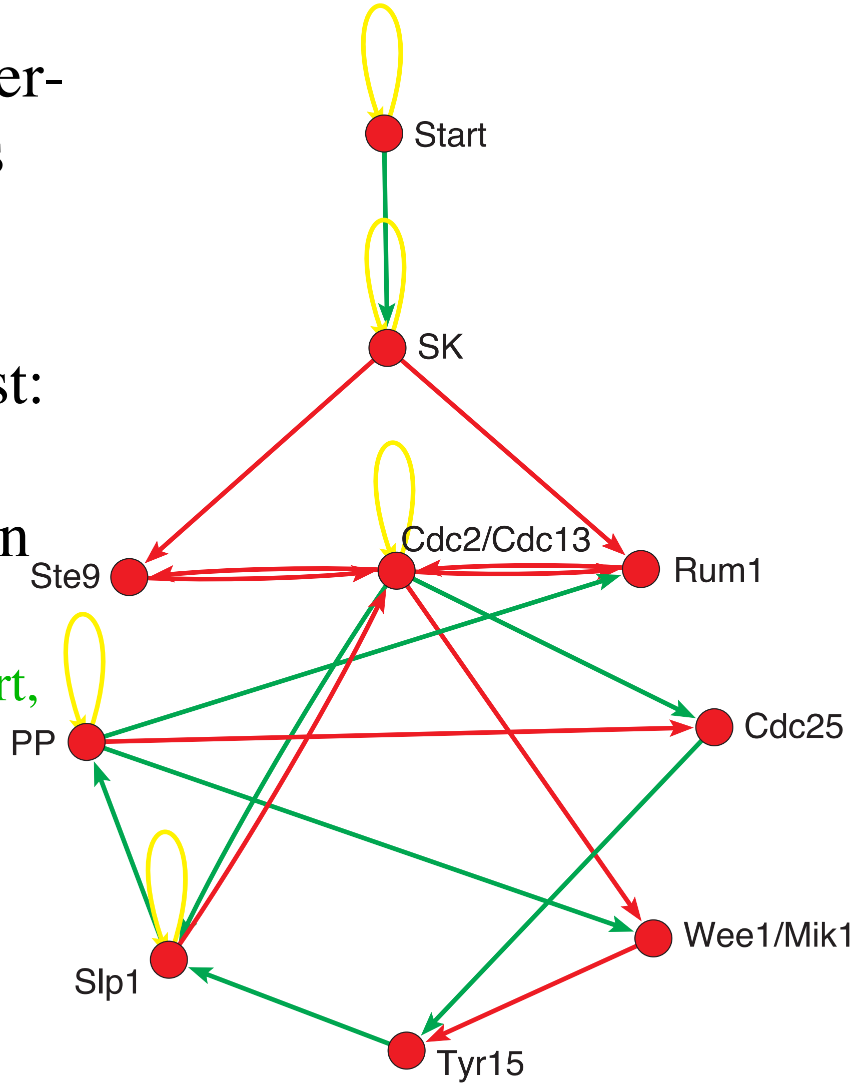
$$G(a,b,c,d)=\frac{2ad}{b-a+bc+ad+\sqrt{(b-a+bc+ad)^2-4ad(b-a)}}.$$

[B Novak et al., Chaos 11 (2001) 277]

Case study: Cell cycle control of fission yeast

- If a biological network is parameter-insensitive, can we drop parameters from the model altogether?

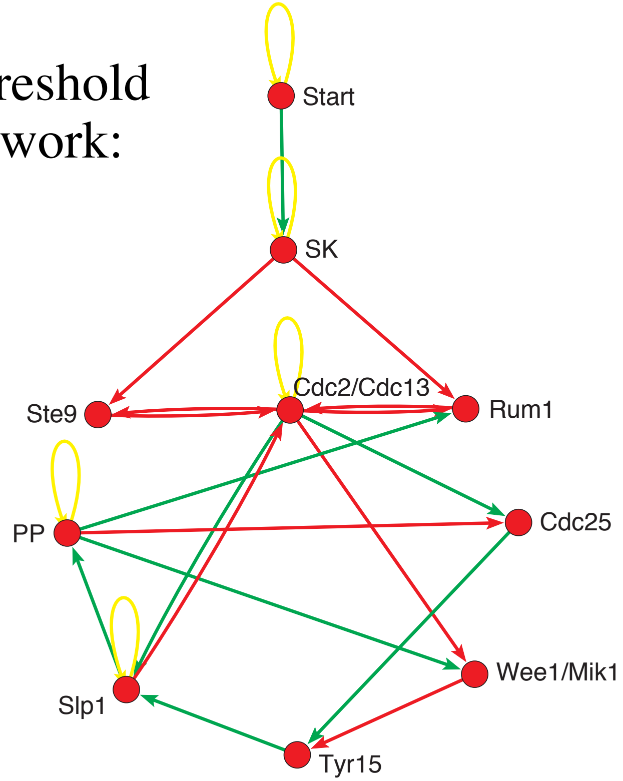
- Much different from budding yeast: This is largely a protein interaction network (non-transcriptional) --- can we model this the Boolean way?
[this worked earlier: Li, Assmann, & Albert, PLoS Biology e312 (2006)]



