Modeling Yeast Cell-cycle
&
Experimental Predictions

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Theoretical & Computational biology

- 1953年,F. Crick & J. Watson 演绎出DNA的结构. DNA的结构模型

- **www.rockefeller.edu/research/area**

Heads of Laboratories	Topics of Current Investigation Include:
Leibler, Stanislas Living Matter	Population dynamics, mathematical modeling of disease transmission and analysis of foodwebs
Libchaber, Albert Experimental Condensed Matter Physics	Turbulence in physical systems using the mathematics of fractal geometry Studies of proton-antiproton collisions using the Collider Detector at Fermilab
Siggia, Eric D. Theoretical Condensed Matter Physics	Genome search for promoters Study of biochemical networks Quantum dots and other bio-resistant fluorophores

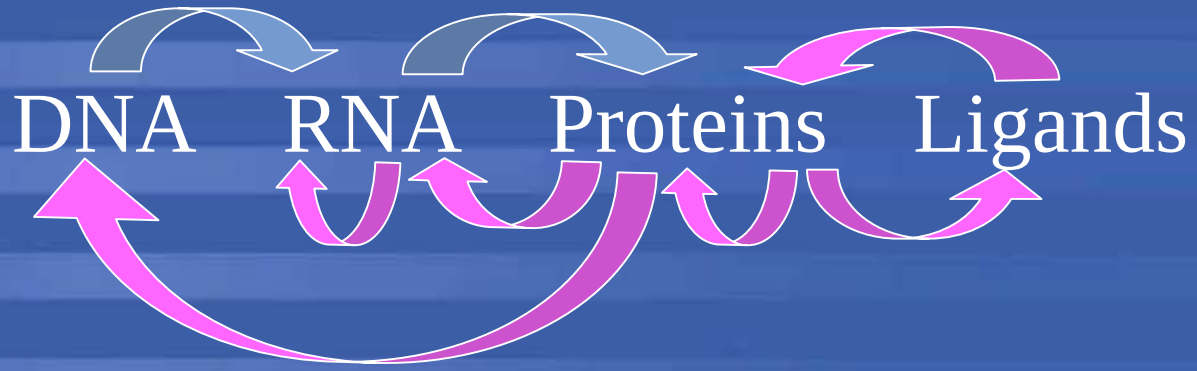
Outline

- Biological networks
- Modeling cell cycle network in budding yeast

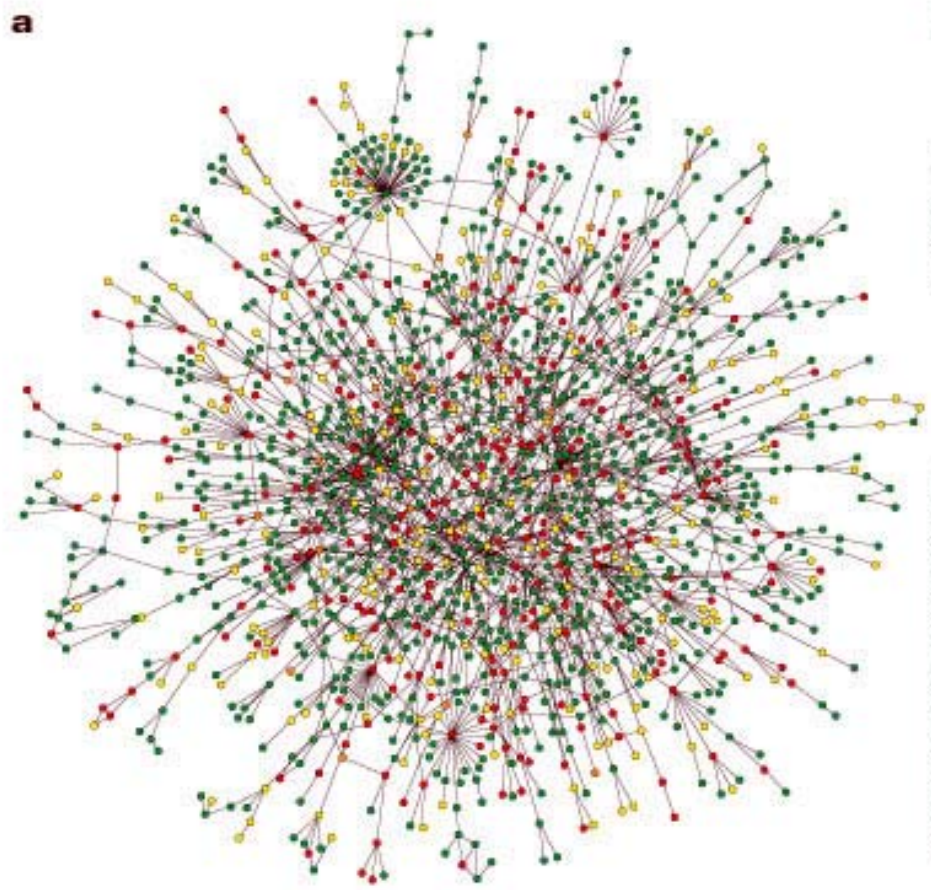
1. Boolean model - The yeast (芽殖酵母) cell cycle network is robustly designed.
2. ODE model of cell cycle – positive feedbacks, negative feedbacks and checkpoints ensure the robustness of cell cycle process.

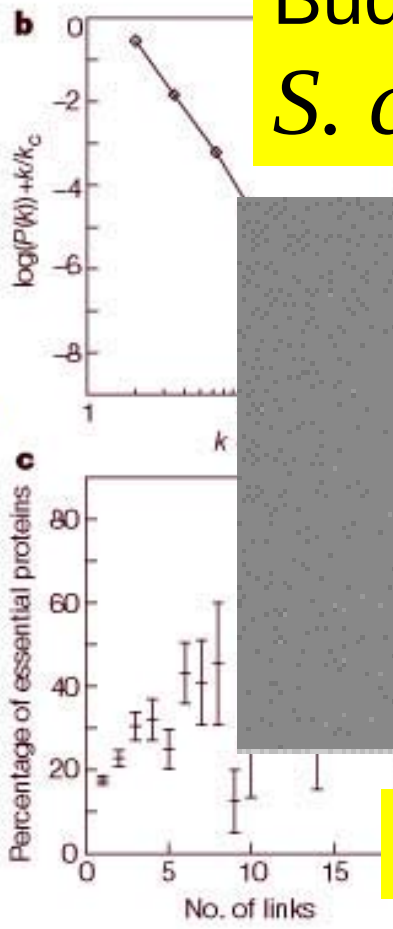
- Experimental predictions
- Further works

Components and interactions in the regulatory network

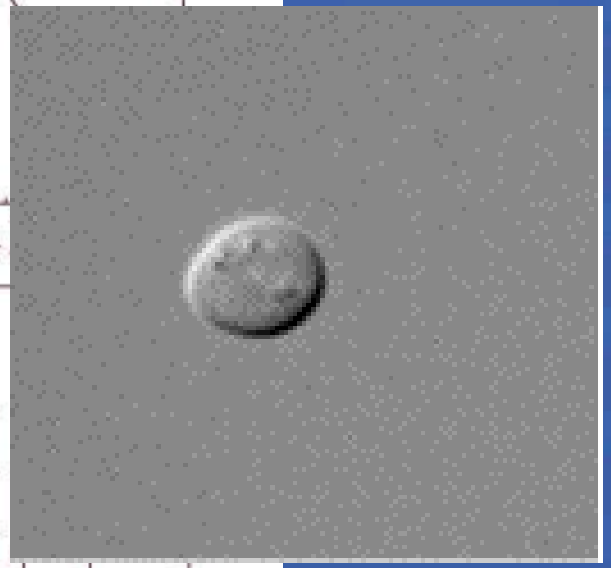


Topological property of protein network in yeast





Budding yeast
S. cerevisiae



Cell cycle

H. Jeong, S. Mason, A.-L. Barabási and Z. N. Oltvai "***Lethality and centrality in protein networks*** " Nature **411**, 41-42 (2001).

R. Albert and A.-L. Barabasi "*Statistical mechanics of complex networks*" Rev. Mod. Phys. **74,** 47-97 (2002).

Nobel Prize Winners for Cell Cycle Regulation in Physiology or Medicine, 2001

Leland Hartwell | Paul Nurse | Tim Hunt

Modeling Cell Cycle

2001 Nobel Prize winner for identified, cloned and characterized CDK (cyclin dependent kinase)

Paul Nurse

A long twentieth century of the cell cycle and beyond CELL, Vol. 100, 71–78, January 7, 2000. "Into the Next Century"

The aim should be to develop a full description of the molecular machines that make up the modules responsible for the different steps of cell cycle progression, to determine how these modules are linked together, and to demonstrate how their operation brings about the reproduction of the cell.

We might need to move into a **strange more abstract world**, more readily analyzable **in terms of mathematics** than our present imaginings of cells operating as a microcosm of our everyday world.

Fred Cross in Rockefeller University, cell cycle in budding yeast

James E. Ferrell in Stanford University, cell cycle in Xenopus

Cell Cycle Modeling and Experiments

Chen KC, Csikasz-Nagy A, Gyorffy B, Val J, Novak B, **Tyson JJ**. Kinetic analysis of a molecular model of the budding yeast cell cycle.

Mol Biol Cell. **2000** Jan;11(1):369-91.

Cross FR, Archambault V, Miller M, Klovstad M. Testing a mathematical model of the yeast cell cycle. Mol Biol Cell. **2002** Jan;13(1):52-70.

Chen KC, Calzone L, Csikasz-Nagy A, **Cross FR**, Novak B, **Tyson JJ.** Integrative analysis of cell cycle control in budding yeast.

Mol Biol Cell. **2004** Aug;15(8):3841-62. Epub 2004 May 28.

Cross FR, Schroeder L, Kruse M, **Chen KC**. Quantitative characterization of a mitotic cyclin threshold regulating exit from mitosis.

Mol Biol Cell. **2005** May;16(5):2129-38.

Pomerening JR, Kim SY, **Ferrell JE Jr**. Systems-level dissection of the cell-cycle oscillator: bypassing positive feedback produces damped oscillations. Cell. **2005** Aug 26;122(4):565-78.

