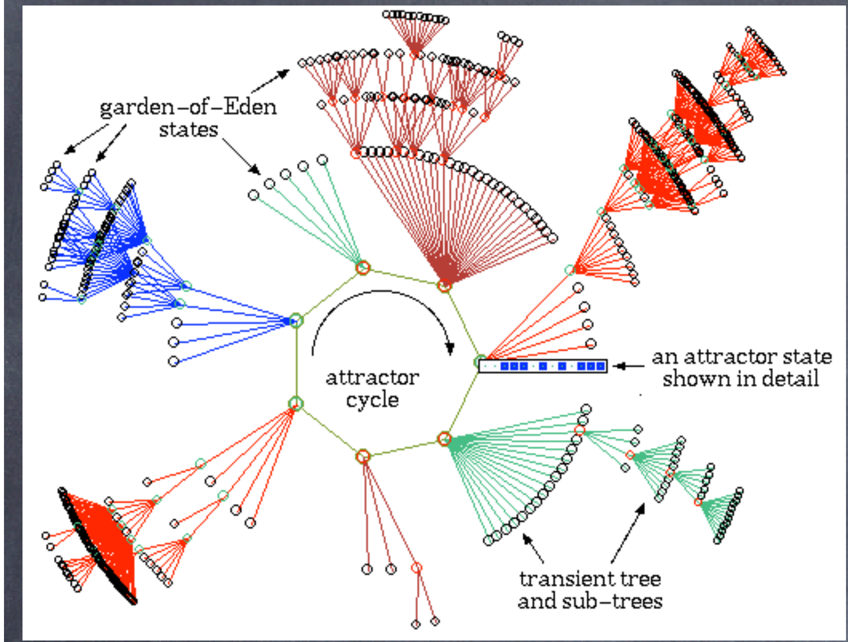
6. Regulatory Models that Mimic Phenotype and Dynamics, Part II

Warning: Statistical Physics.
It only works on average.

http://regan.med.edu/CVRB-course.php

Rhythm and its robustness



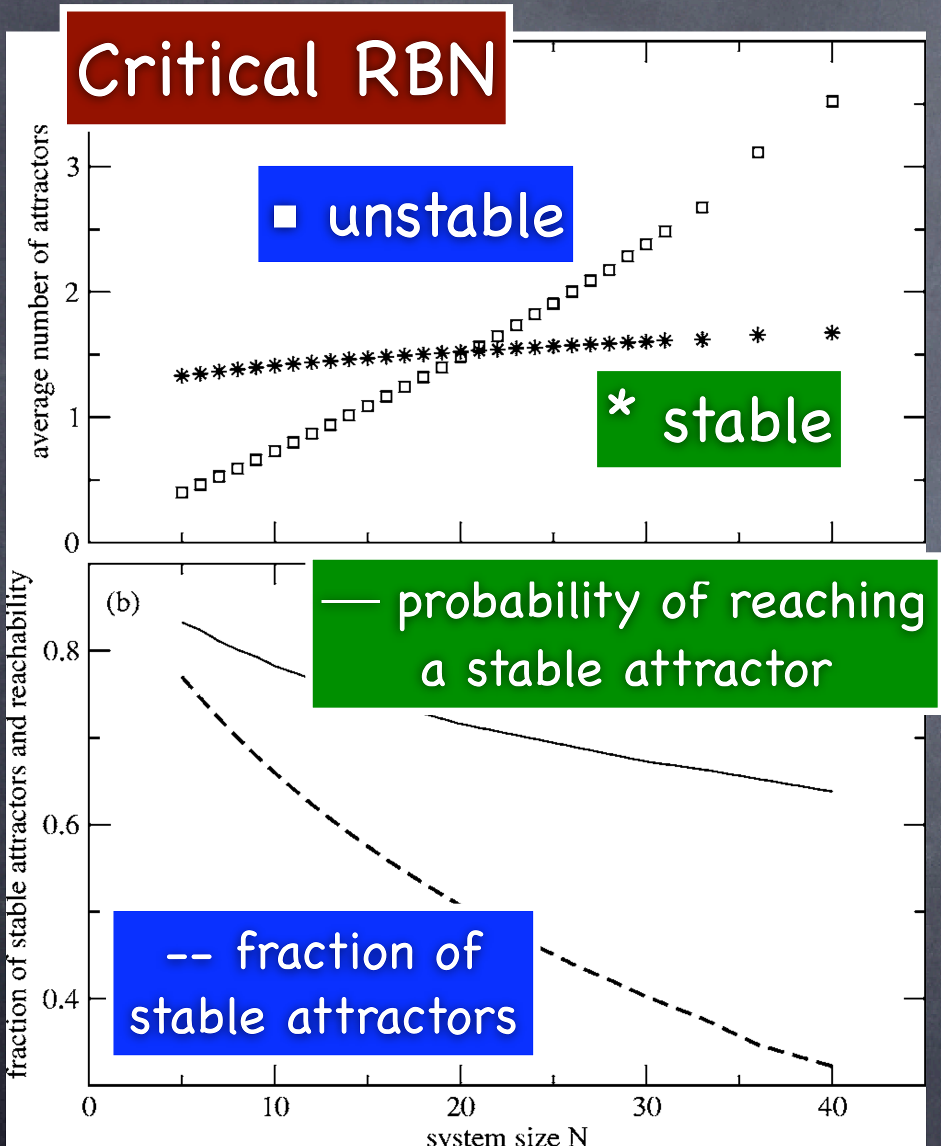
- Limit cycle attractors
  - ➡ no single steady state
  - ➡ potentially sensitive to fluctuating time delays

Are cyclic attractors artifacts of synchronous update?

