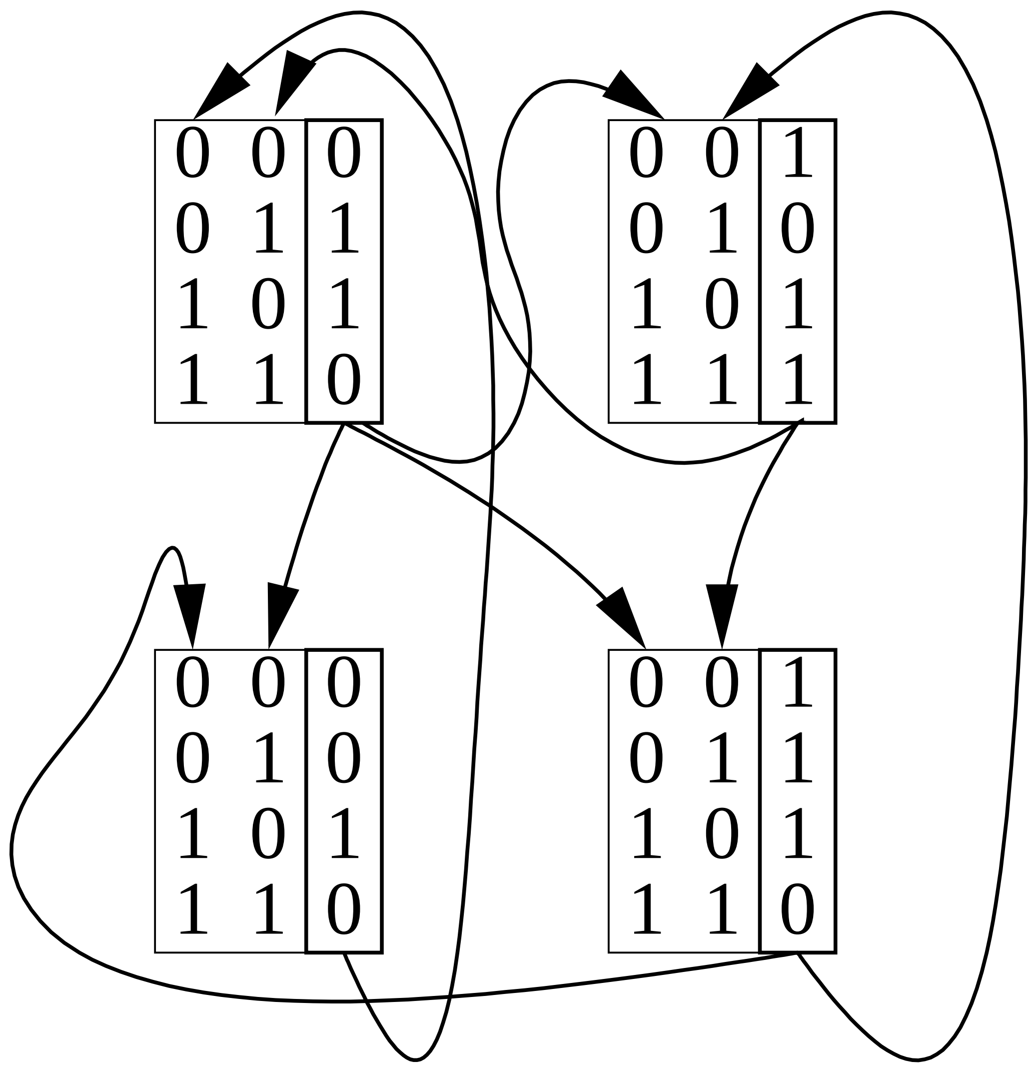
Stable and unstable attractors in Boolean networks

Konstantin Klemm
Bioinformatics, Dept. of Computer Science
University of Leipzig, Germany

Overview

- Boolean network model for gene regulatory circuits
- Attractor scaling in critical Boolean networks
- Which attractors are biologically relevant?
- Check stability under fluctuating response times
- Stable and unstable attractors: system size scaling