Modeling cellular dynamical processes

gene sequence

protein sequence

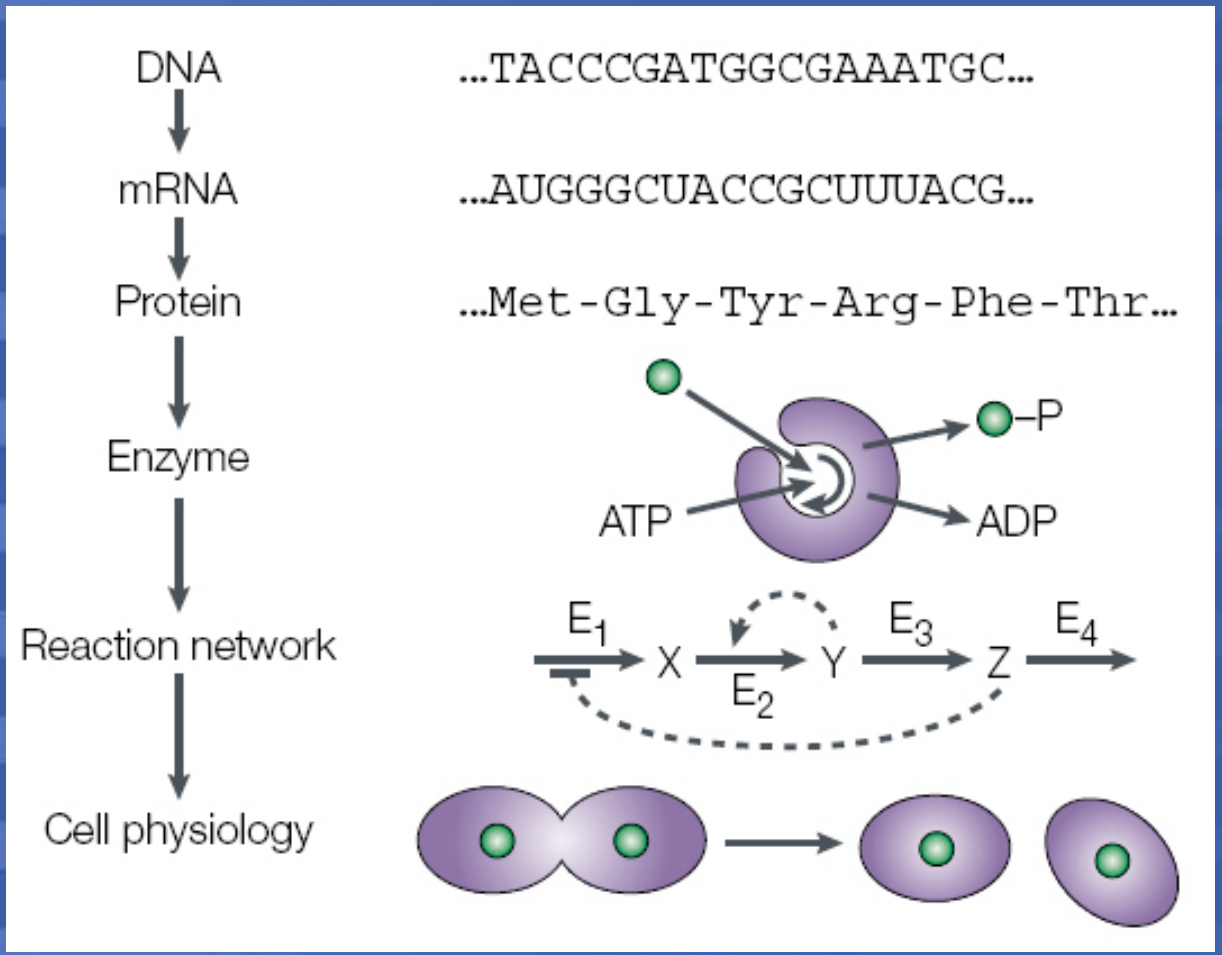
protein structure

protein function

protein network

cell physiology

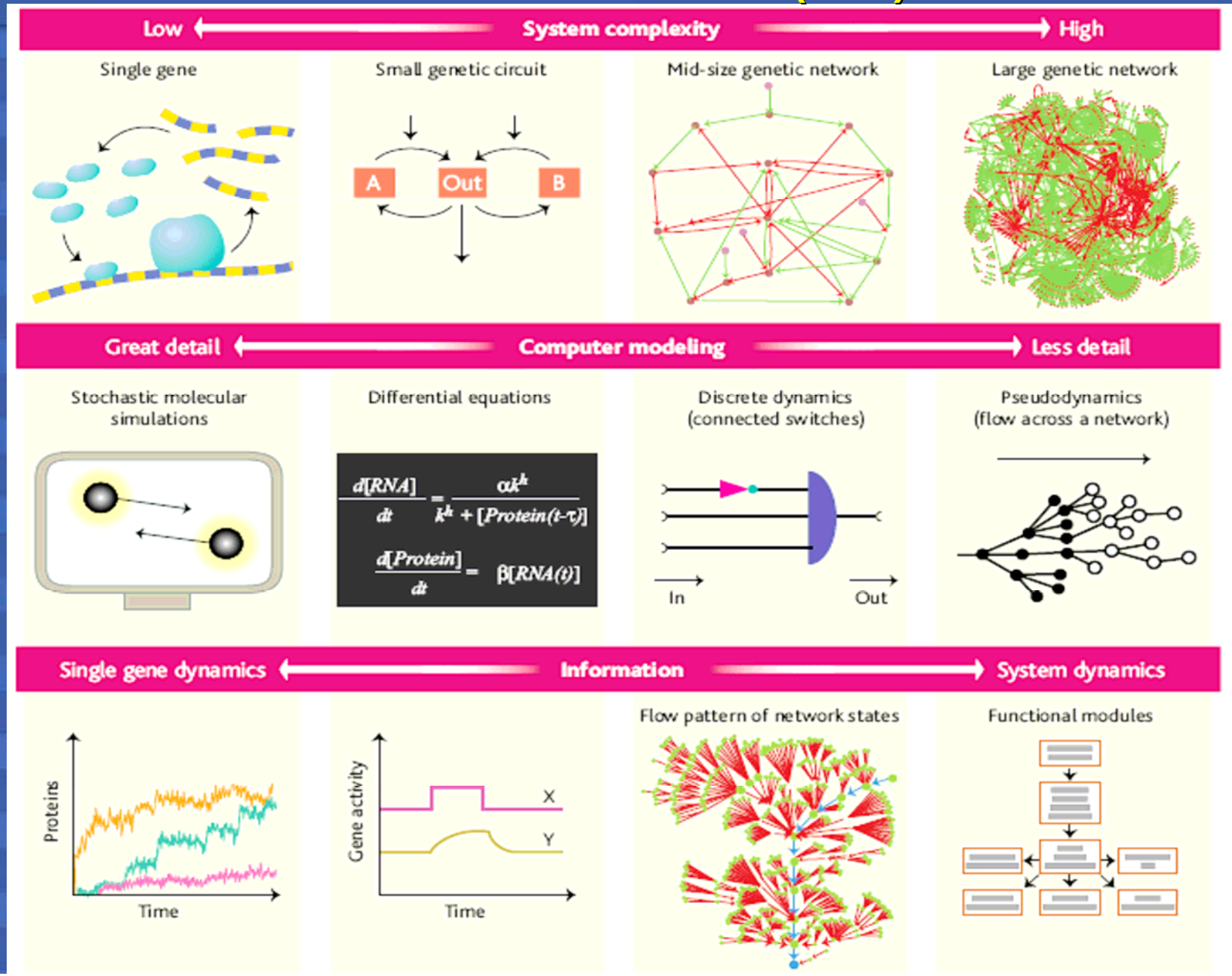
event order, cell physiology, biological function…



Tyson, Chen, Novak. 2001. Network Dynamics and Cell Physiology
Nature Review Mol. Biol. 2:908

Less is more in modeling large genetic network

Science (2005) 310:449



Modeling cellular process

Stochastic simulations

Transitions given by master equation

$$\frac{\partial}{\partial t}P(\boldsymbol{X},t)=\sum_{r}\left(\beta_{r}P(\boldsymbol{X}-\boldsymbol{v}_{r},t)-\alpha_{r}P(\boldsymbol{X},t)\right)$$

Nonlinear ordinary differential equations

$$\frac{\mathrm{d}[\mathrm{R}]_{\mathrm{i}}}{\mathrm{d}t}=sythesis+transformation-degradation.$$

Parameter setting & vast space and parameter space!!

Boolean networks

Assumptions:

-- Protein is in active and inactive states

-- Boolean function b_i determines state change in time

$$x_i(t+1)=b_i(\boldsymbol{x}(t))$$

Properties

-- State space has 2^N elements

-- Limit cycles or fixed points

Robustness of cellular functions

-- Computational & Systems Biology

- Hiroaki Kitano 2002 Systems biology: a brief overview Science 295:1662

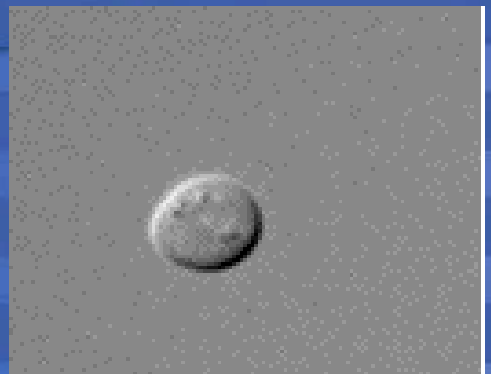
Robustness is an essential property of biological systems:

the adaptation parameters insensitivity graceful degradation

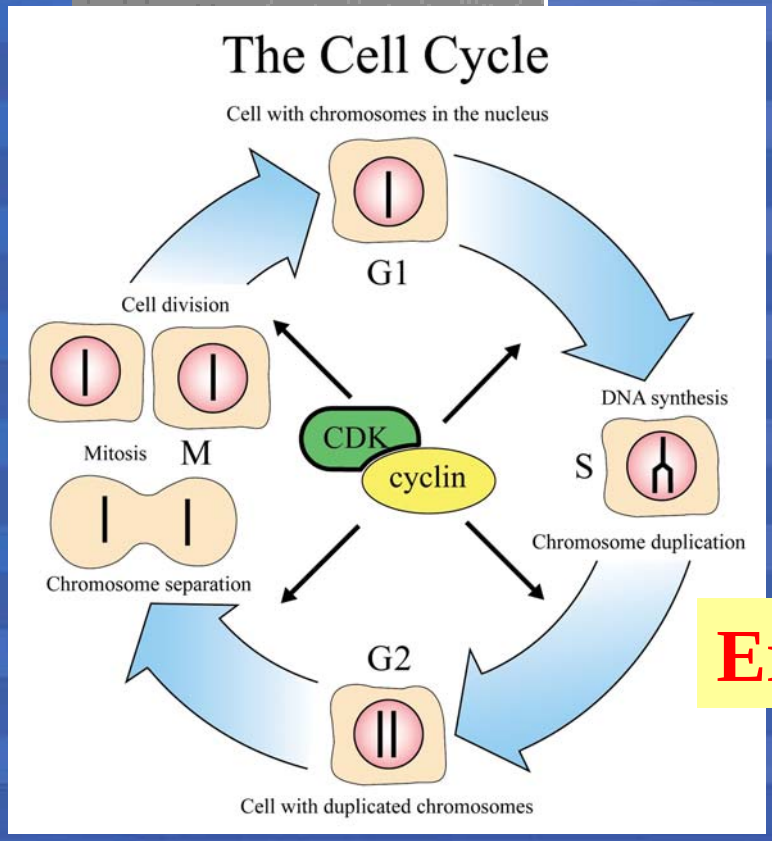
- Stelling J, Sauer U, Szallasi Z, Doyle FJ 3rd, Doyle J. 2004 Robustness of cellular functions. Cell 118(6):675-85. Review.