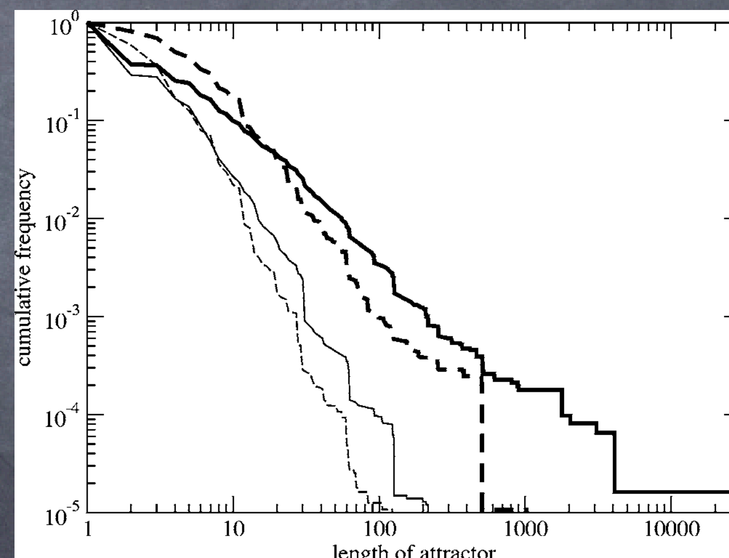
- Noise in synchronous update
  - ➡ continuous time
  - ➡ low-pass filter on node switching
    - ➡ the "command" from the gate driving a node has to stay consistent for a time s < 1

- Reliable attractor:
  - ➡ small random time delay on nodes: ε << s
  - ➡ all possible perturbations in time delay lead to the same attractor

In random Boolean networks...



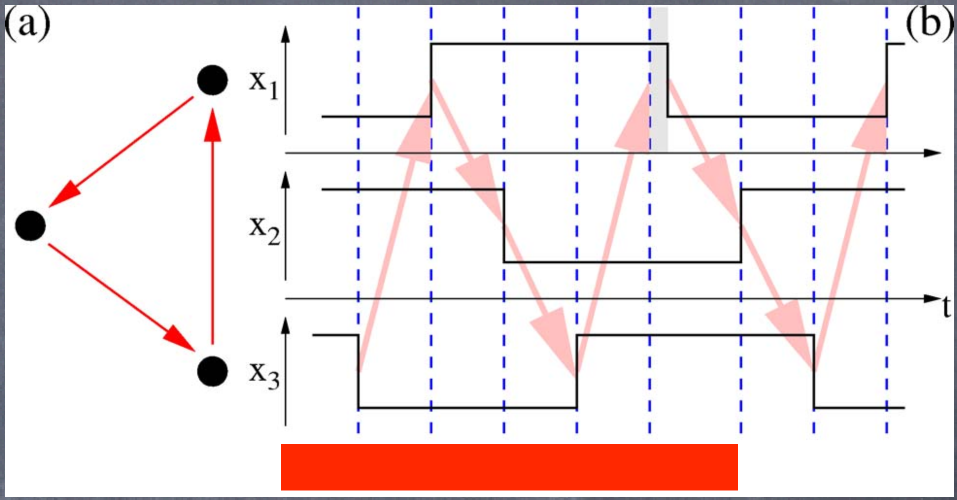
- Not so many stable attractors!
- They have larger basins of attraction

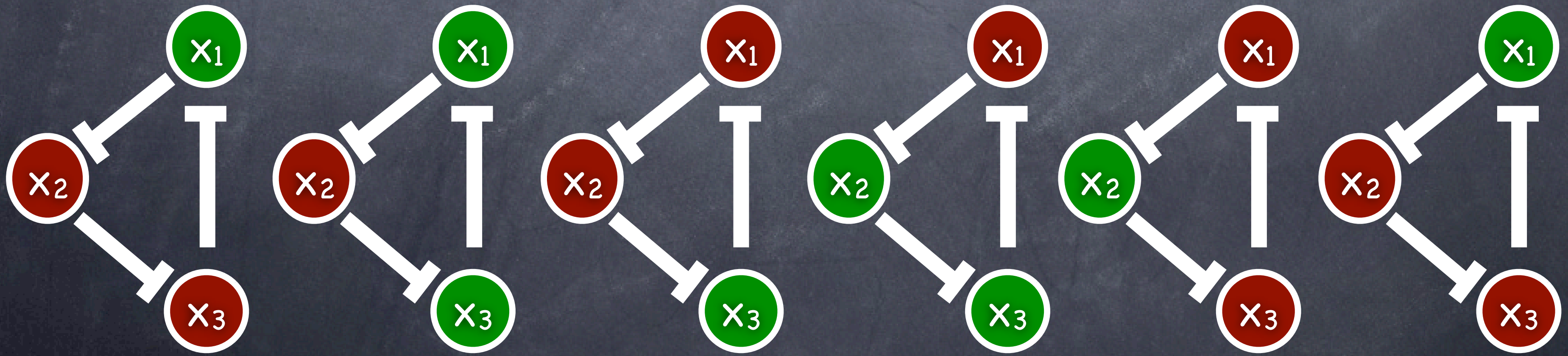


- They tend to have longer cycles!

