Modeling Yeast Cell-cycle
&
Experimental Predictions

李方廷

Center for Theoretical Biology
Peking University

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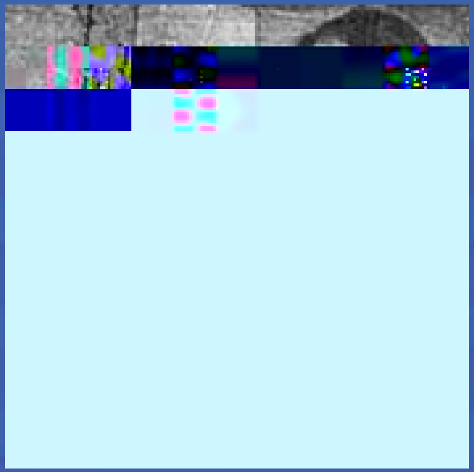
http://ctb.pku.edu.cn

Theoretical & Computational biology



- 1953 ,F. Crick & J. Watson
DNA . DNA

- **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

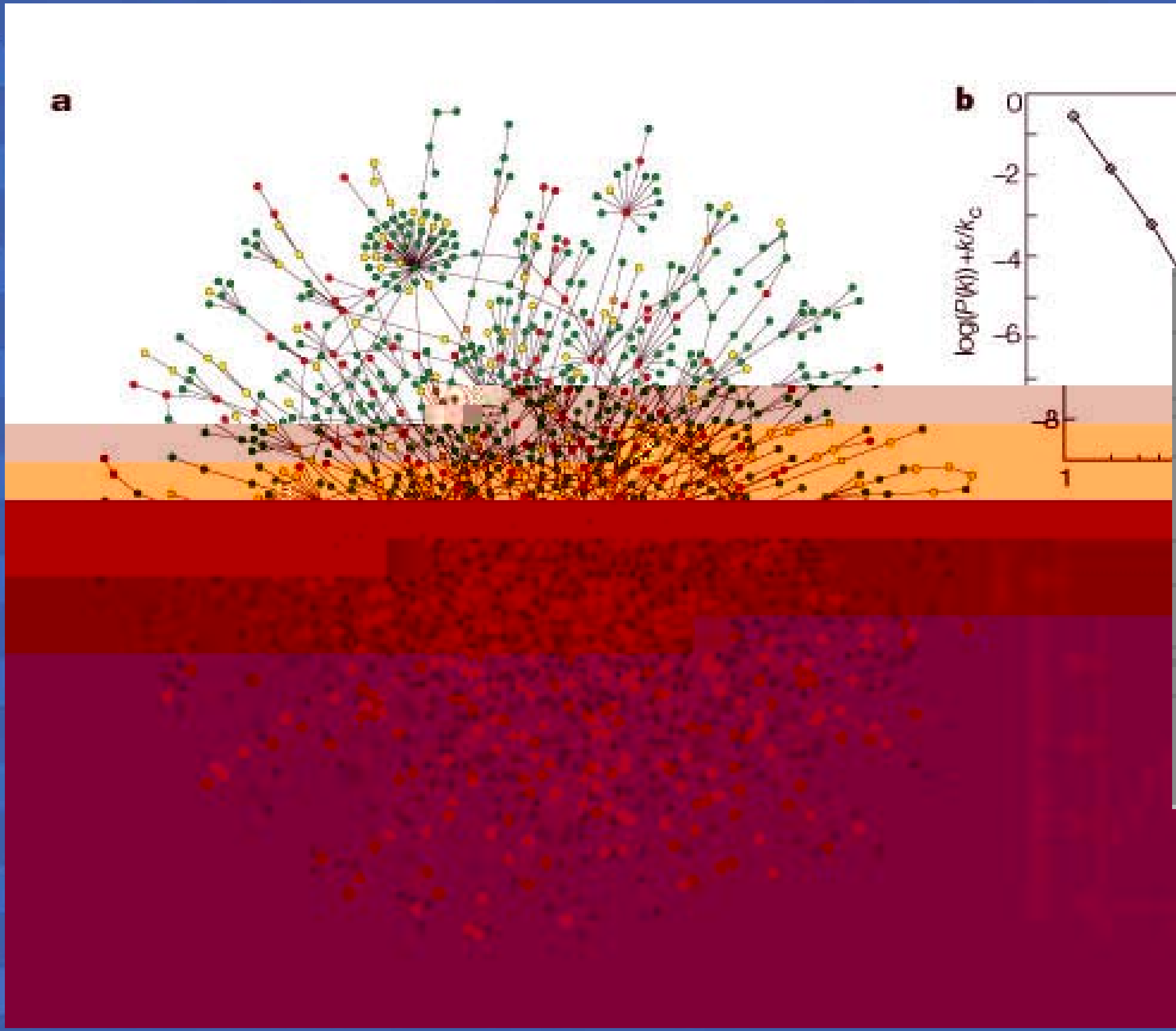
- Biological networks
- Modeling cell cycle network in budding yeast

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).