Boolean network model: coupled switches



Model setup and dynamics

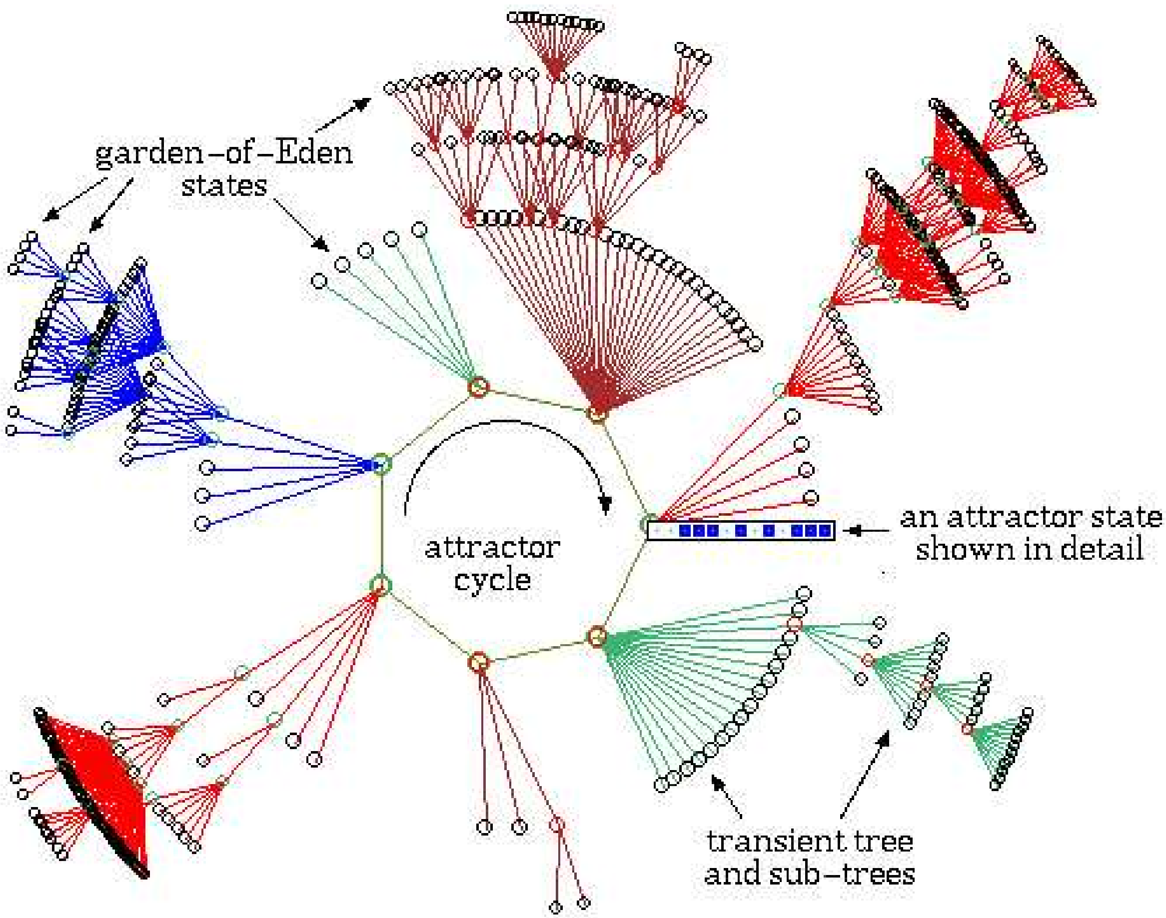
- Abstract model of coupled biological switches

- Model setup: Directed network of N units with binary states $x_i \in \{0, 1\}$

- Dynamics with synchronous update

$$x_i(t+1) = \text{Bool}_i(x_{i(1)}(t), x_{i(2)}(t), ..., x_{i(k)}(t)) \qquad (1)$$