What type of wiring makes a non-reliable attractor?

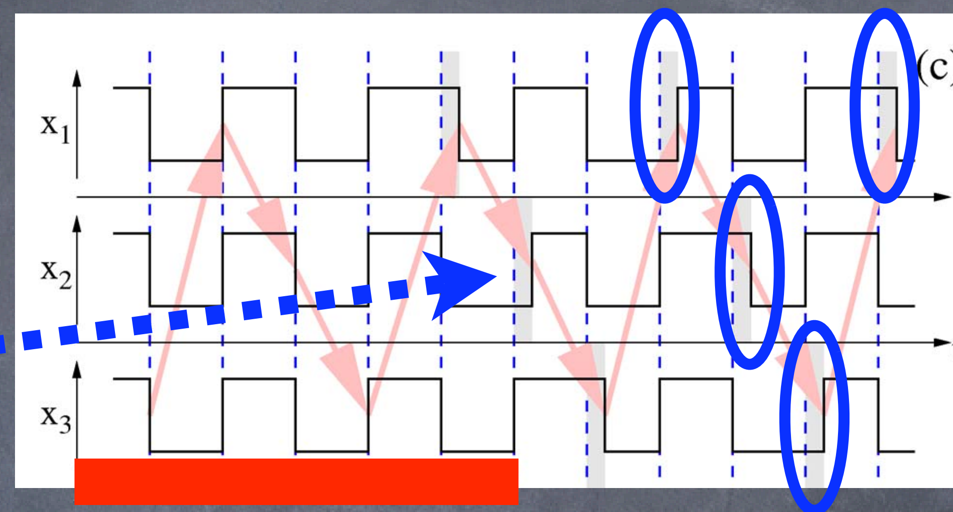
- Extreme modularity (causally disconnected network components)
- More than one cascade of switching events!

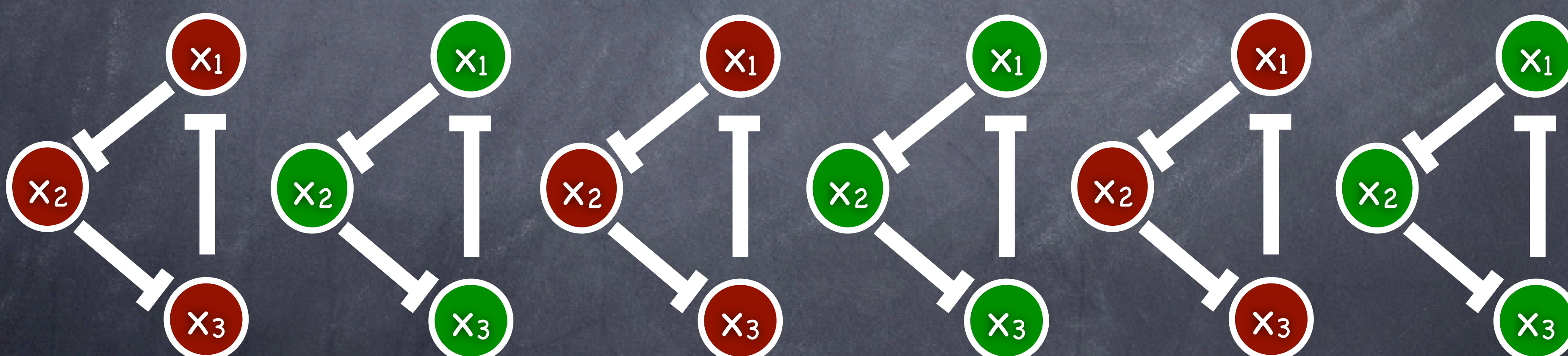




Juggling is unstable

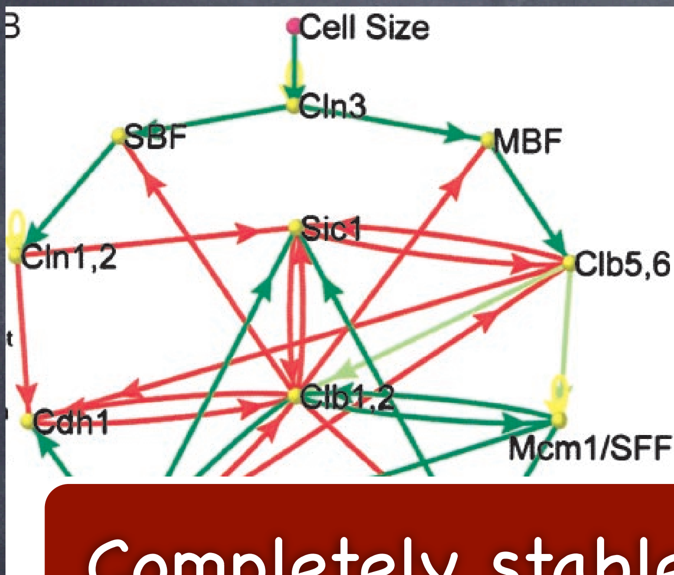
- More than one cascade of switching events!
- Causal cascades can accumulate phase shift and loose synchrony