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.

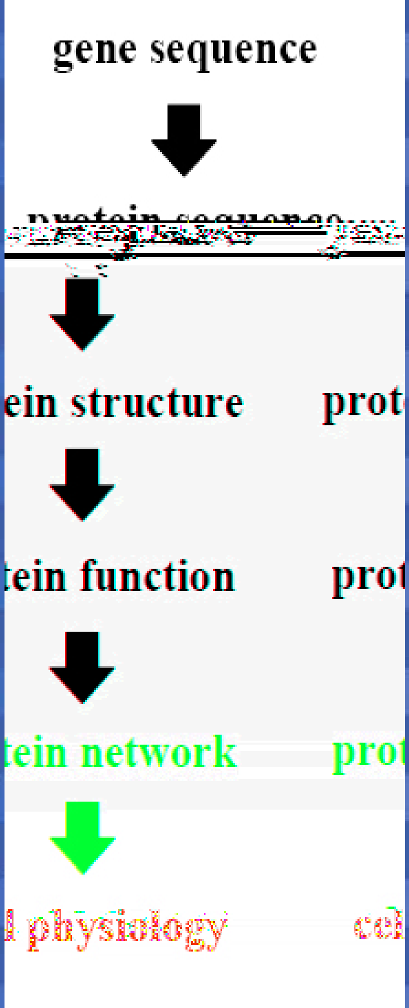
Cross FR, Schroeder L, Kruse M, **Chen KC**. Quantitative characterization of a mitotic cyclin threshold regulating exit from mitosis.

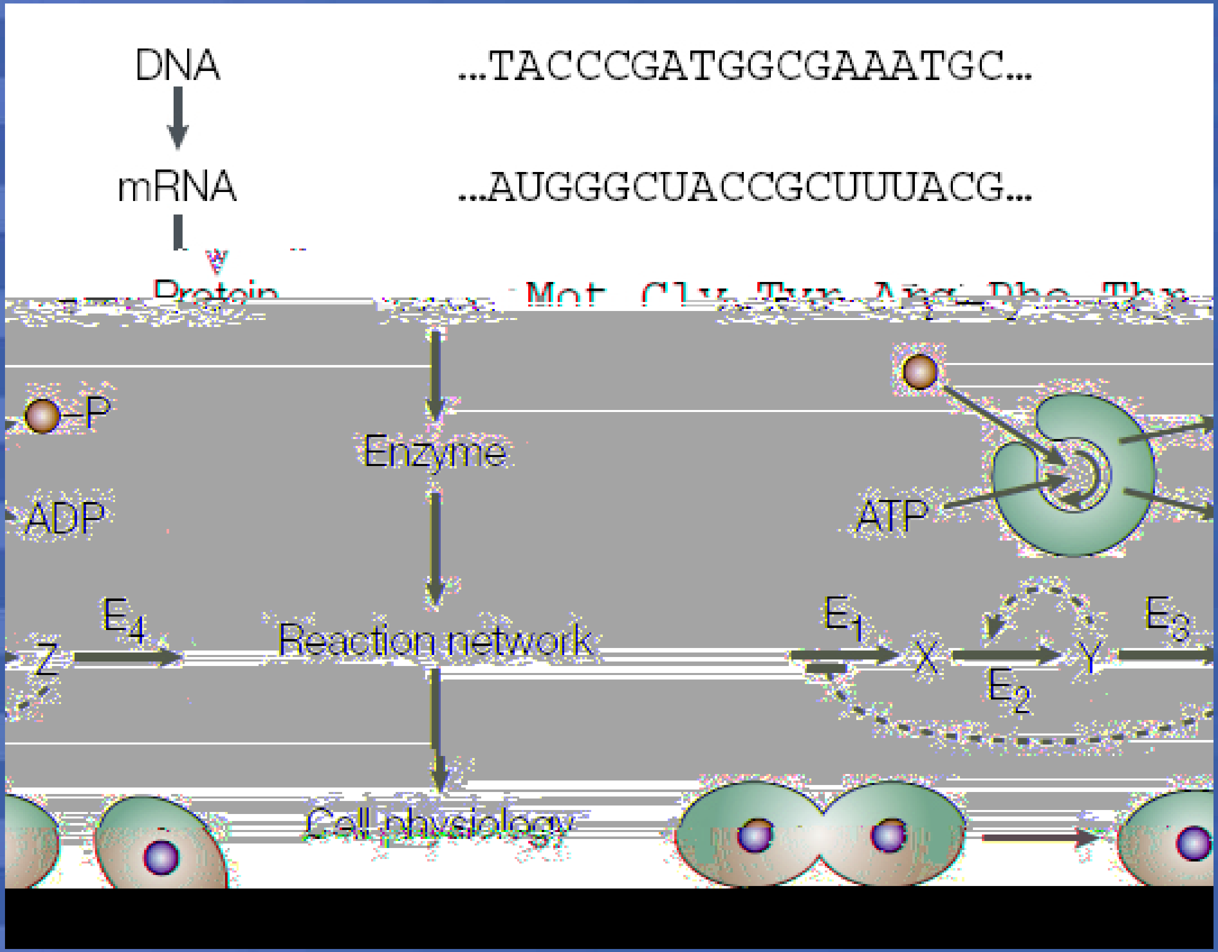
Mol Biol Cell. **2005** May;16(5):2129-38.