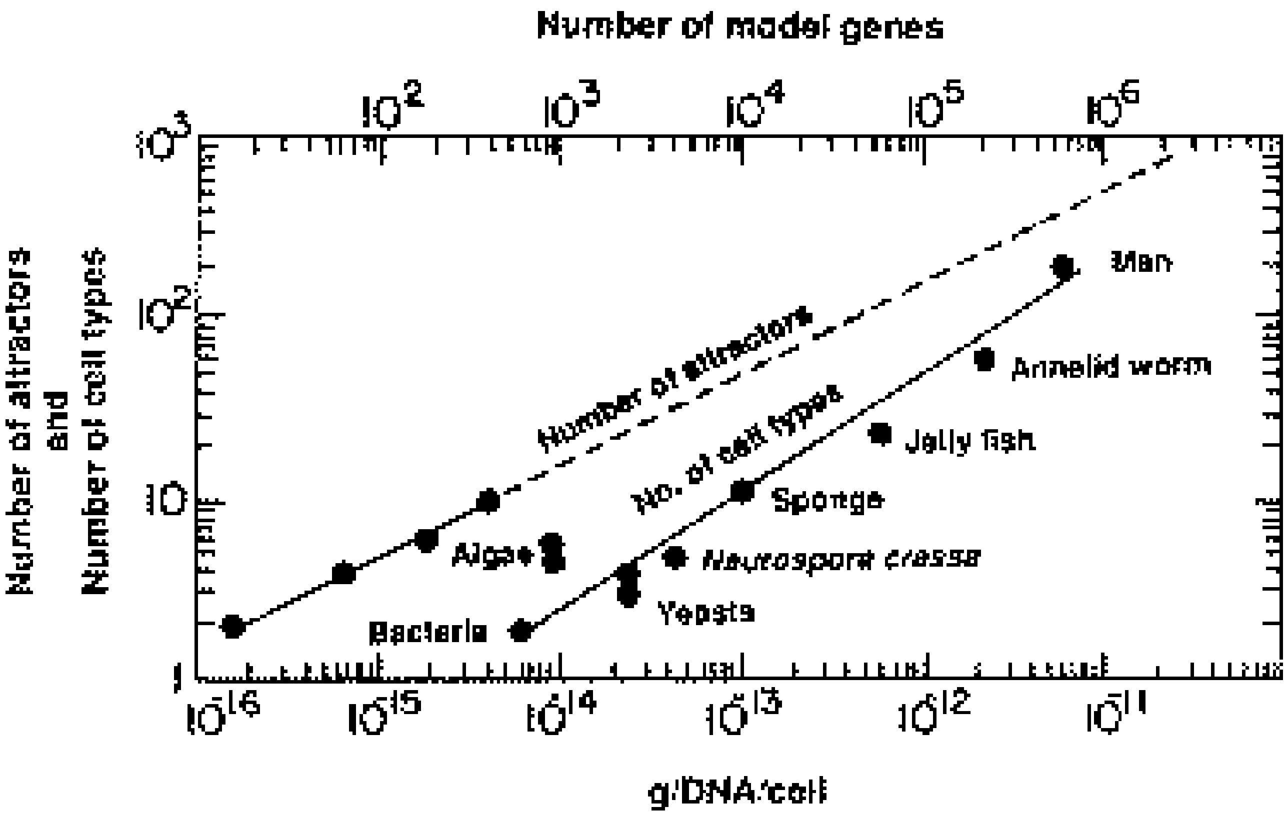
An attractor and its basin



(Andy Wuensche, 1998)

Data: # cell types vs. genome size

Sublinear attractor scaling



(Kauffman, 1993)

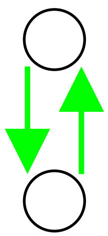
The history of attractor scaling

- Kauffman (1969): sublinear, #attractors $\propto \sqrt{\#\text{nodes}}$
- Bilke and Sjunesson (2001): linear
- Socolar and Kauffman (2003): superlinear
- Samuelsson and Troein (2003): superpolynomial

END of story?

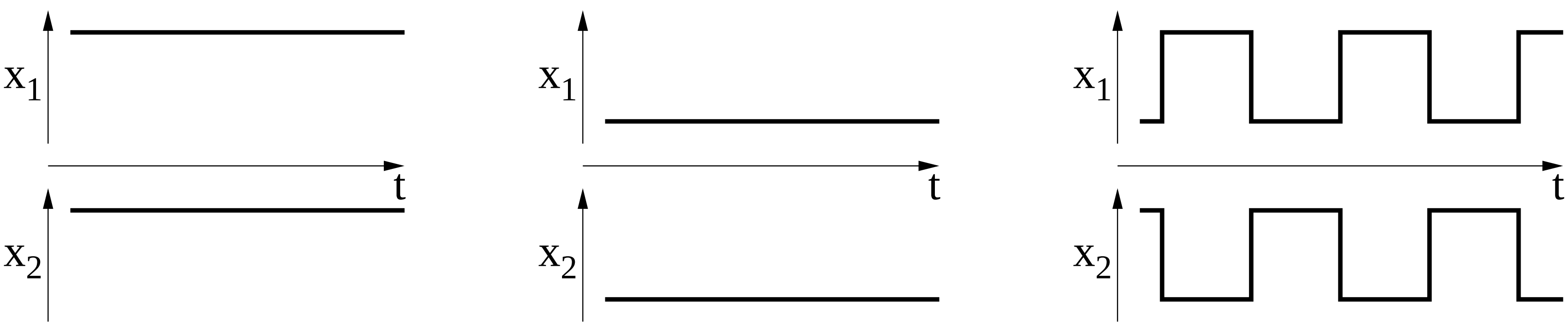
Are all attractors biologically relevant?