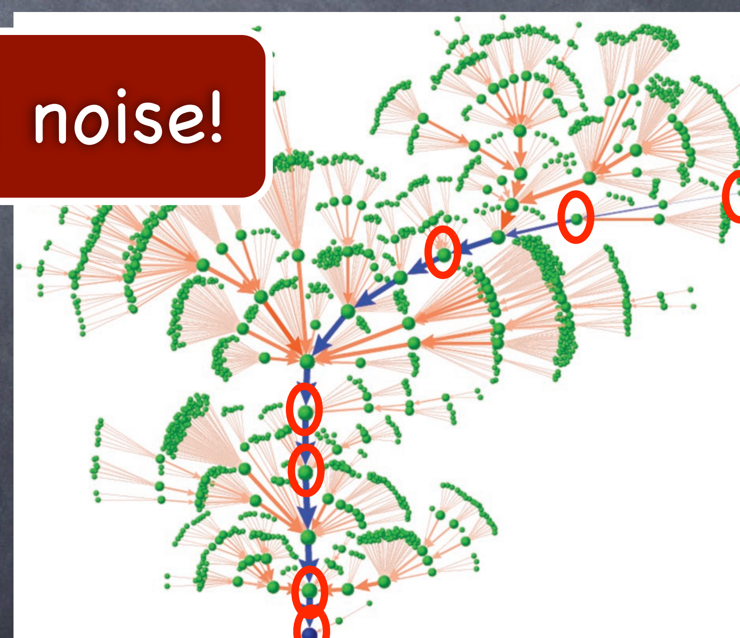
Causal switching chains need to stay in lock-step!

Back to biology: cell cycle revisited



- Same model of yeast CC
- Same update gates
- Noise in signal propagation time
  - ➡continuous time
  - ➡low-pass filter for switching
- Cycle: state S1 triggers Cln3 activation

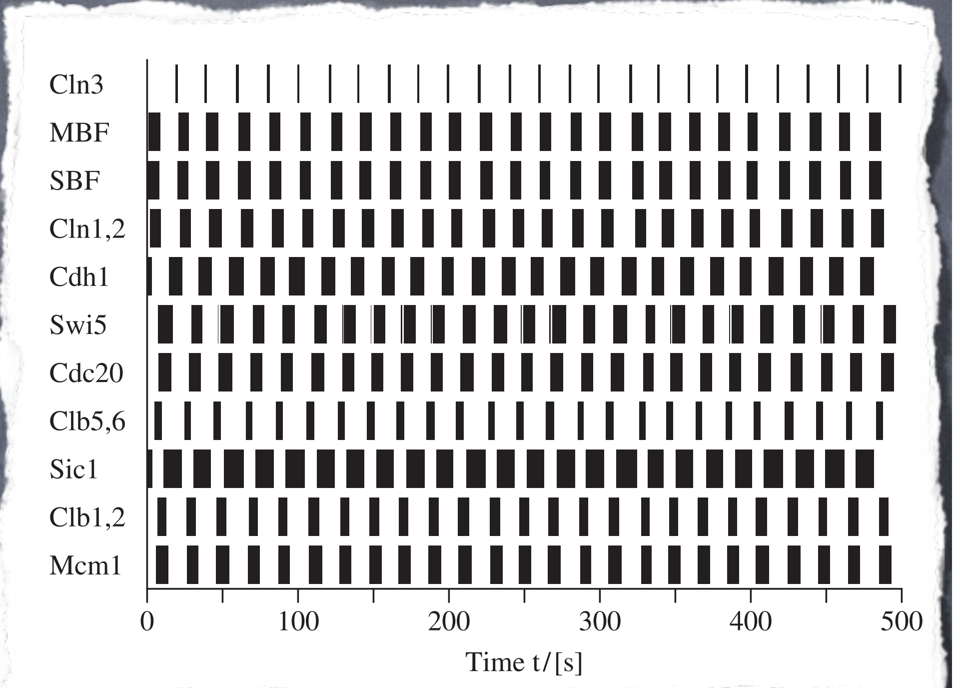
Completely stable for small noise!



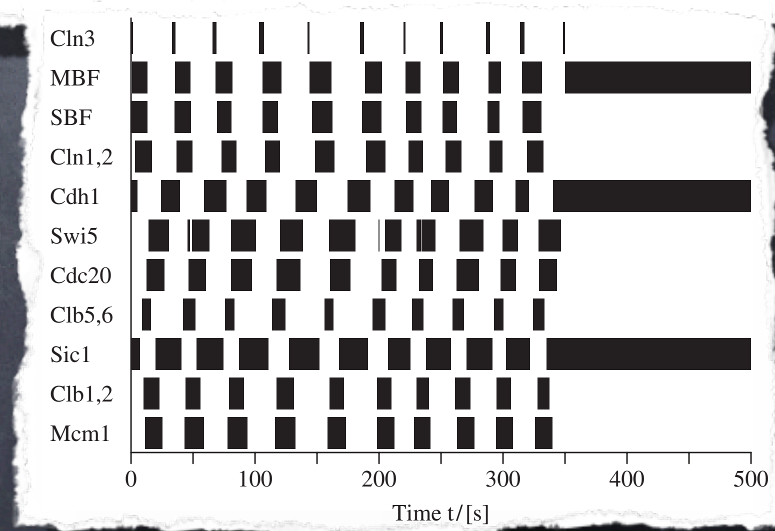
Buffer steps with change in just 1 node!