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

event order, cell physiology, biological function…

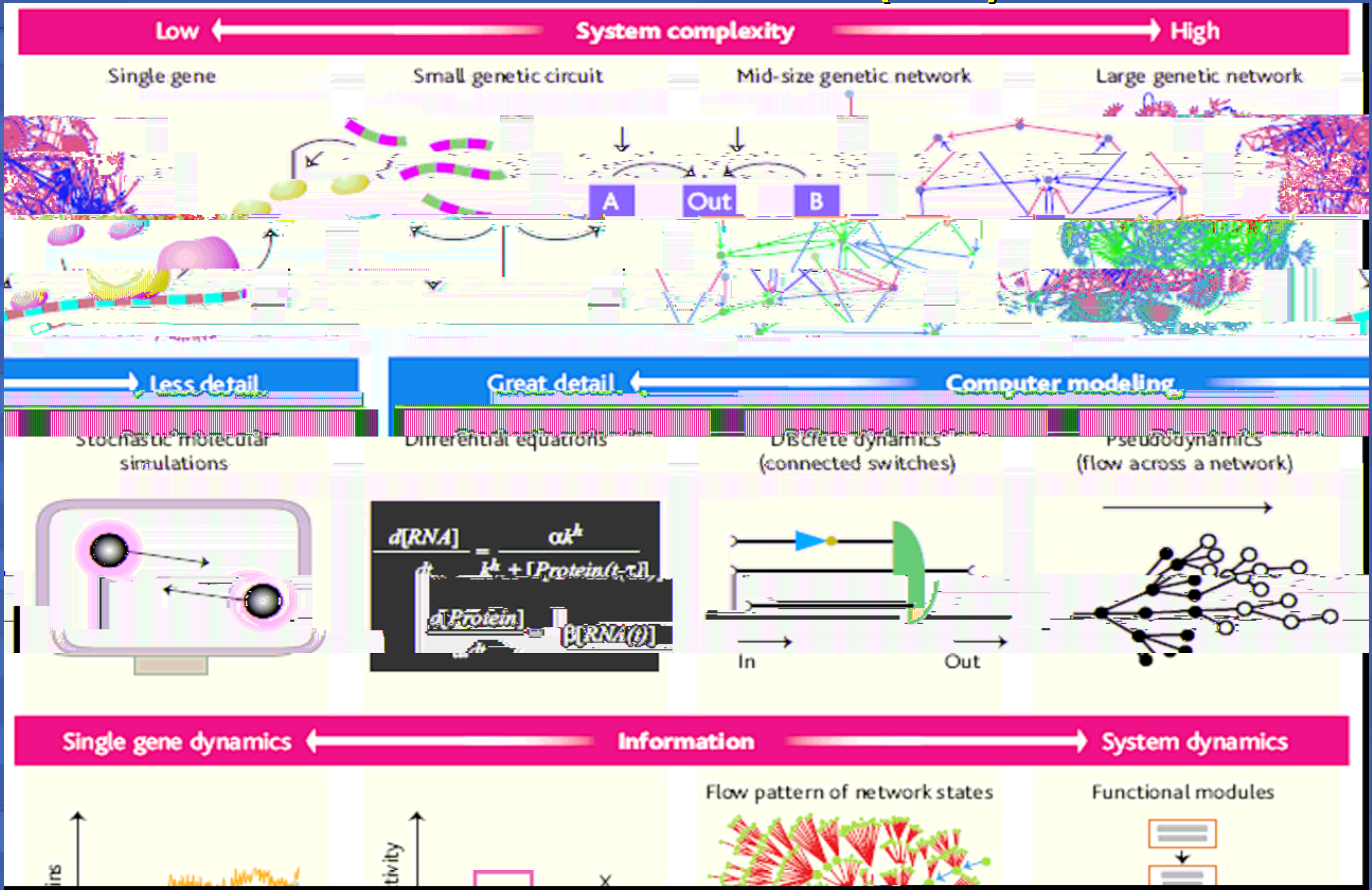




Tyson, Chen, Novak. 2001. Network Dynamics and Cell Physiology Nature Review Mol. Biol. 2:908

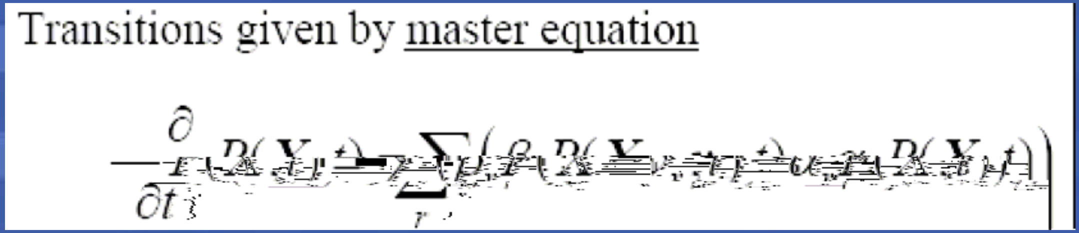
Less is more in modeling large genetic network

Science (2005) 310:449



Modeling cellular process

Stochastic simulations



Transitions given by master equation