- consider toy cell — two regulatory genes, 3 attractors



$$x_1(t+1) = x_2(t)$$

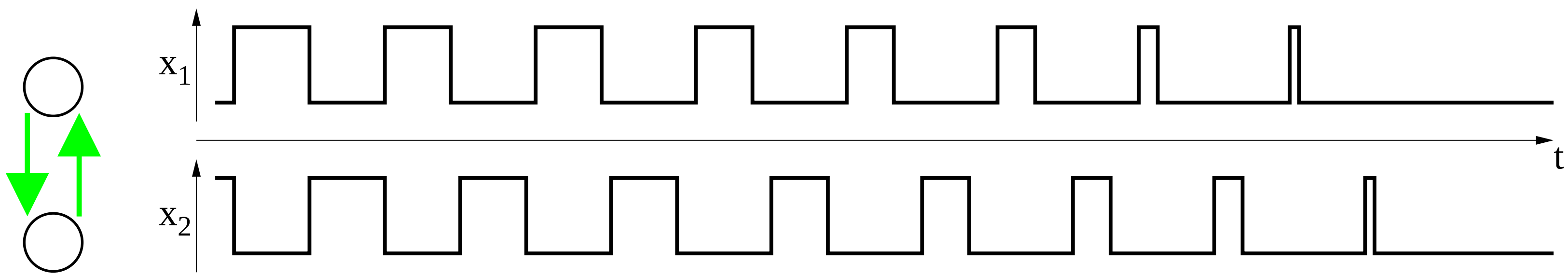
$$x_2(t+1) = x_1(t)$$



Fluctuating response times

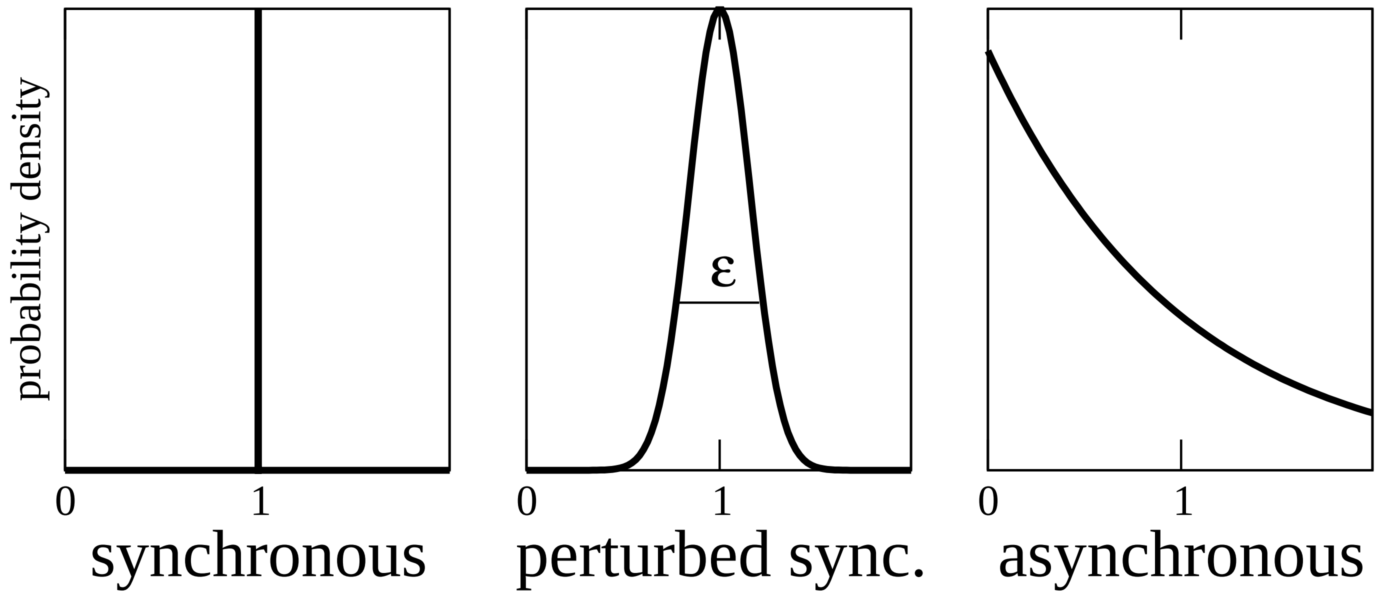
- Biological switches are noisy $\Rightarrow$ non-deterministic timing

- No central clock to sustain synchrony



- Attractors with unstable timing are not relevant for biological systems.

"Update modes"



"Update mode" = response time distribution

Stability criterion

Perturbing synchronous switching:

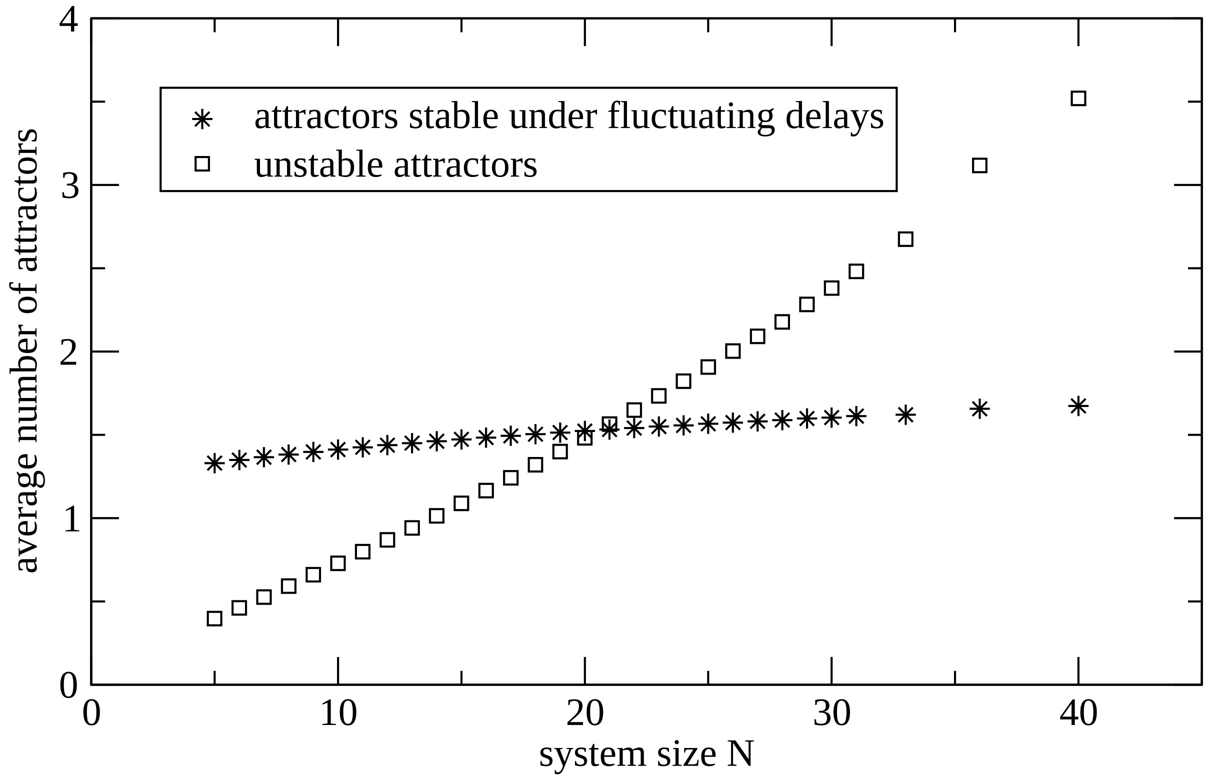
1. Let system run until time T.