Does the cell cycle juggle?

- Stronger noise
  - allow delays past 1/2 the propagation time unit
- Looser stability measure
  - G1 is regularly assumed for a time period long enough to trigger CC restart



The system stays within the same attractor!



- Although attractor switch is possible

Is reliability evolvable?

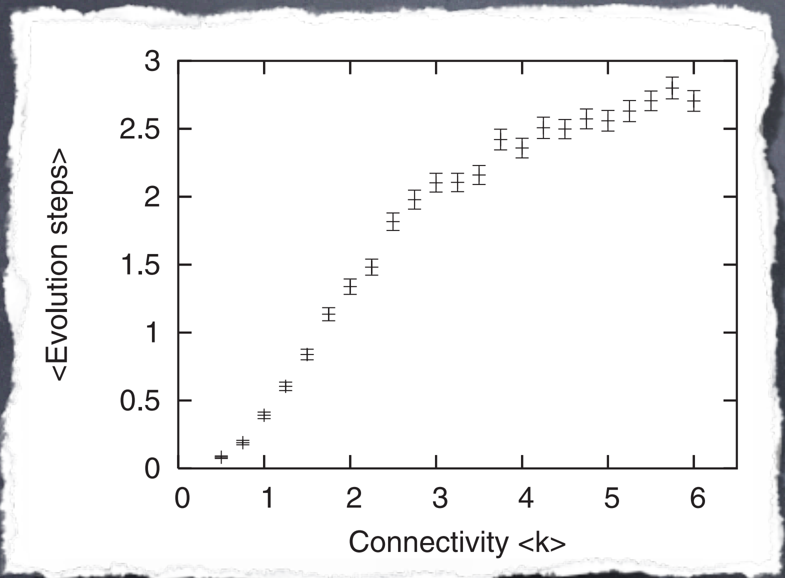
- Random threshold networks
  - ➡ map attractor landscape
  - ➡ record stable and unstable attractors
  - ➡ fitness score

- Evolutionary dynamics
  - ➡ rewire 1 link
  - ➡ measure new fitness
  - ➡ if higher than original, keep new network

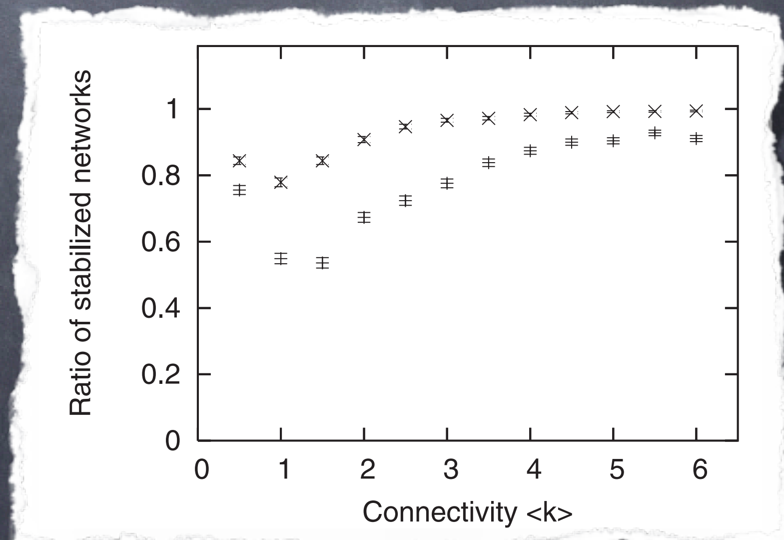
A) Full attractor landscape
<u>sum of stable basin sizes</u>

B) Functional attractor
<u>largest stable attractor basin size</u>

Evolving a stable landscape is easy!