[M. Davidich & S.Bornholdt (2007) arxiv.org/abs/0704.2200]

Constructing a dynamical model of the fission yeast cell cycle

- Threshold network:



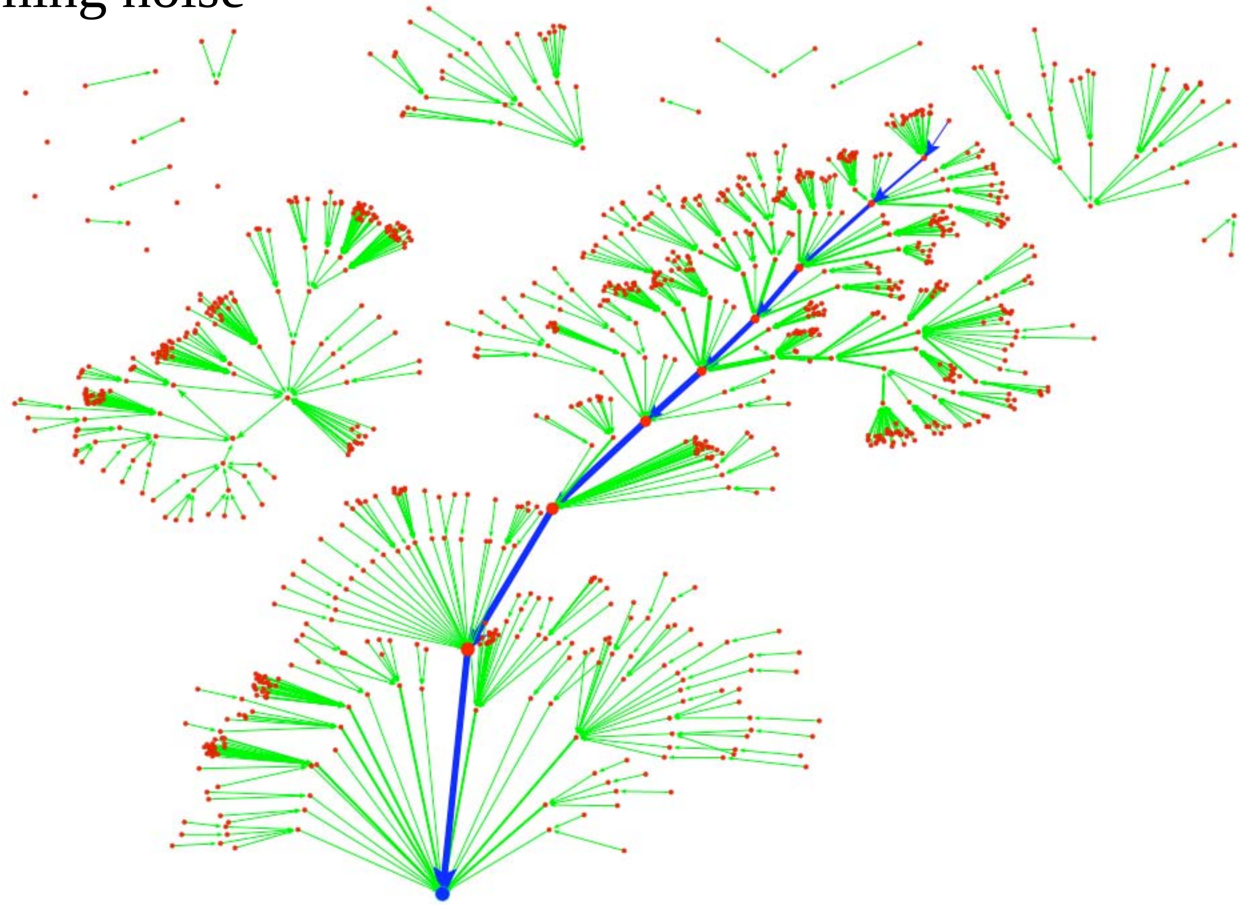
$$S_i(t+1) = \begin{cases} 1, & \sum_j a_{ij} S_j(t) > 0 \\ 0, & \sum_j a_{ij} S_j(t) < 0 \\ S_i(t), & \sum_j a_{ij} S_j(t) = 0 \end{cases}$$