2. Keep subset $\mathcal{S}$ of switches frozen during $[T, T + \epsilon]$.

3. Let system run normally again.

The attractor is stable iff all such perturbations $(\mathcal{S}, T)$ heal, i.e. the system always returns to synchronous switching.

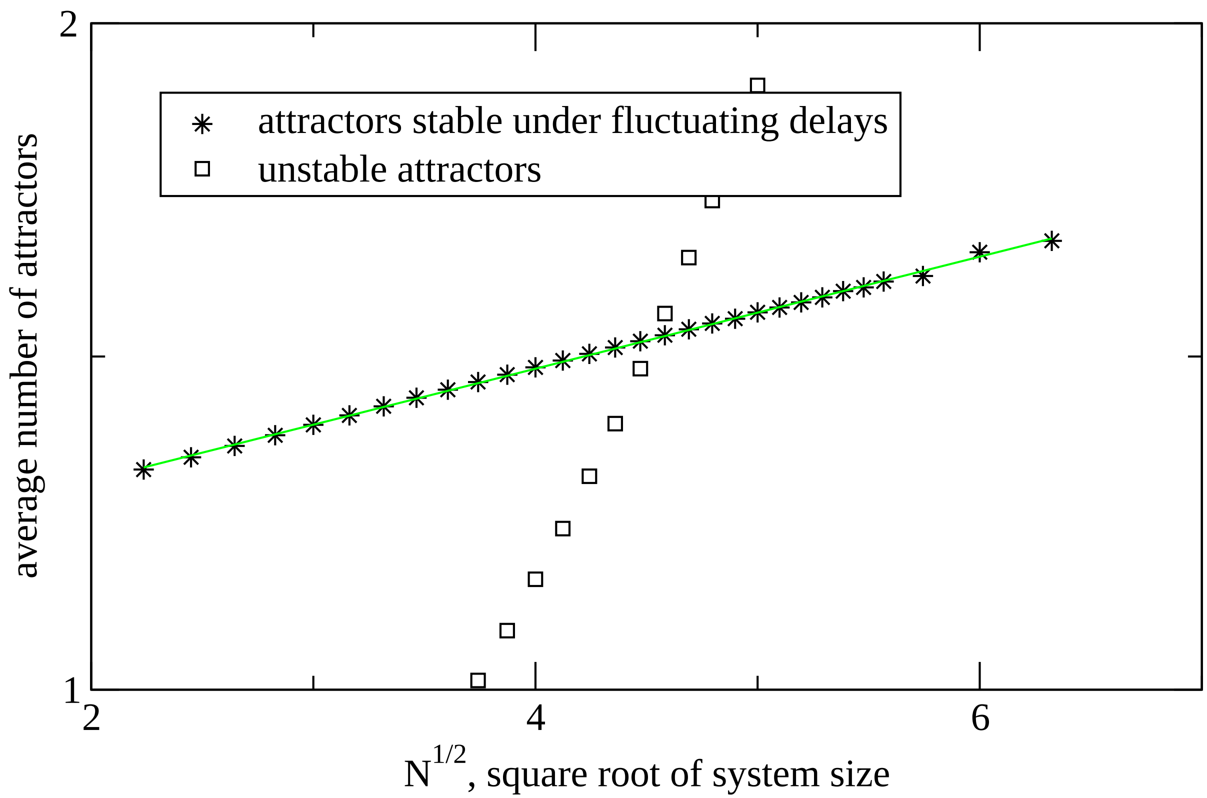
Counting stable and unstable attractors



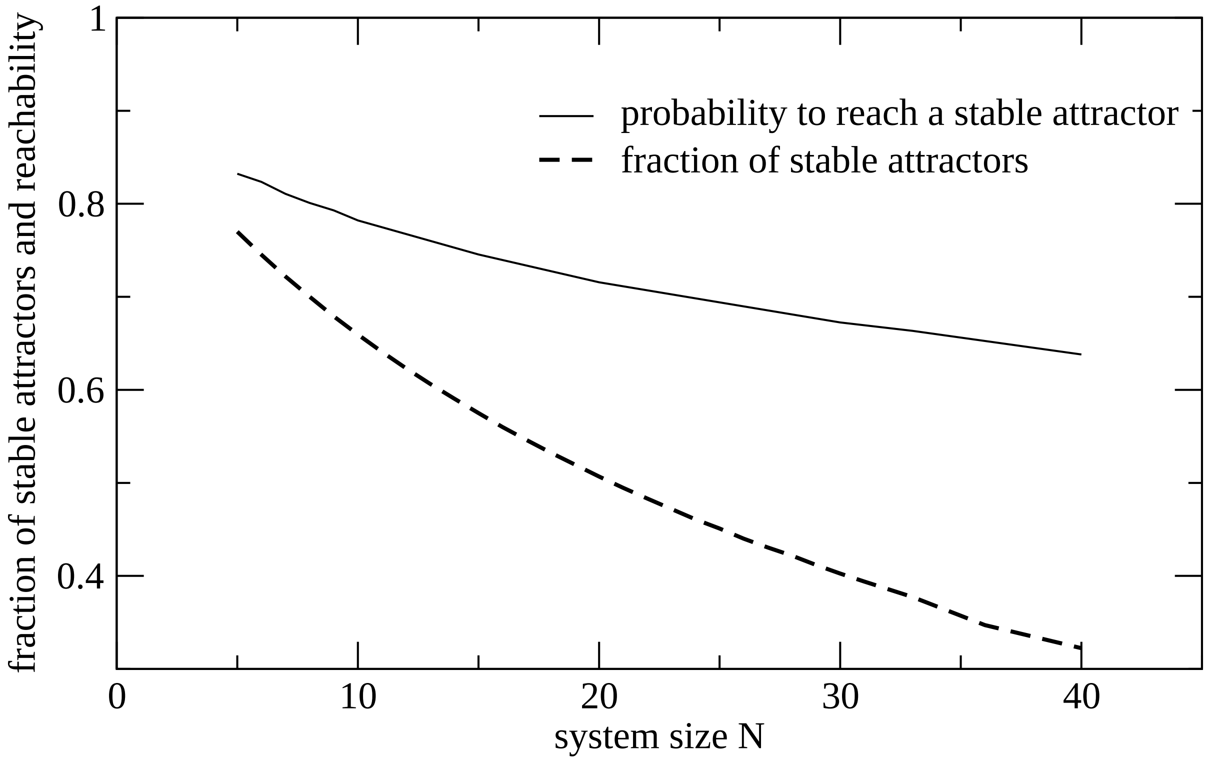
critical random Boolean networks, $K = 2$ inputs per node

exhaustive enumeration of state space

Stable attractors: square root scaling