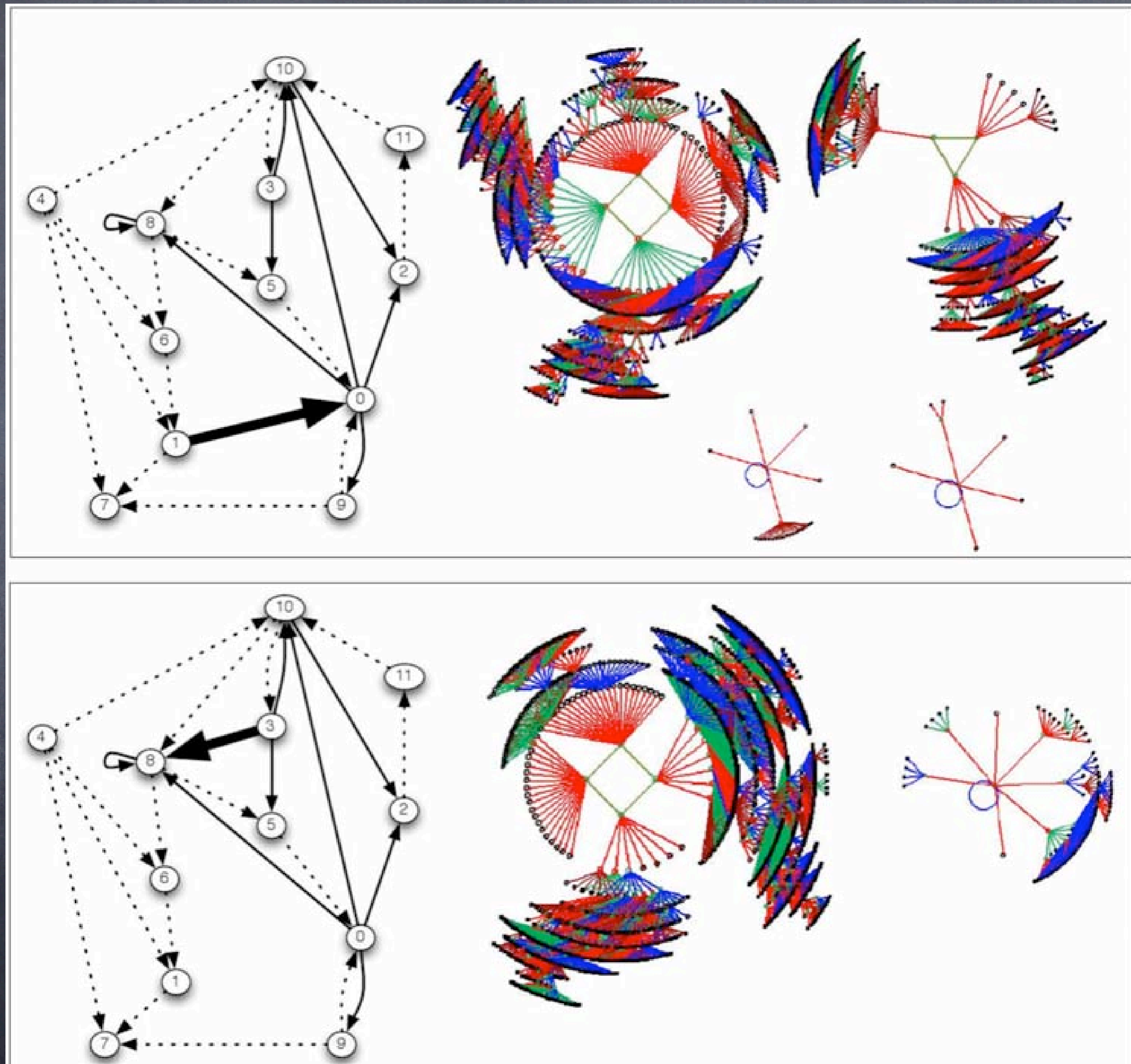


- How about one "functional" attractor basin?
  - ➡ evolution stops when half of the configuration space belongs to the stable, functional attractor



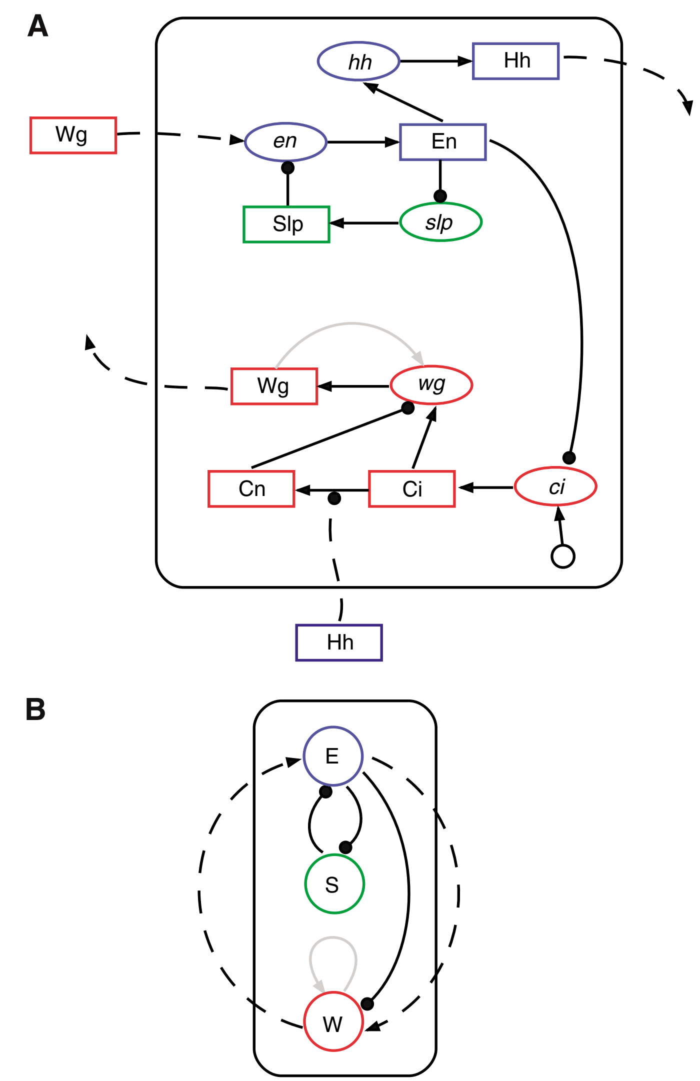
Larger <k> is better!