- Couplings activating/inhibitory $a_{ij}=1$/ $a_{ij}=-1$
- Degradation $S_i(t+1) = 0$ if no input for more than 1 time step
- Synchronous dynamics for all nodes (genes/proteins)

[M. Davidich & S.Bornholdt (2007) arxiv.org/abs/0704.2200]

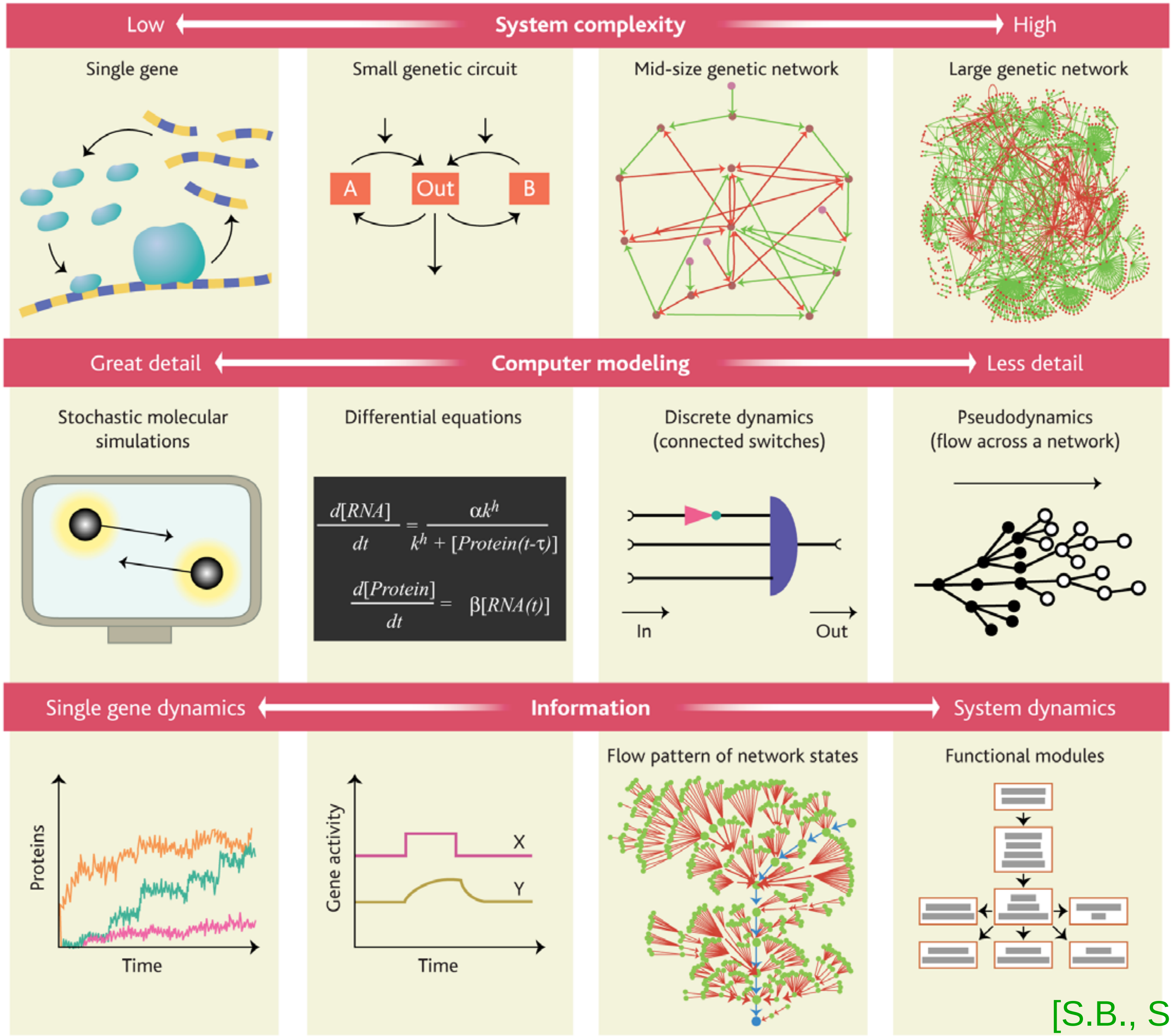
Fission yeast state space: Attractor landscape