Stable attractors: larger basins



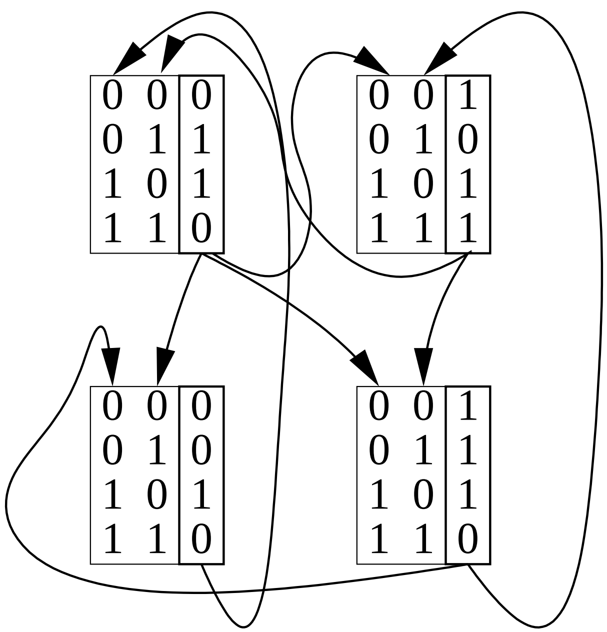
By sampling state space one preferentially finds stable attractors.

Summary

- Studied Critical Boolean networks with noisy updating
- Almost all attractors are unstable against small amounts of noise
- Sublinear growth of number of stable attractors with system size
- Mimics sublinear growth of number of celltypes with genome size

Klemm & Bornholdt, Phys. Rev. E **72**, 055101(R) (2005);
PNAS **102**, 18414 (2005).