An example



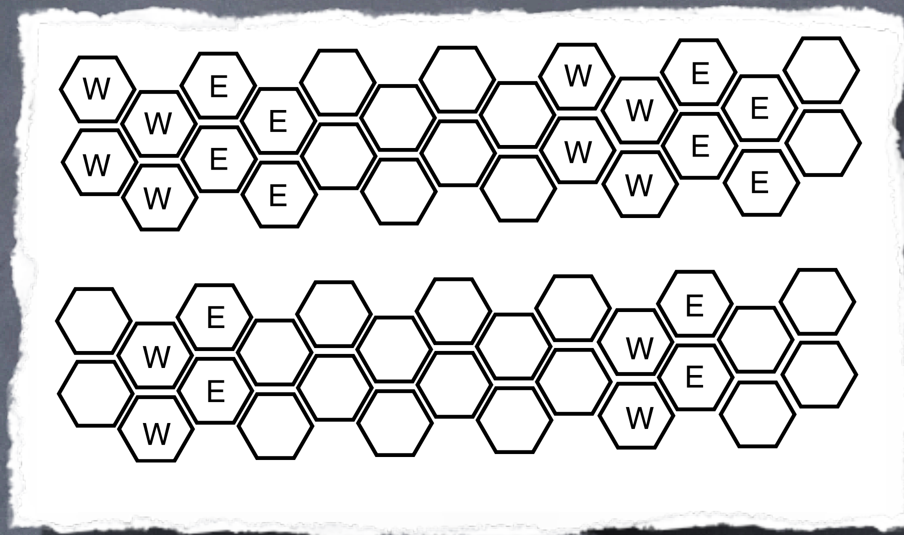
Does function dictate structure?

- Let's find ALL small networks that could perform the segment polarity patterning in Drosophila
  - ➡ how many of these are robust?
- Enumerated all possible 3-node networks
  - ➡ each can regulate itself and others
  - ➡ each link can be inter- and extracellular
    - ➡ restrict to 2 of 3
    - ➡ 14,348,907 topologies

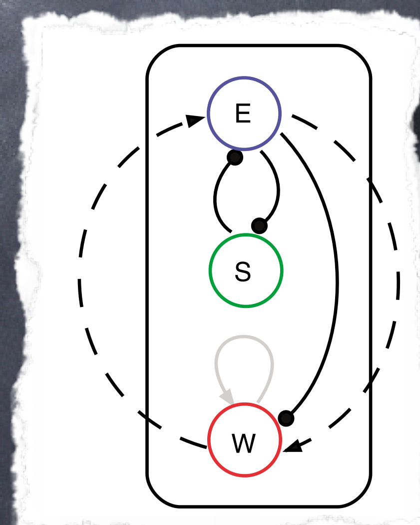


Does function dictate structure?

- A network is functional if:
  - ➡ has perform correct patterning
  - ➡ robustness: fraction of parameter space that can perform the function
    - ➡ (ODE's), parameters sampled at random