- State space: 2^{10}=1024 states, 18 attractors (fixed points)
- Largest attractor (722 states) = biologically stable final state
- Trajectory after start signal follows the biological time sequence
- insensitive to timing noise

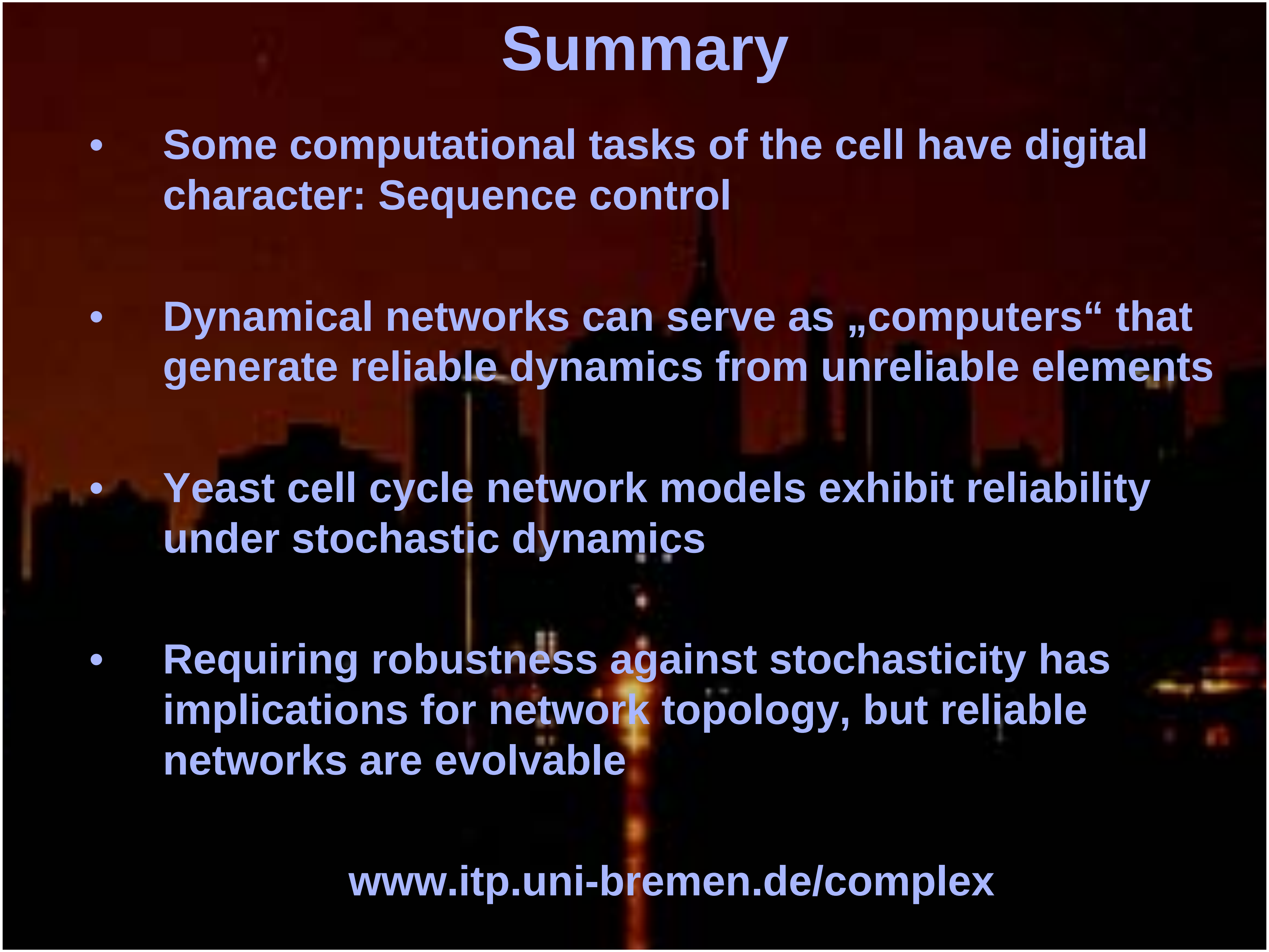


[M. Davidich & S.Bornholdt (2007) arxiv.org/abs/0704.2200]

Models of cellular networks



[S.B., Science 2005]



Summary

- Some computational tasks of the cell have digital character: Sequence control
- Dynamical networks can serve as „computers“ that generate reliable dynamics from unreliable elements
- Yeast cell cycle network models exhibit reliability under stochastic dynamics
- Requiring robustness against stochasticity has implications for network topology, but reliable networks are evolvable

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