$$\frac{\partial}{\partial t}P(\mathbf{X},t)=\sum_{r}\left(\beta_r P(\mathbf{X}-\nu_r,t)-\alpha_r P(\mathbf{X},t)\right)$$

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

$$x_i(t+1)=b_i(x(t))$$

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

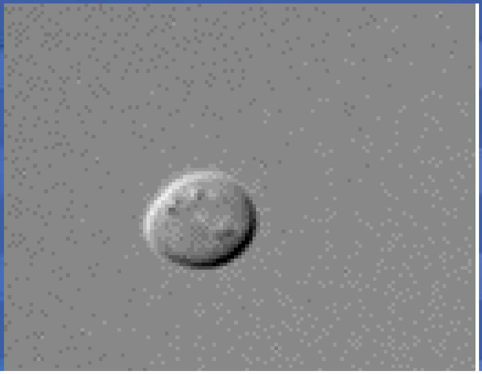
Robustness is an essential property of biological systems:

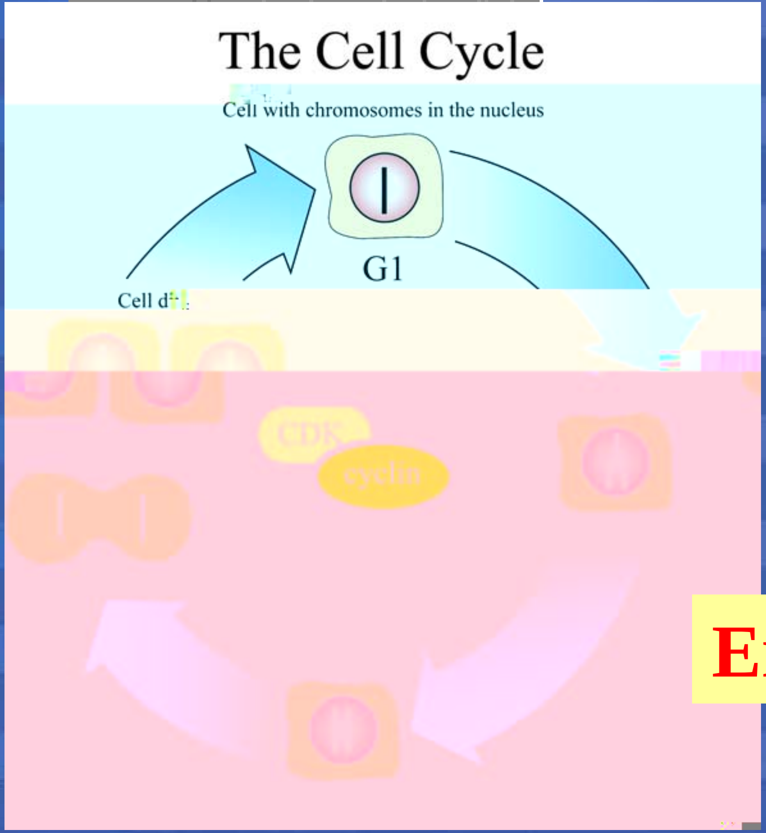
the adaptation parameters insensitivity graceful degradation