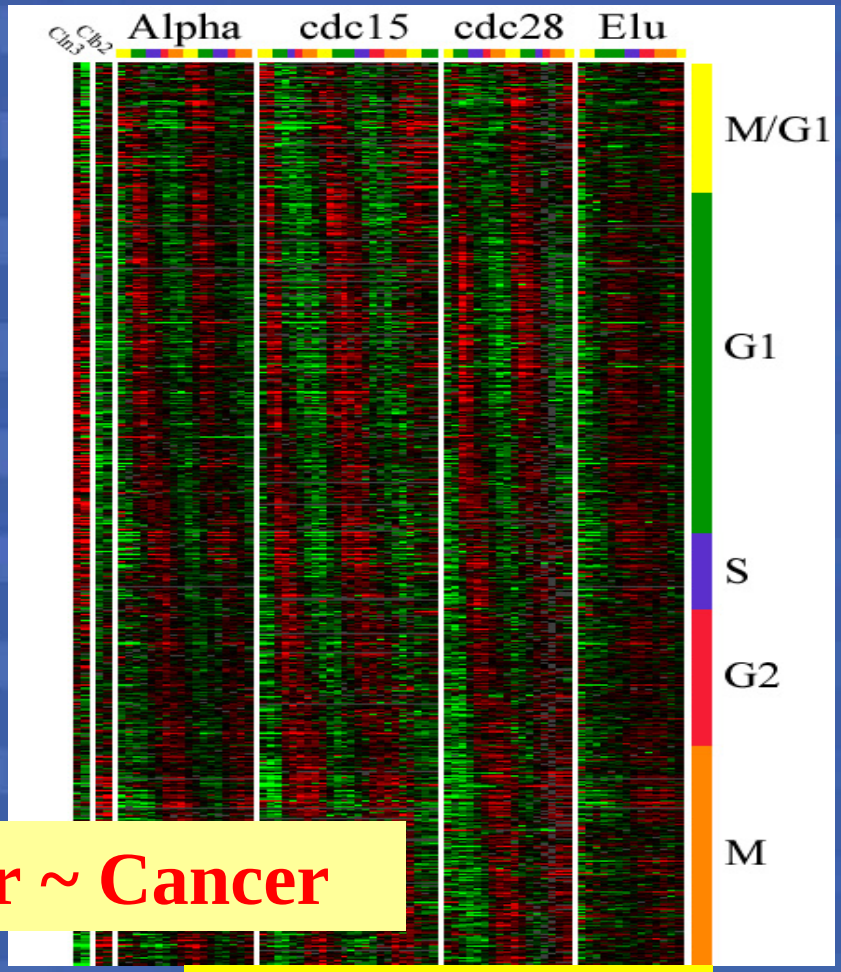
Fluctuations and noise inside and outside of CELL

The Cell Cycle in budding yeast



800 Genes involved in Yeast Cell Cycle





Error ~ Cancer

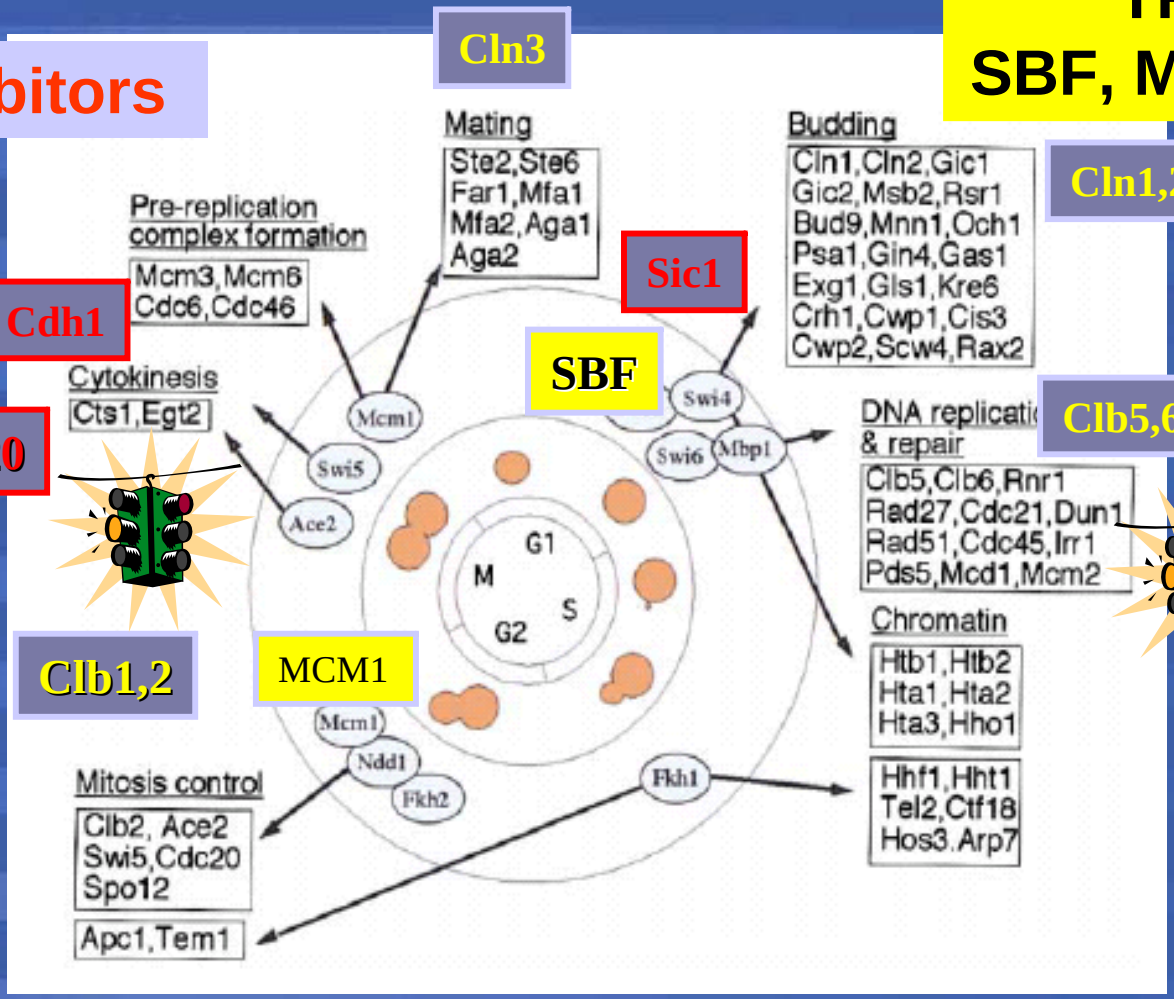
Spellman, et al. (1998)