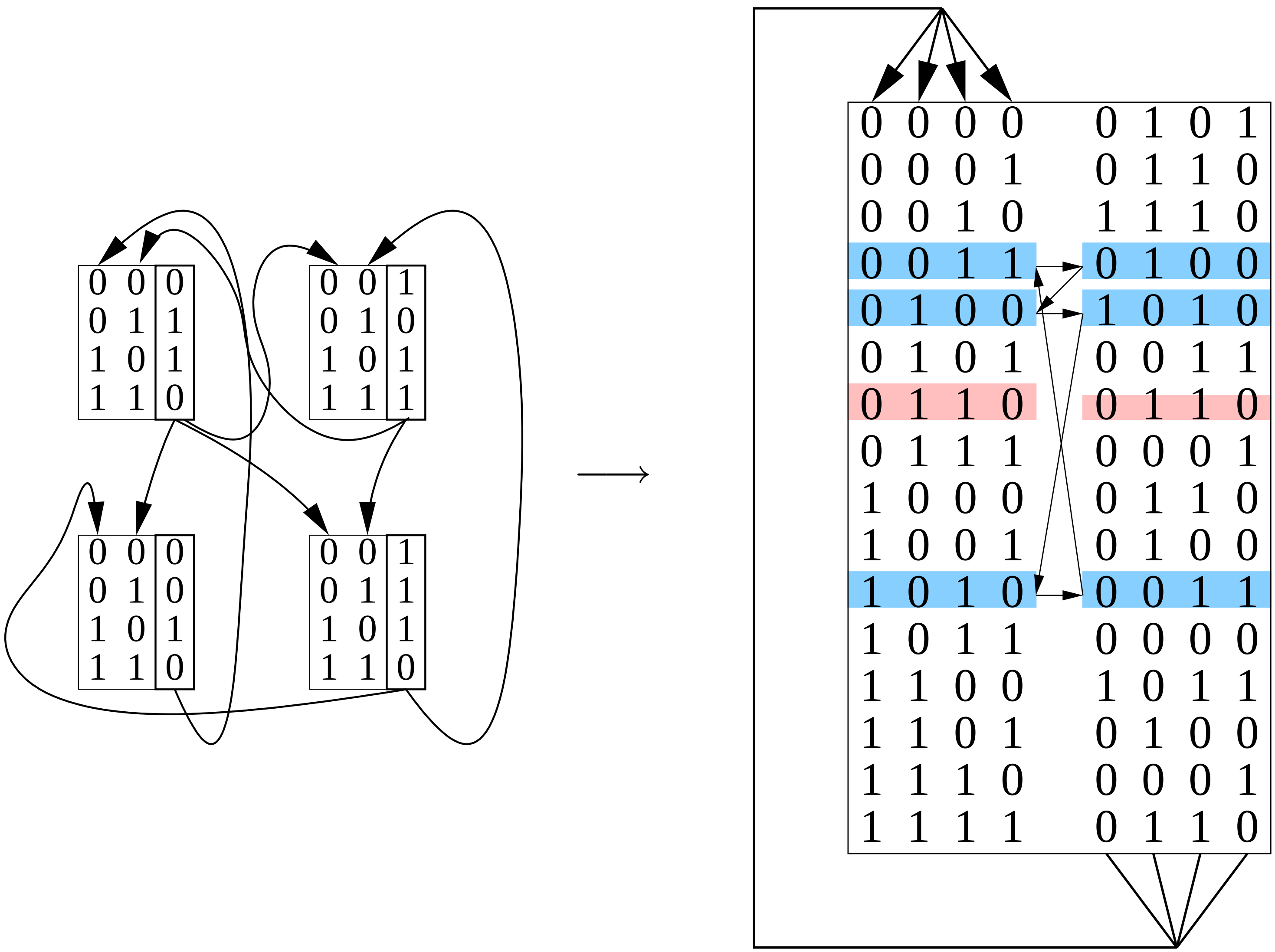
From Boolean network to discrete map



$\longrightarrow$

0	0	0	0	0	1	0	1
0	0	0	1	0	1	1	0
0	0	1	0	1	1	1	0
0	0	1	1	0	1	0	0
0	1	0	0	1	0	1	0
0	1	0	1	0	0	1	1
0	1	1	0	0	1	1	0
0	1	1	1	0	0	0	1
1	0	0	0	0	1	1	0
1	0	0	1	0	1	0	0
1	0	1	0	0	0	1	1
1	0	1	1	0	0	0	0
1	1	0	0	1	0	1	1
1	1	0	1	0	1	0	0
1	1	1	0	0	0	0	1
1	1	1	1	0	1	1	0