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

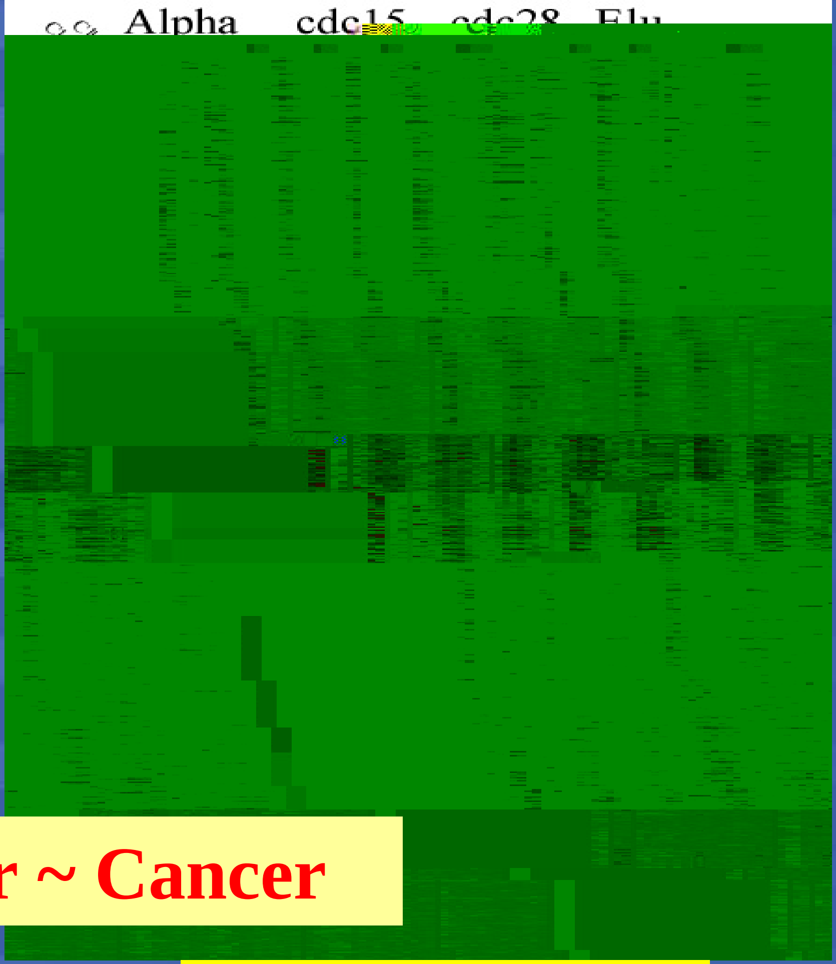
Fluctuations and noise inside and outside of CELL