A vital process that is highly conserved in eukaryotes

Regulators of the Yeast Cell Cycle

TFs 转录因子
SBF, MBF, Mcm1, Swi5

Inhibitors



Checkpoints

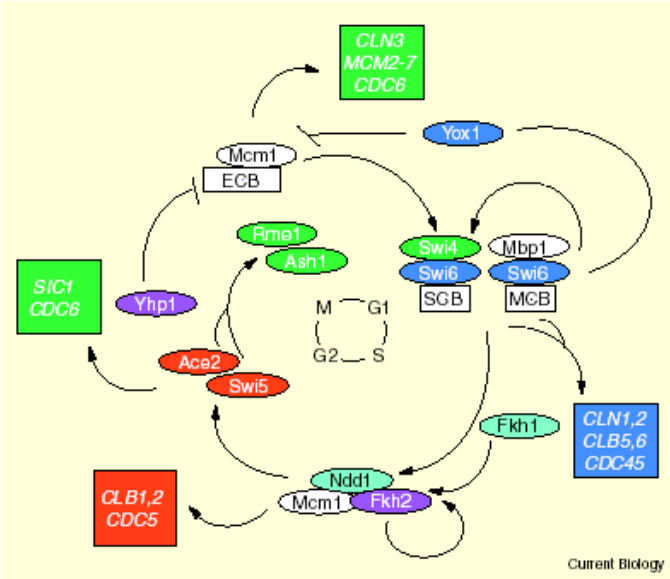
Cyclins Cycling

Cdc28/CDK

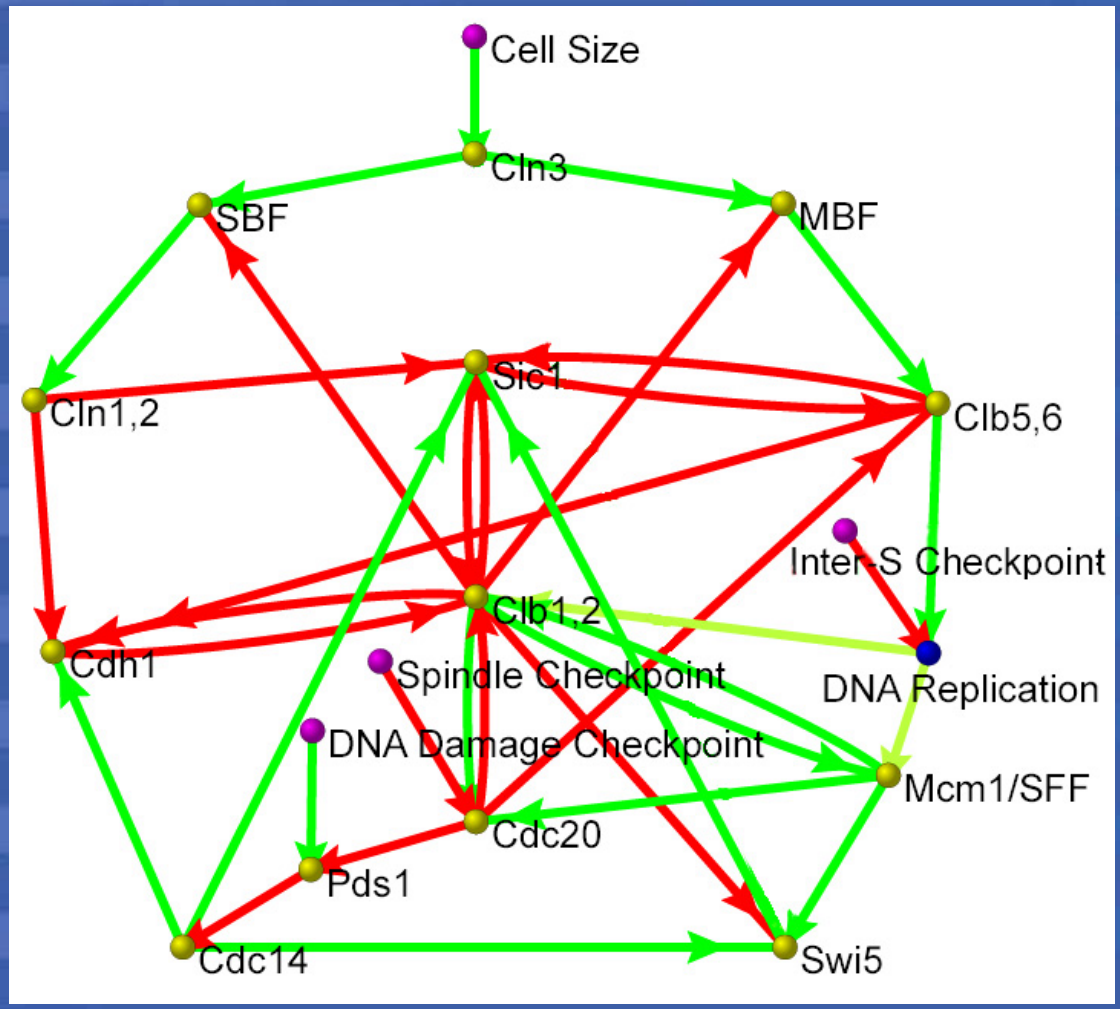
Simon et. al 2001
Cell 106:697

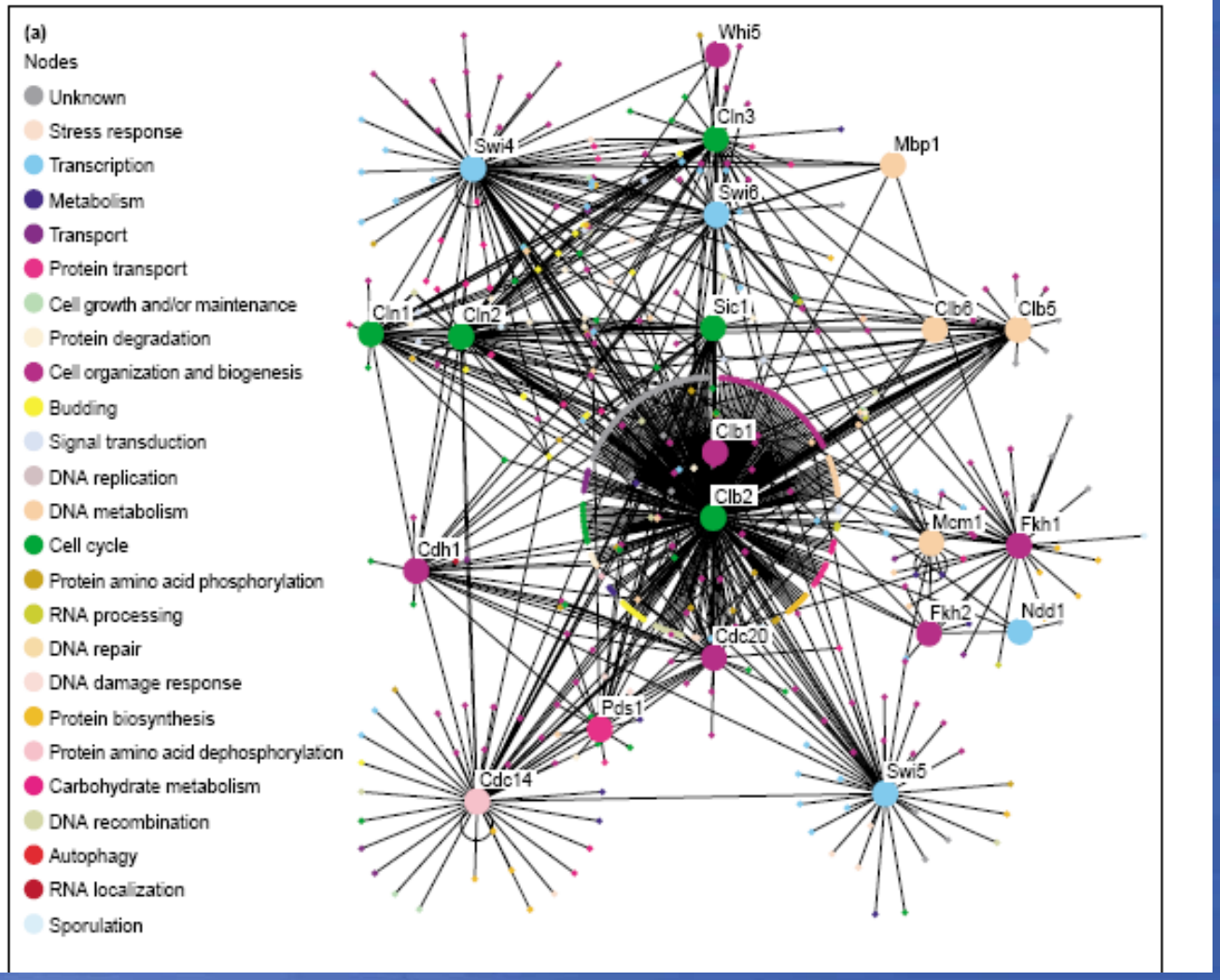
如何 简化调控网络?

Regulatory Network of Yeast Cell Cycle



Breeden 2003 Current Biology 13: R31-R38

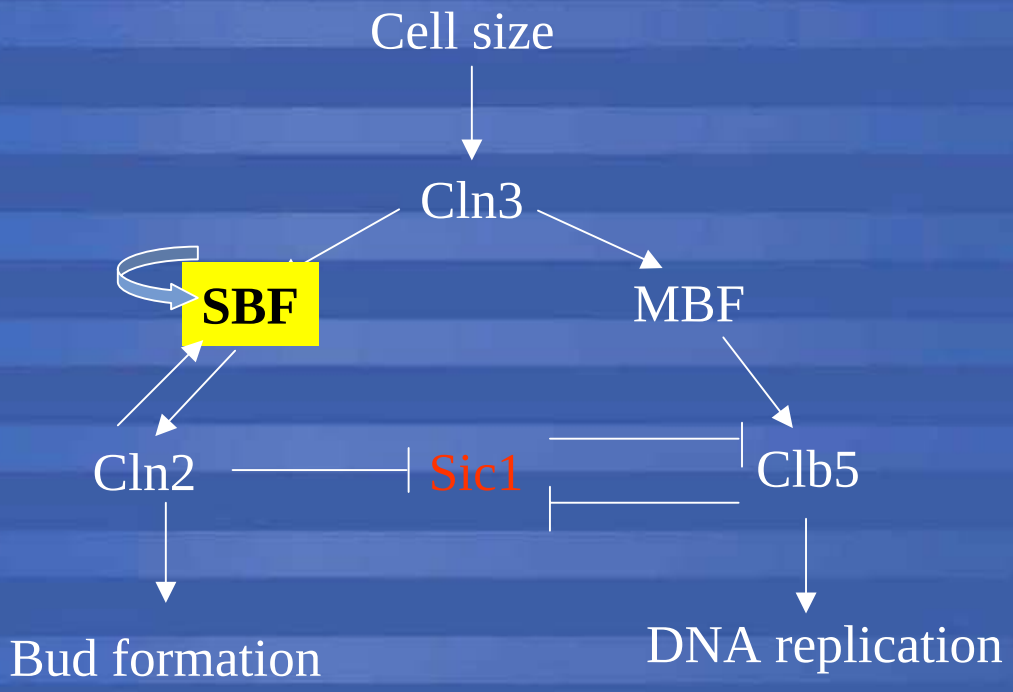




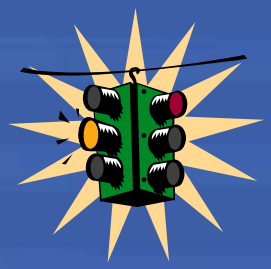
Extant physical and genetic interaction network assembled around 11 core cell cycle components, comprising 796 interactions between 524 genes/proteins, as derived from 264 literature sources, including high throughput datasets.

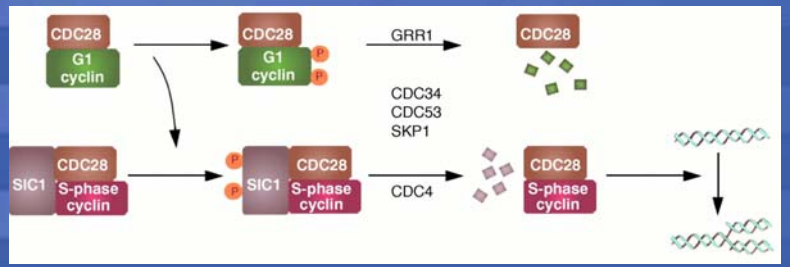
Mike Tyers 2004 Current Opinion in Cell Biology 16:602–613

The START point and DNA replication

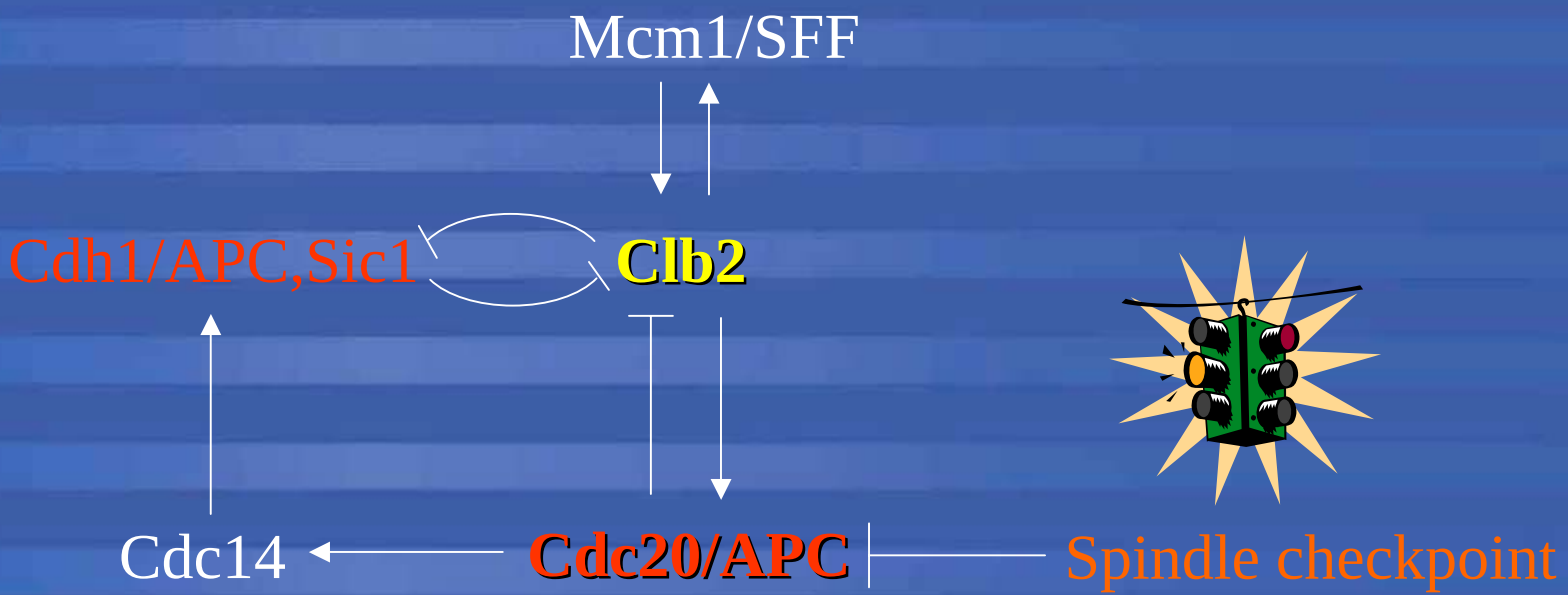


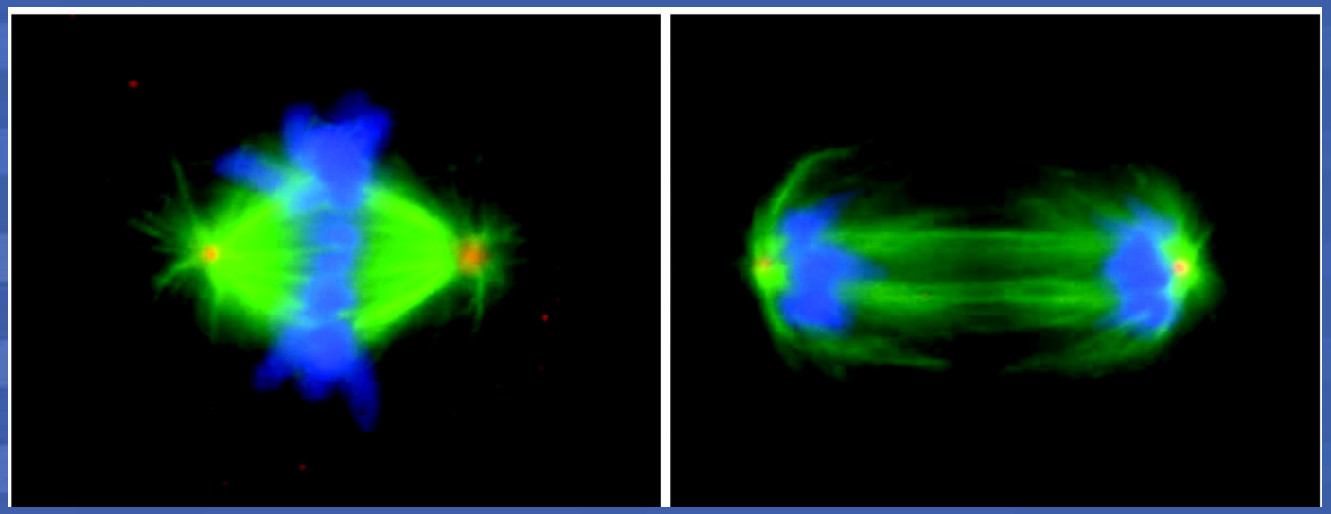
Genotype	Size
Wild type	
CLN3-1^{D}	
4×CLN3	
Δcln3	