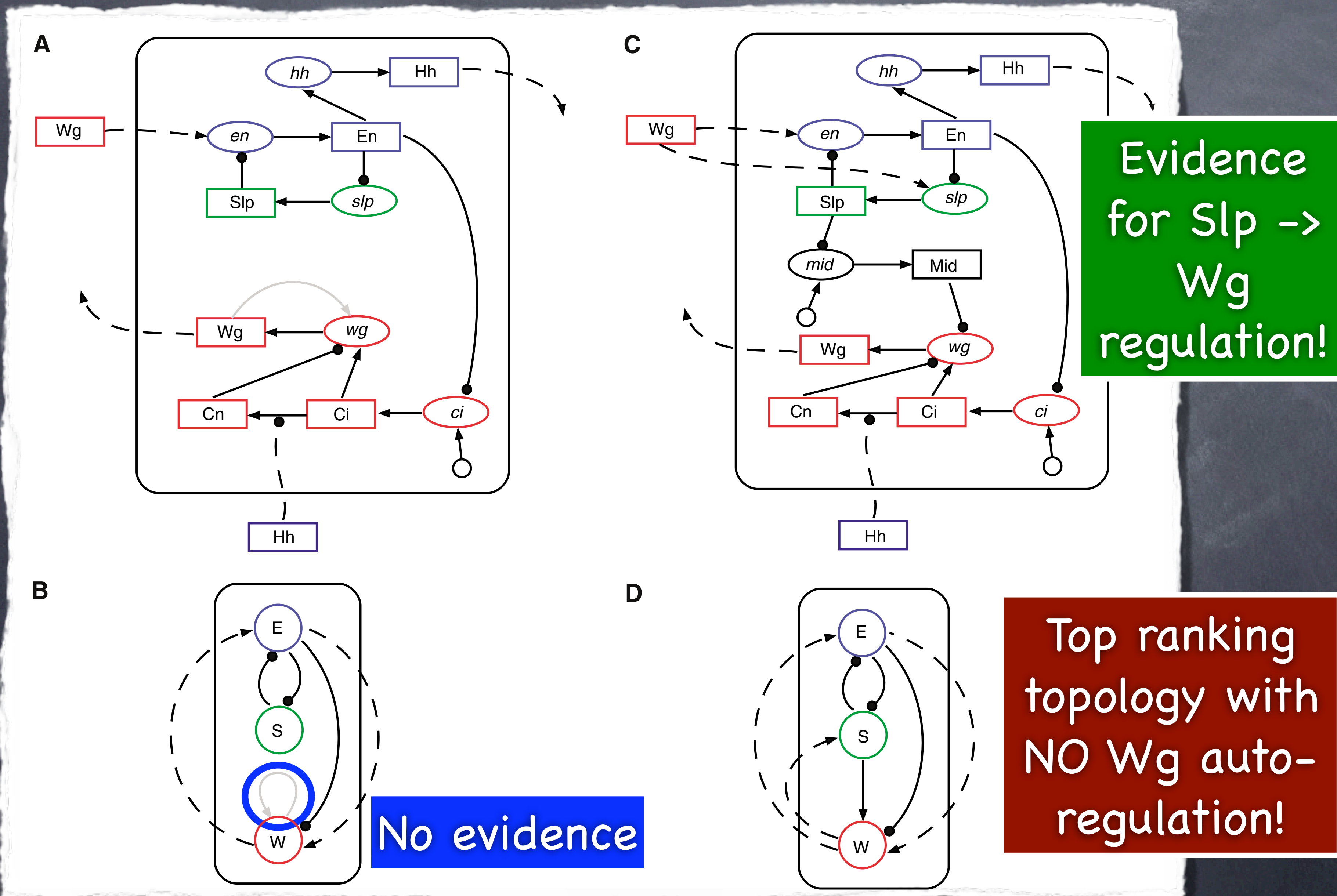


Biological topology: high score, not highest.

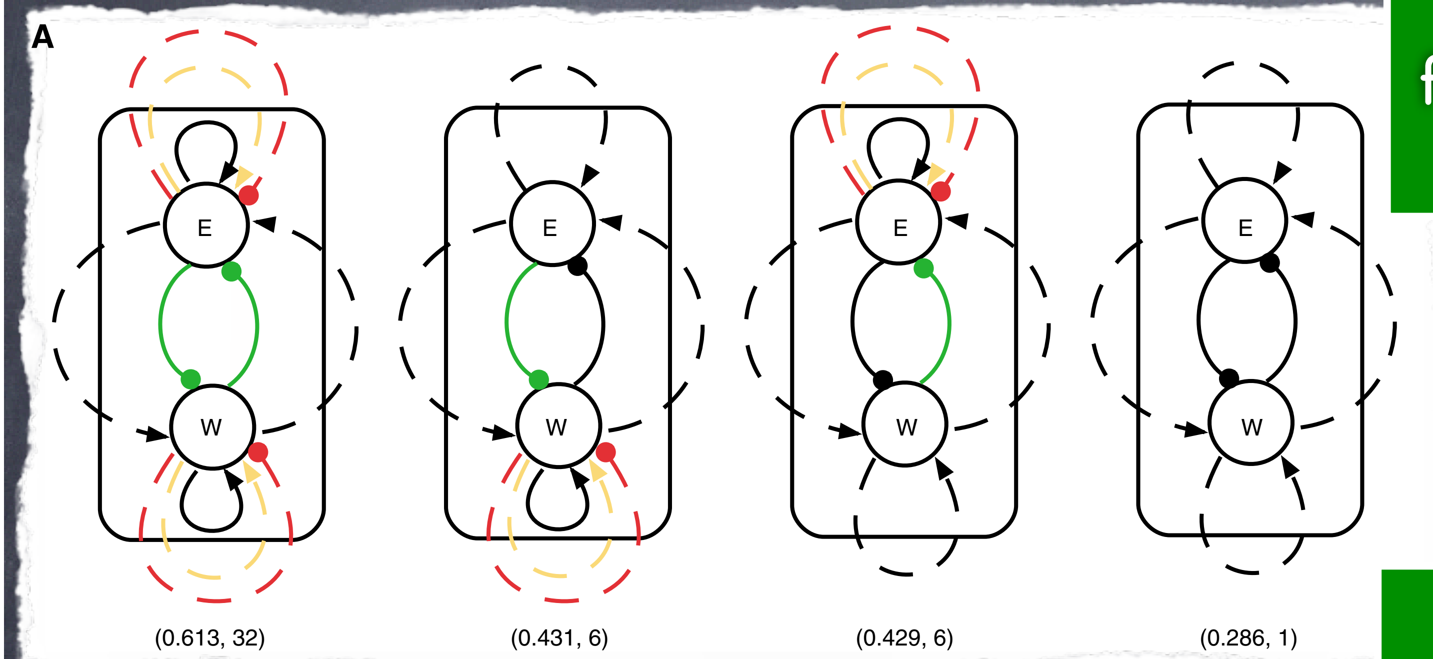


Excluding direct auto-regulation on E and S

A twist on polarity models



Actually, 2 nodes are enough for patterning...



Positive feedback on E and W

E and W neighbors express W/nothing OR E/nothing! Bistable in E and W

Mutual intracellular E – W inhibition

Sharp boundary: E next to W only

4 core topologies: black links are required for robust patterning

- Green: neutral
- Orange: bad
- red: very bad

7. Transcriptional Regulation from Microarray Data

June 22

12 PM