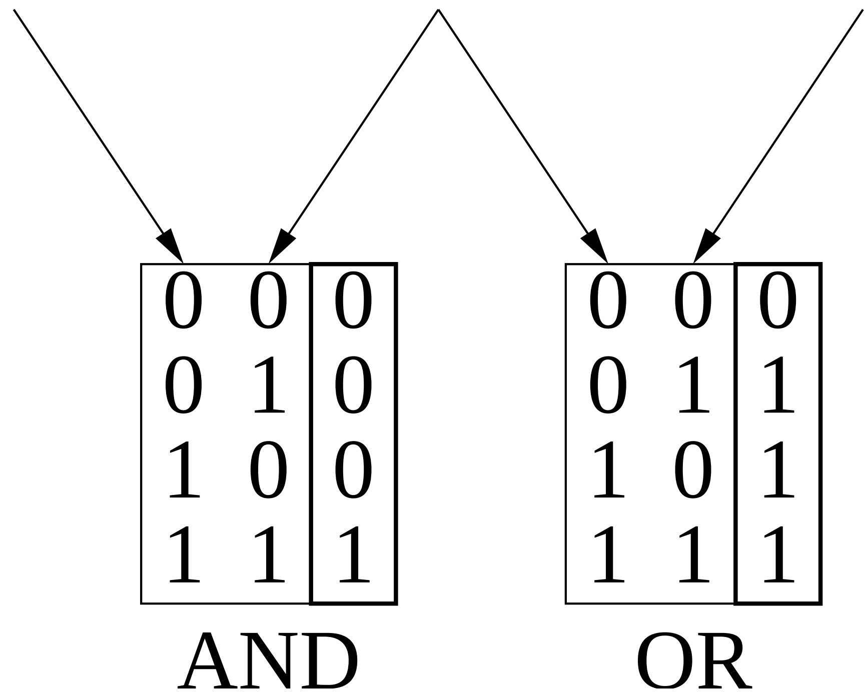
Attractors in discrete map



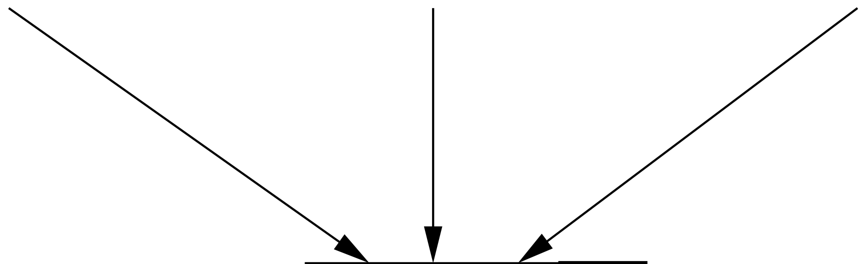
Efficient search for attractors?

- # states in attractors $\ll 2^N$
- full enumeration of state space is not an efficient method for finding all attractors
- Node removal (Bilke and Sjunnesson, 2001): reduce N recursively by eliminating constant nodes and nodes that do not influence other nodes
- Can reduction go beyond?

Node-node correlations and contraction



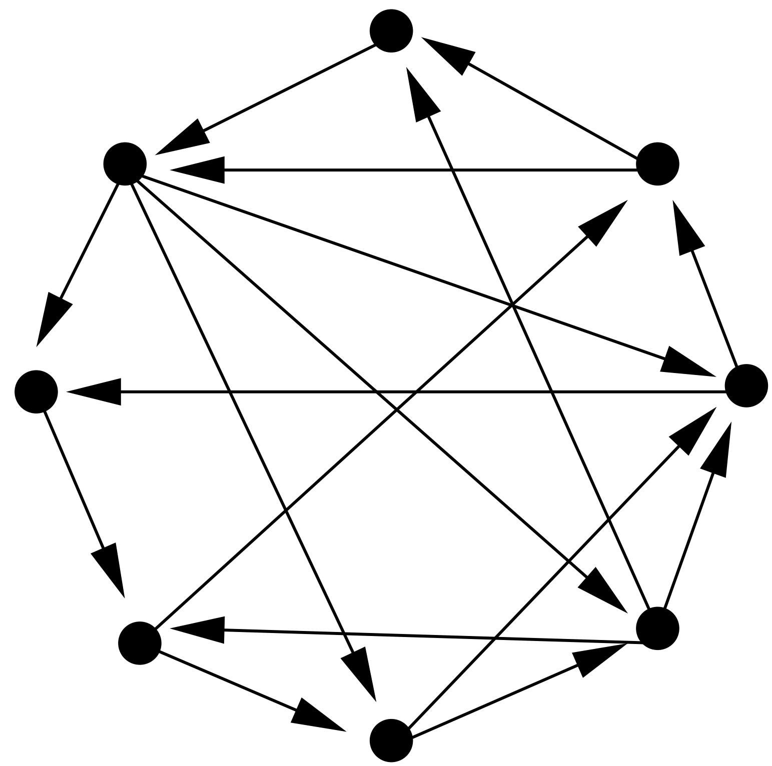
Node-node correlations and contraction



0	0	0	0
0	0	1	1
0	1	0	1
0	1	1	1
1	0	0	0
1	0	1	1
1	1	0	2
1	1	1	2

Test case

- Test recursive node contraction in networks that cannot be decimated directly.
- Use only Boolean functions that depend on both inputs ($K = 2$).
- Each node is "seen" by at least one other node.



Shrinking state space