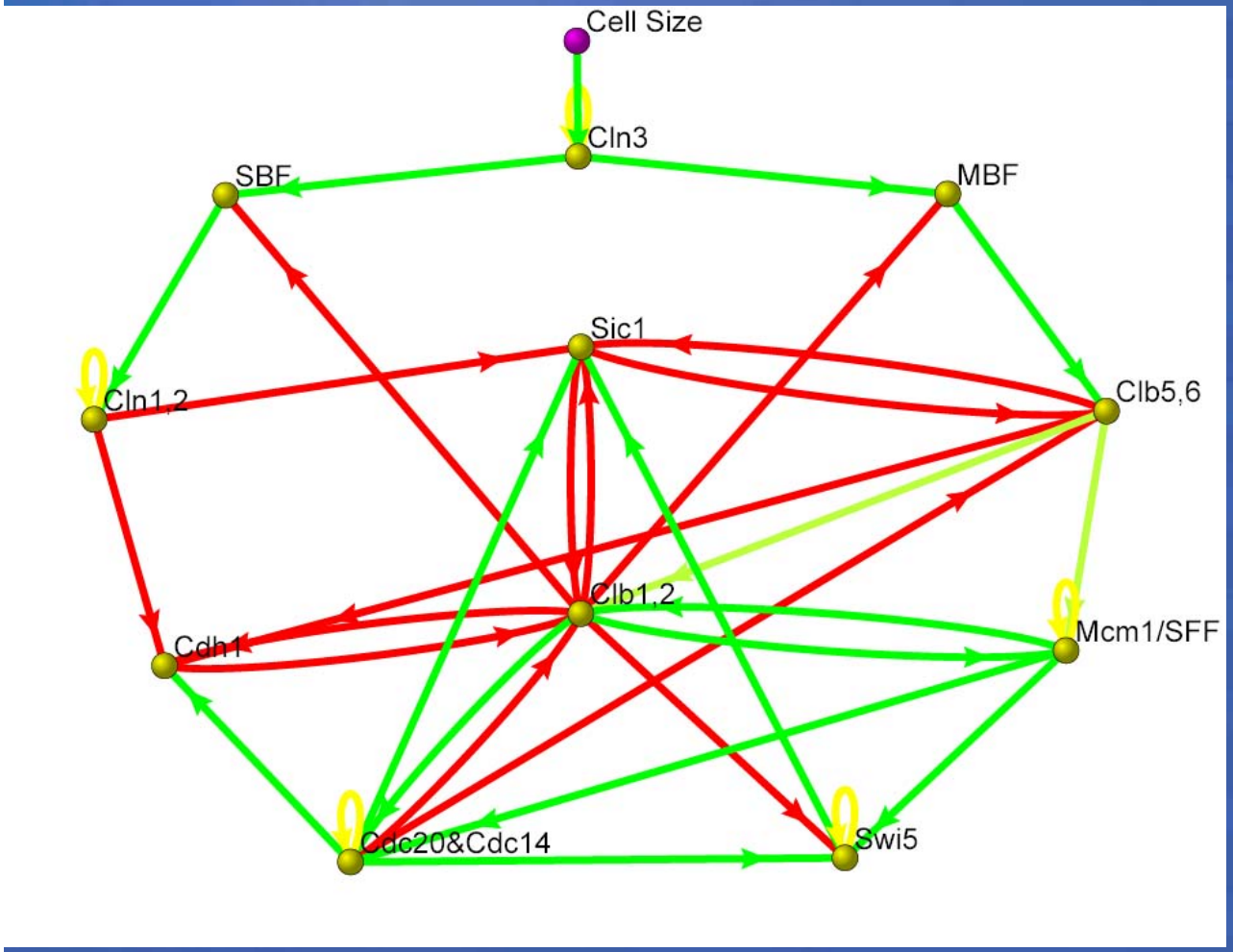
Mitosis





Movie

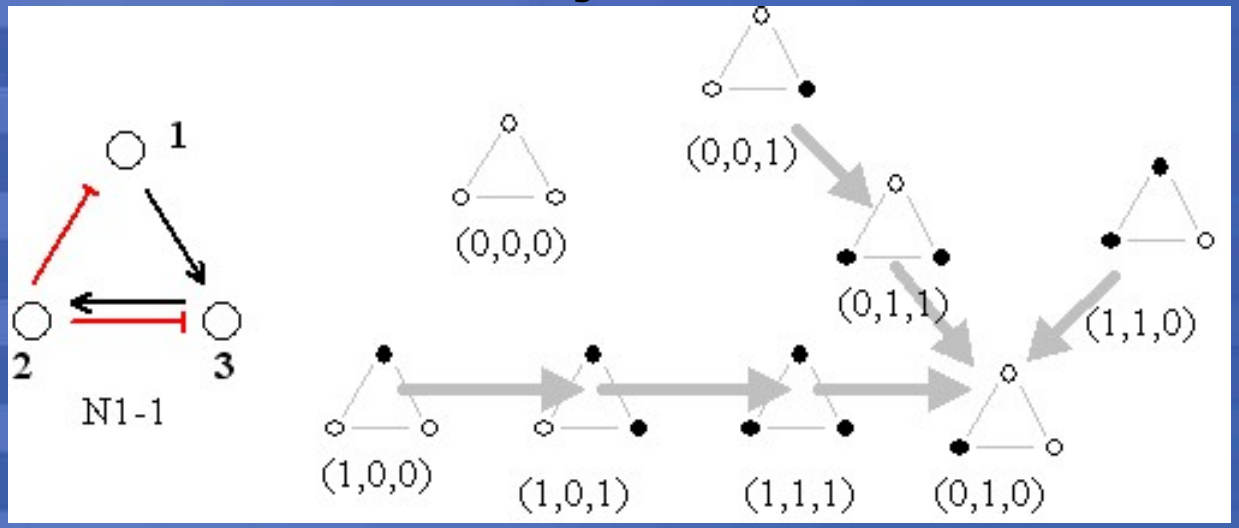
Simplified cell-cycle network and Boolean network model

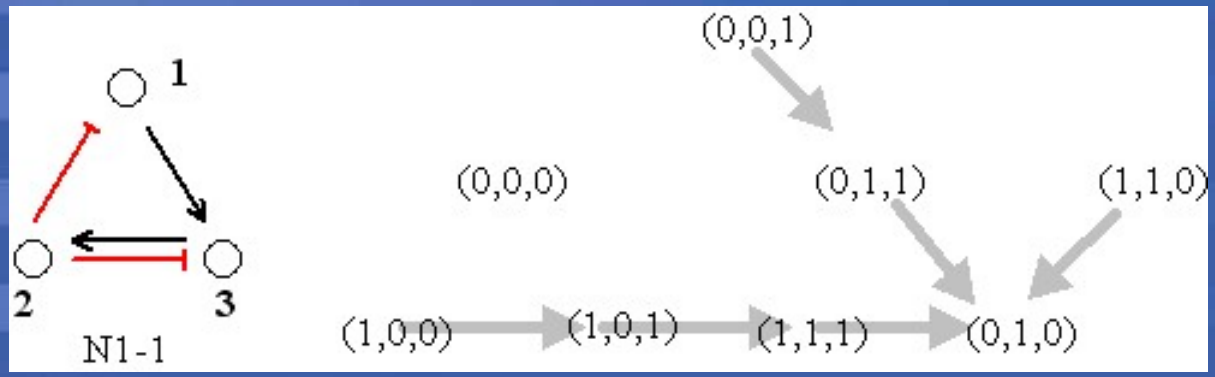


11Nodes; 16 Green lines; 13 Red lines; 5 Yellow lines

For the nodes without negative control, we add yellow lines to simulate protein decay.

Network and its dynamical attractors





a_{ij} **(green) = 1,**
a_{ij} **(red) = -100**

3-node network has 8 states
Fixed points – attractors: (000) and (010)
Attractive basin: 1 and 7

Another dynamical rule…

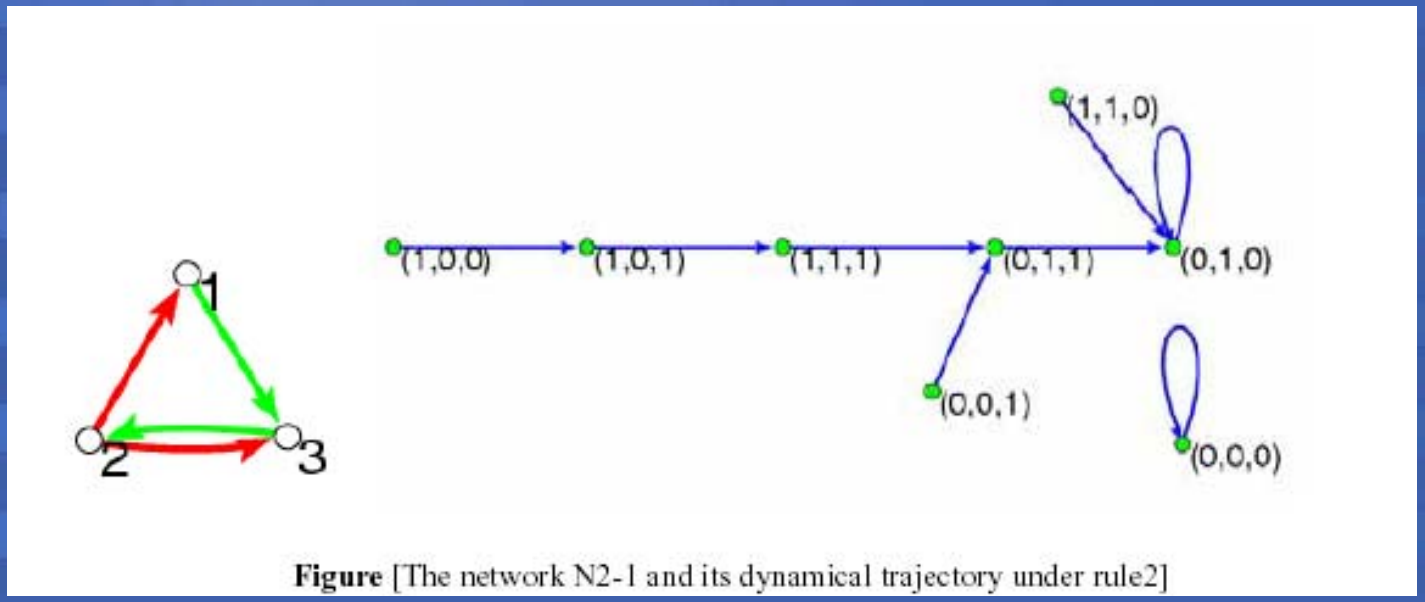
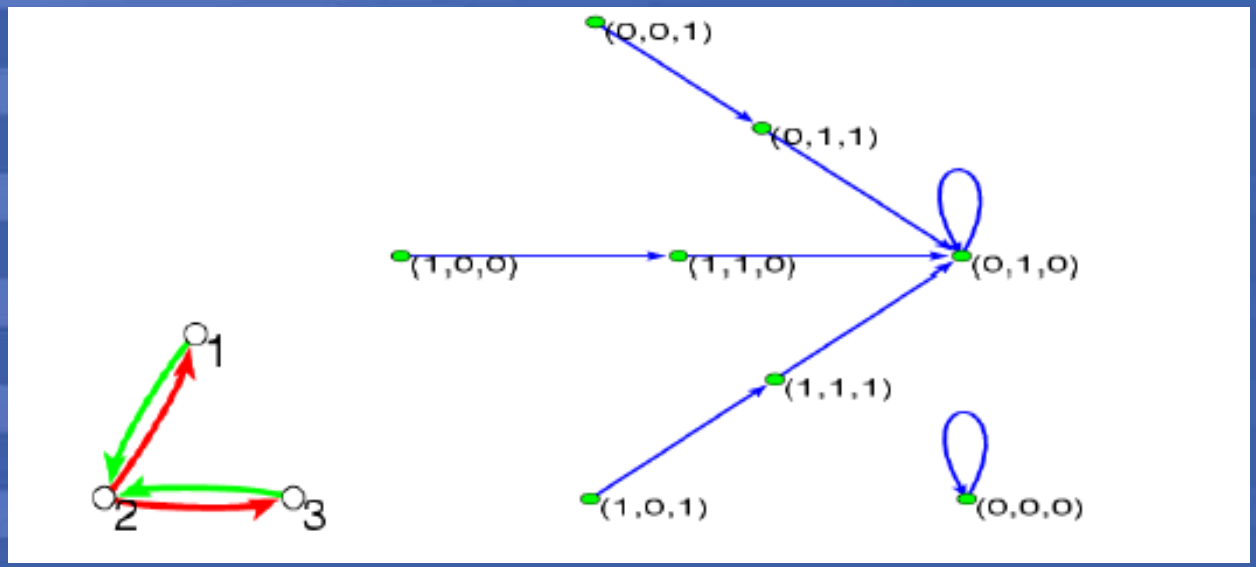
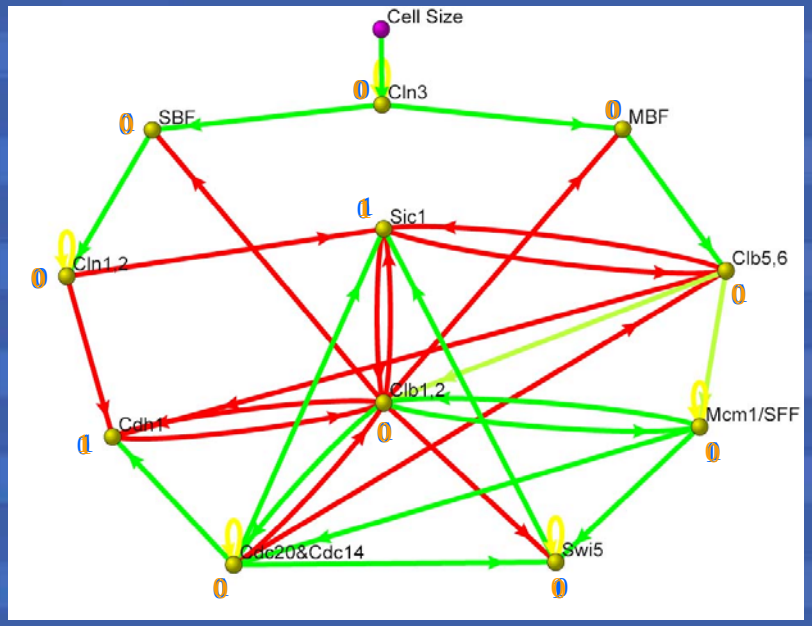


Figure [The network N2-1 and its dynamical trajectory under rule2]

a_{ij} **(green) = 1,**
a_{ij} **(red) = -1**

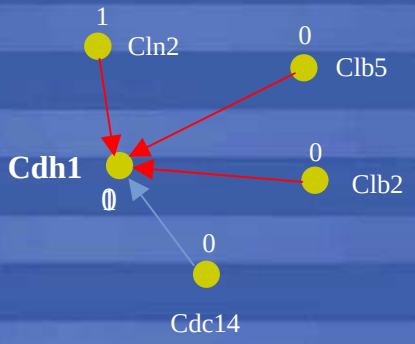


A Simple Dynamic Model



Protein state: $S_i = \begin{cases} 0, & \text{inactive} \\ 1, & \text{active} \end{cases}$

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



2^{11}=2048 "cell states"

a_{ij} (green) = 1, a_{ij} (red) = -1

t_d = 1

Trajectory of Cell Cycle Sequence

Signal: Cln3 from 0 to 1.

Protein Step	Cln3	MBF	SBF	Cln2	Cdh1	Swi5	Cdc20& Cdc14	Clb5	Sic1	Clb2	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	
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	
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	
8	0	0	0	0	0	1	1	0	0	1	1	
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	
11	0	0	0	0	1	1	1	0	1	0	0	
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	Stationary G_1

Fixed point of the dynamics

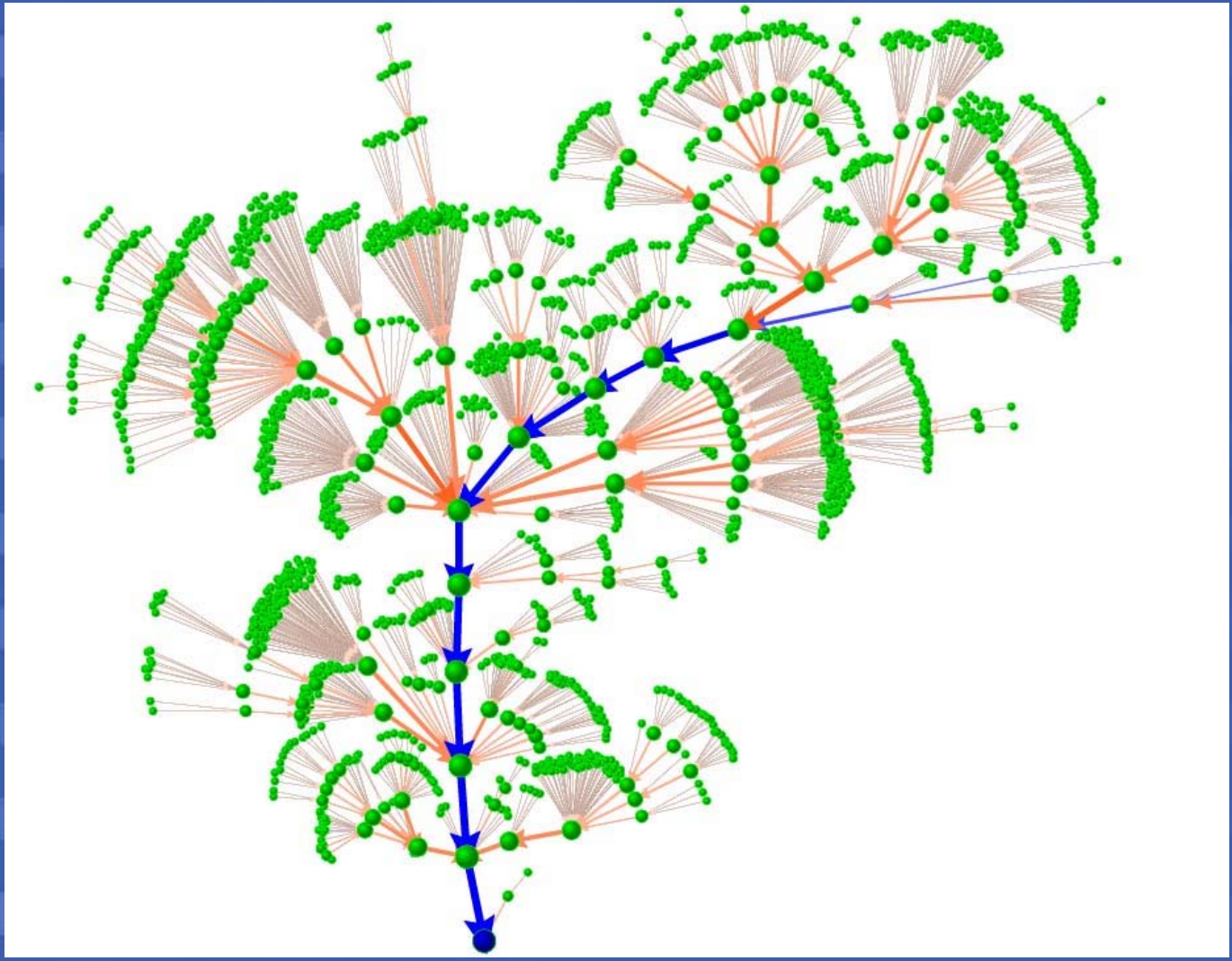
2048 initial states

Question: **the distribution of attractor size of the network.**

Basin size	Cln3	MBF	SBF	Cln2	Cdh1	Swi5	Cdc20	Clb5	Sic1	Clb2	Mcm1
1764	0	0	0	0	1	0	0	0	1	0	0
151	0	0	1	1	0	0	0	0	0	0	0
109	0	1	0	0	1	0	0	0	1	0	0
9	0	0	0	0	0	0	0	0	1	0	0
7	0	1	0	0	0	0	0	0	1	0	0
7	0	0	0	0	0	0	0	0	0	0	0
1	0	0	0	0	1	0	0	0	0	0	0

1764 of 2048 initial states (86%) evolve to G1 states. Making the **G1 state the only global attractor**.

Global flow diagram



1. Pink arrows: <64; Orange arrows: 64~128; Red arrows: >128;
   Blue arrows: Biological Pathway
2. Big blue node: Biological ground G1 state.

Compare with random networks

The random nets are of the same numbers of nodes and green, red, yellow arrows.

Compare

(1) attractors size distributions

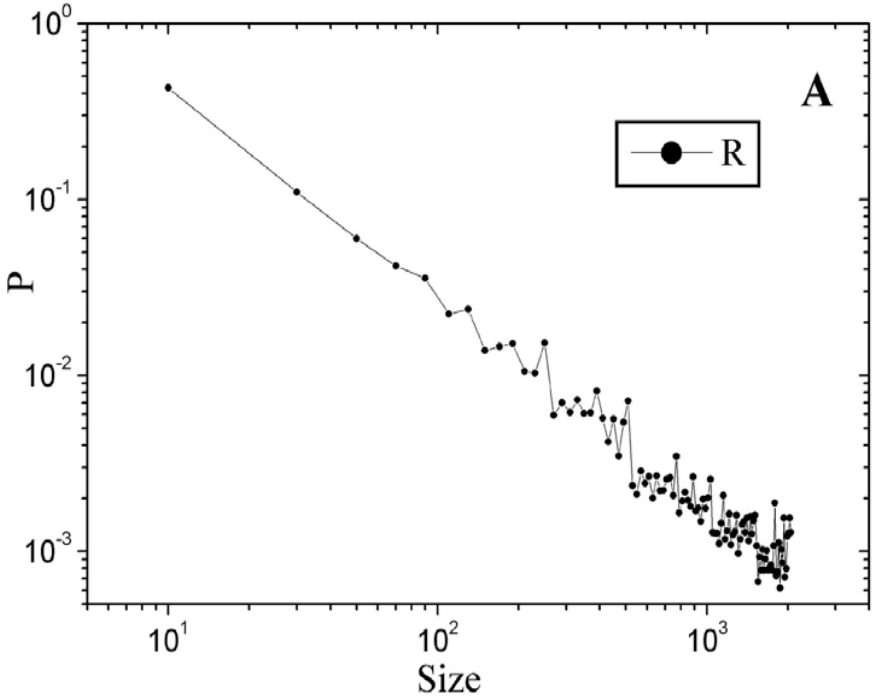
(2) Evolution Trajectory (using W value)

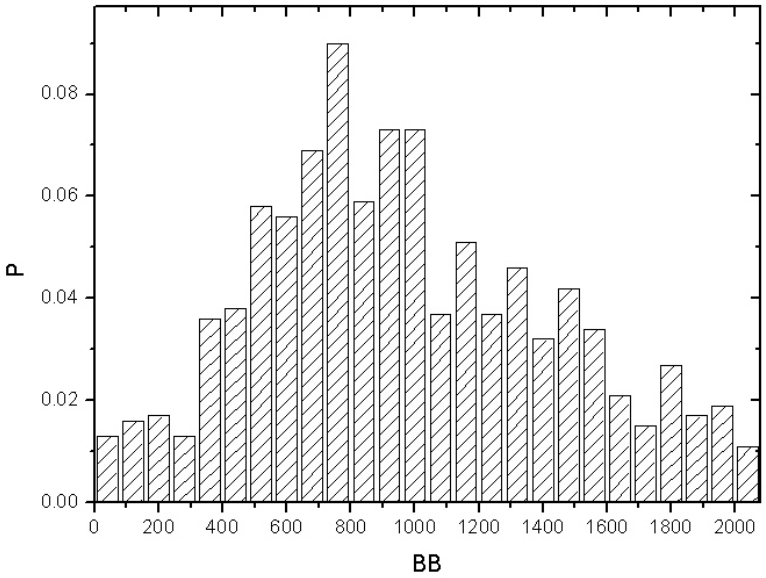
$$W_i = \frac{\sum \text{weight-of-every-step}}{\text{step-length}}$$

$$W = \langle W_i \rangle$$

(3) Stability against different perturbations

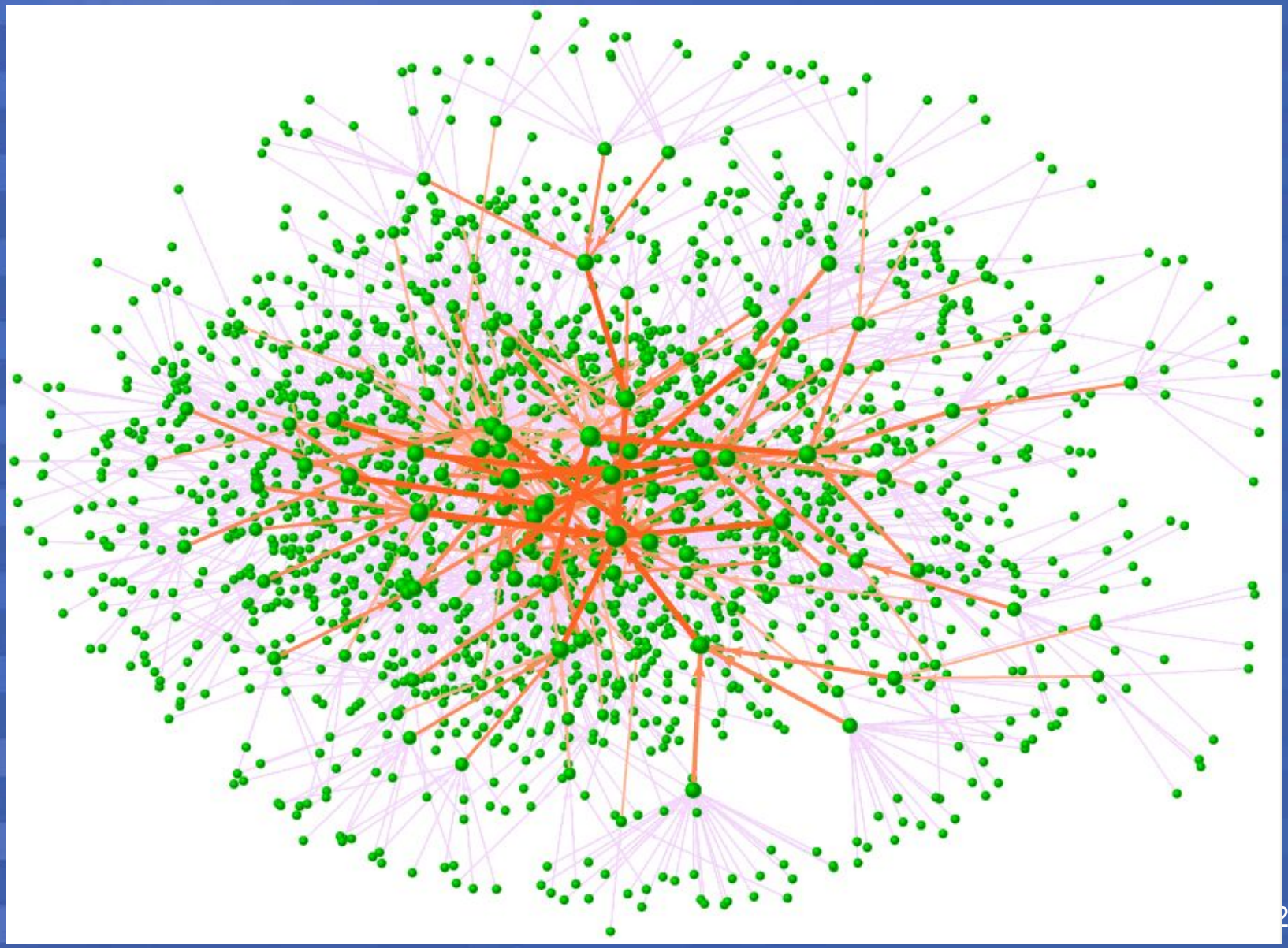
Attractor size distribution



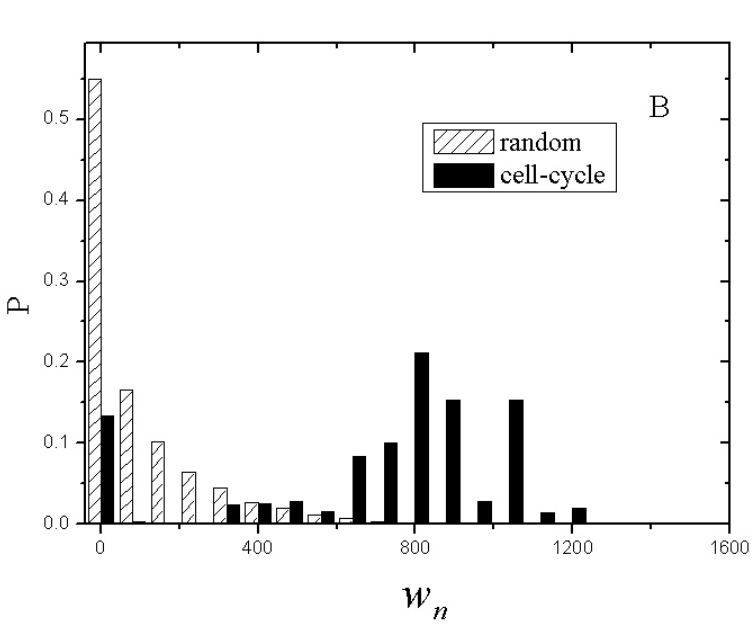


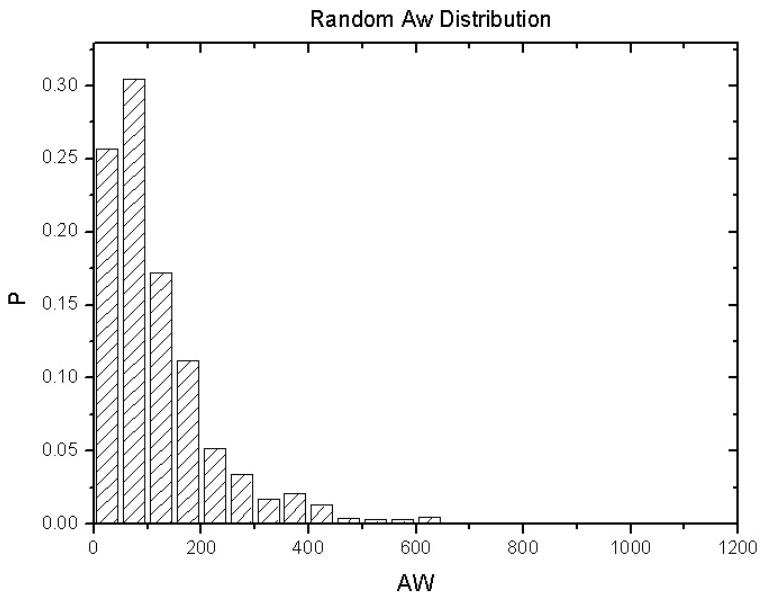
P(BB>1764) = 0.1

Flow diagram of random networks



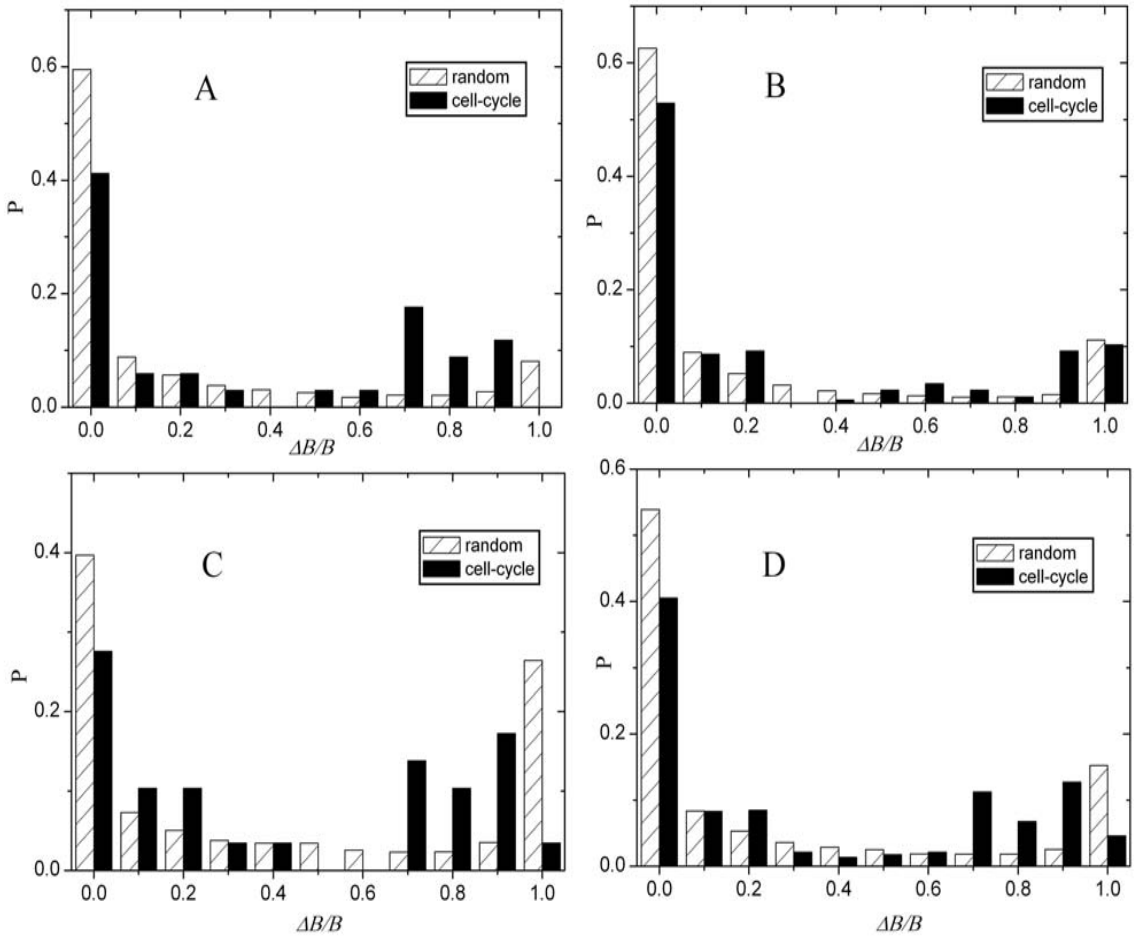
Distribution of W

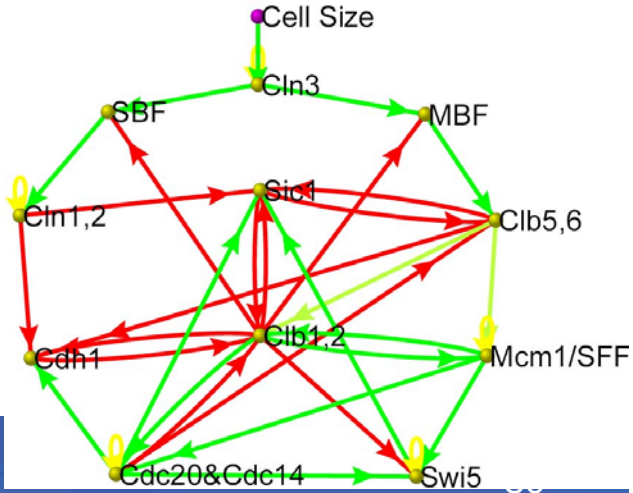




P(AW>743)=0.0025

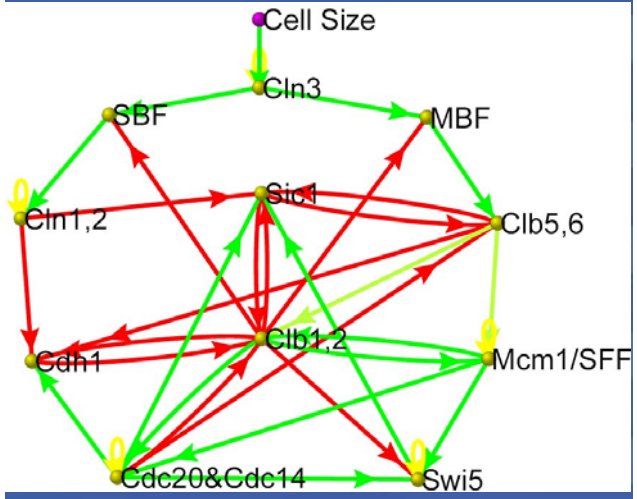
Stability analysis (I)

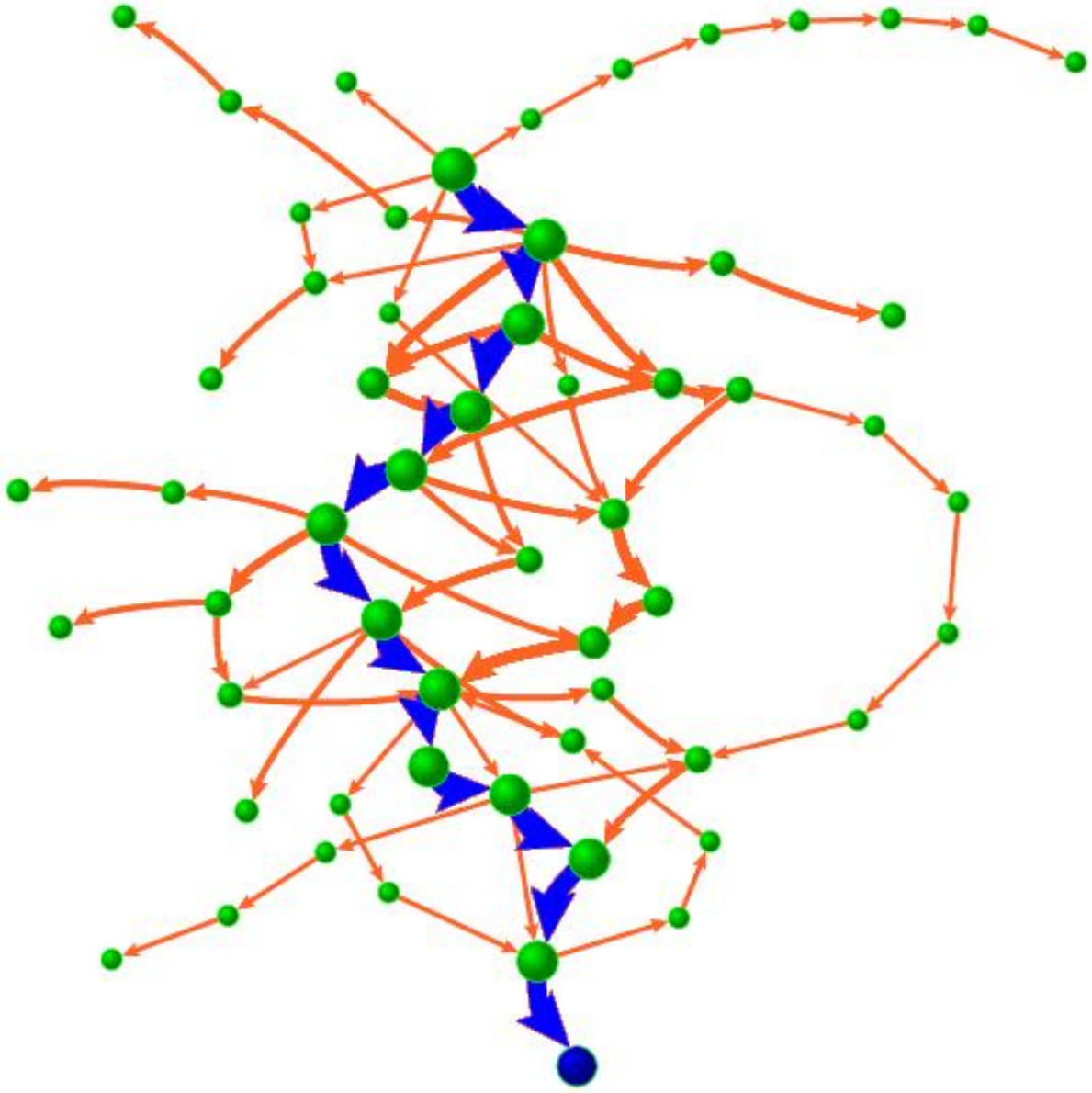




Stability analysis (II)

Deletion, addition, color-switching -- 41.2%, 57.4%, 64.7%





The yeast cell-cycle network is robustly designed

- PNAS 2004 101: 4781-4786

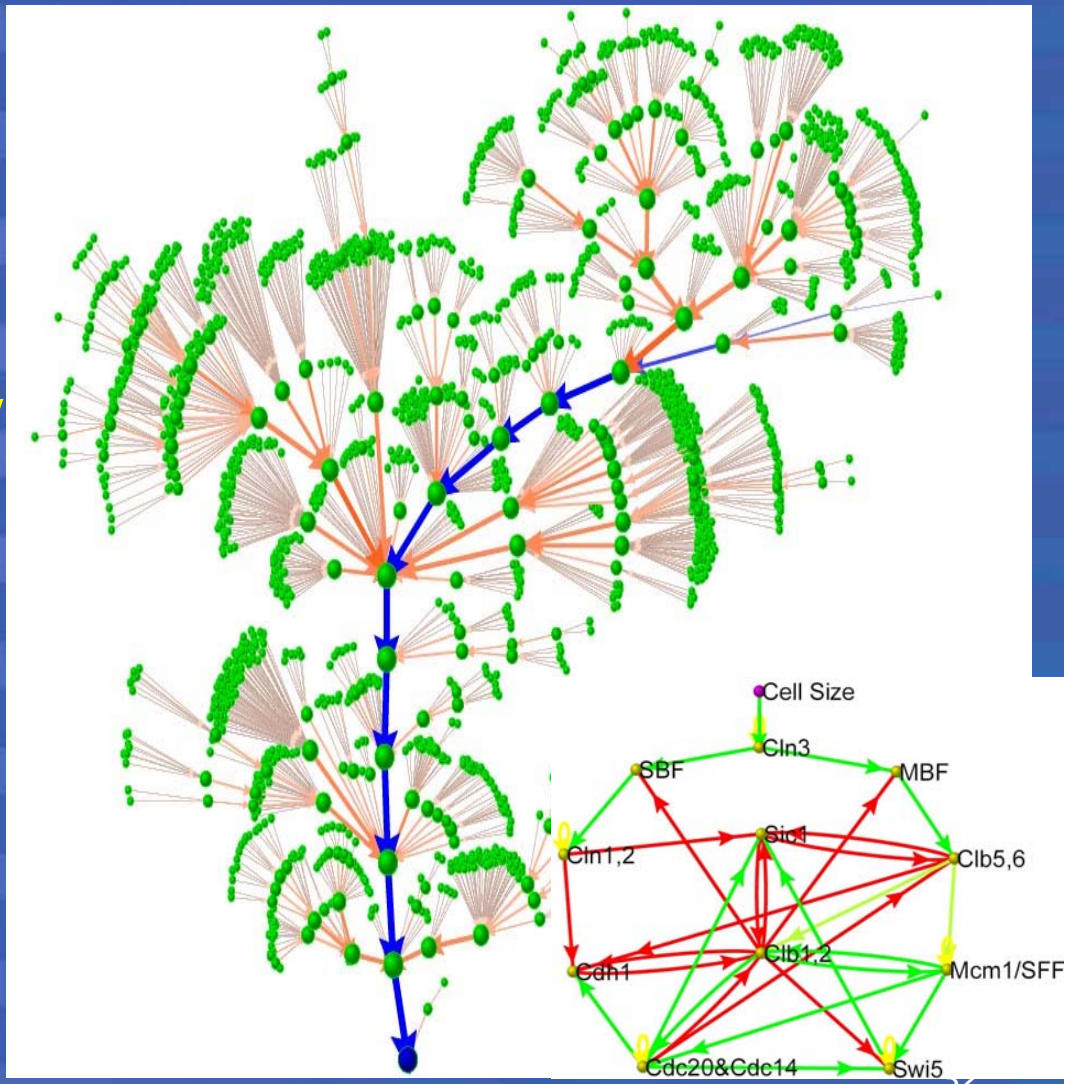
- Dynamical Robustness

  Global attractor

  Globally attracting trajectory

  Robust against /changes/ perturbations/damage/parameters

- WHY?
- The relationship between the **topological** and **dynamical** properties of network



Cross FR, Schroeder L, Kruse M, Chen KC. Quantitative characterization of a mitotic cyclin threshold regulating exit from mitosis. Mol Biol Cell. 2005 May;16(5):2129-38.

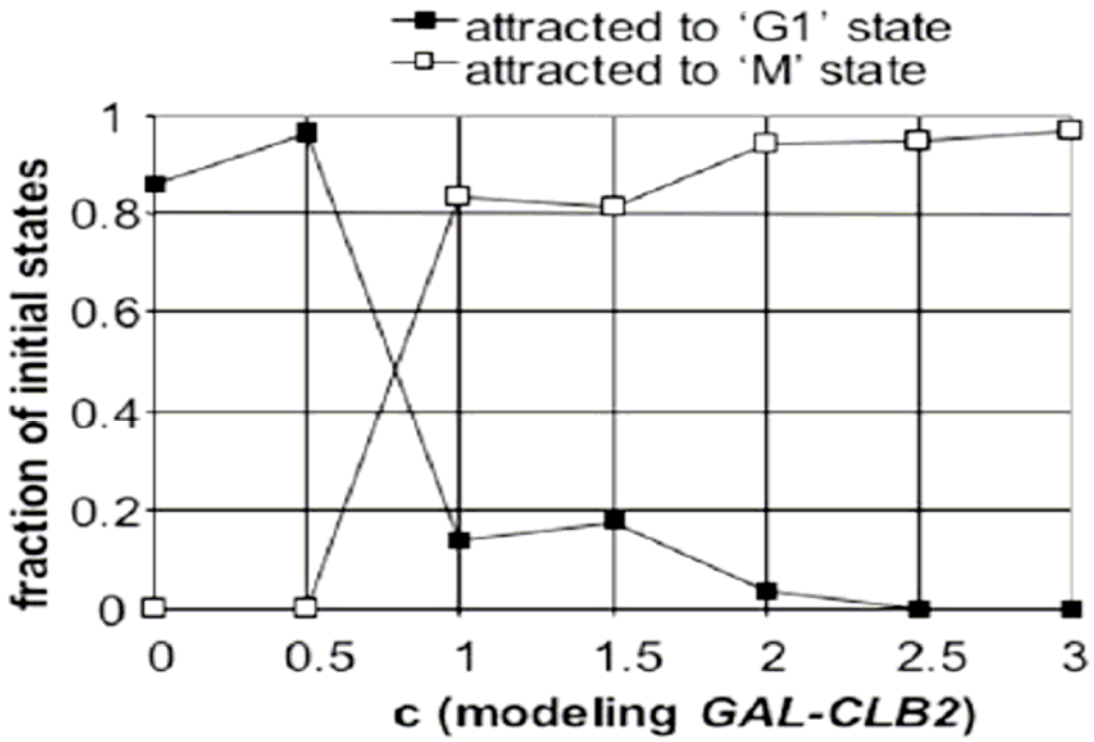


Figure 7. Boolean network predictions. The Boolean network model of Li *et al.* (2004) was implemented using Matlab software (code available on request). Equation 1 of the model was modified by adding a constant c to the Σ(aij*Sj(t)) term for the Clb2 node (j = 10). This has the effect of adding a fixed positive input to the Clb2 node. For the indicated values of c, the 2048 distinct starting configurations of the network were run until a steady state was reached. The proportions of states arriving at the G_1 state of Li *et al.* (2004), or arriving at the M-phase state 9 of Li *et al.* (2004), are plotted for each value of c.

Molecular Biology of the Cell

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