The Cell Cycle in budding yeast





800 Genes involved in Yeast Cell Cycle

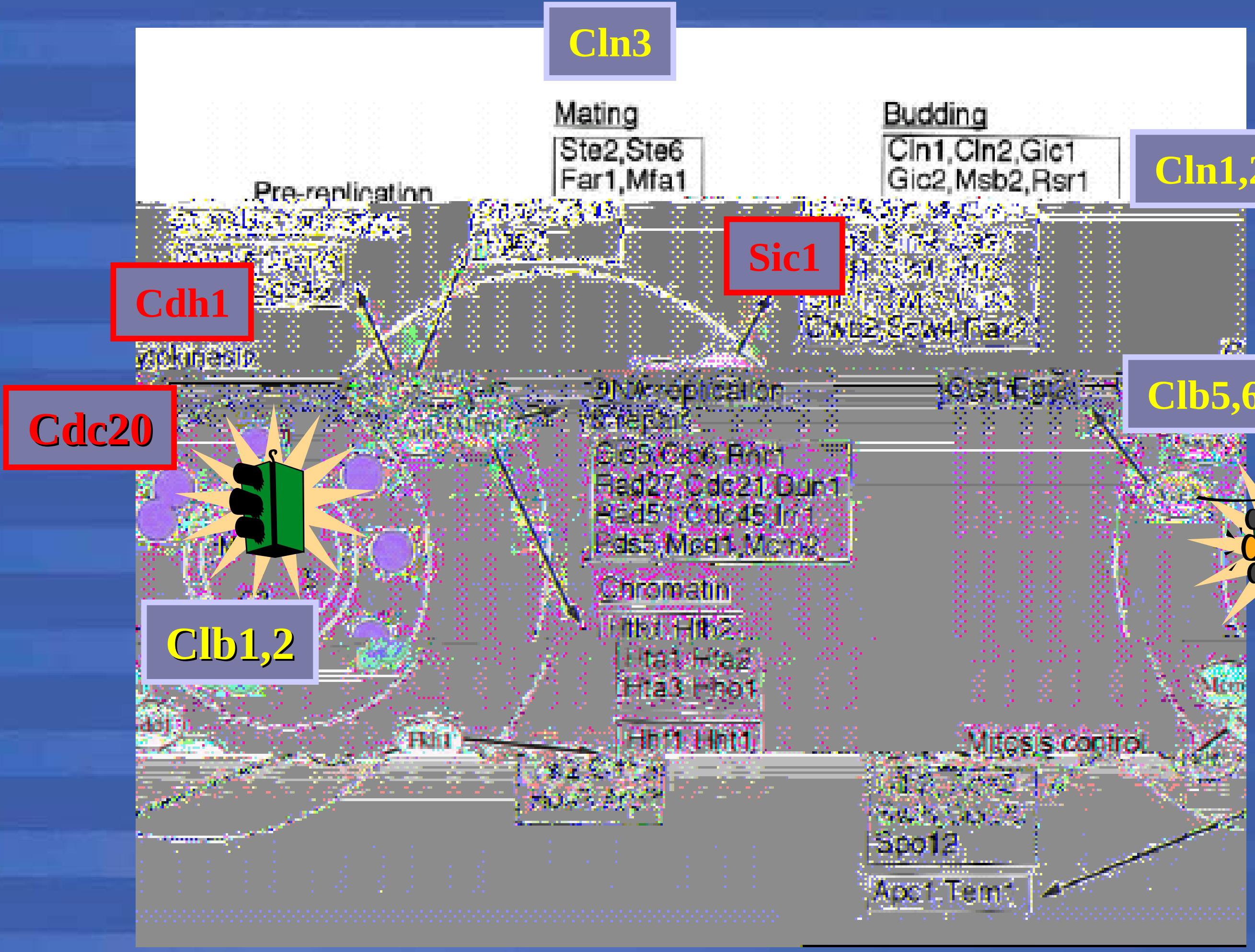


Error ~ Cancer

Spellman, et al. (1998)

A vital process that is highly conserved in eukaryotes

Regulators of the Yeast Cell Cycle



Cln3

Cln1,2

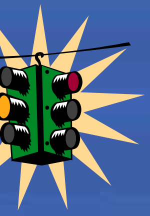
Sic1

Cdh1

Cdc20

Clb5,6

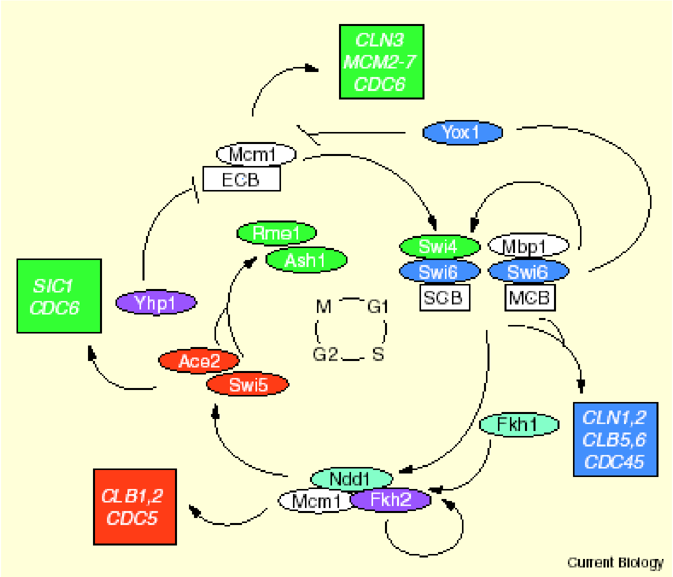
Clb1,2

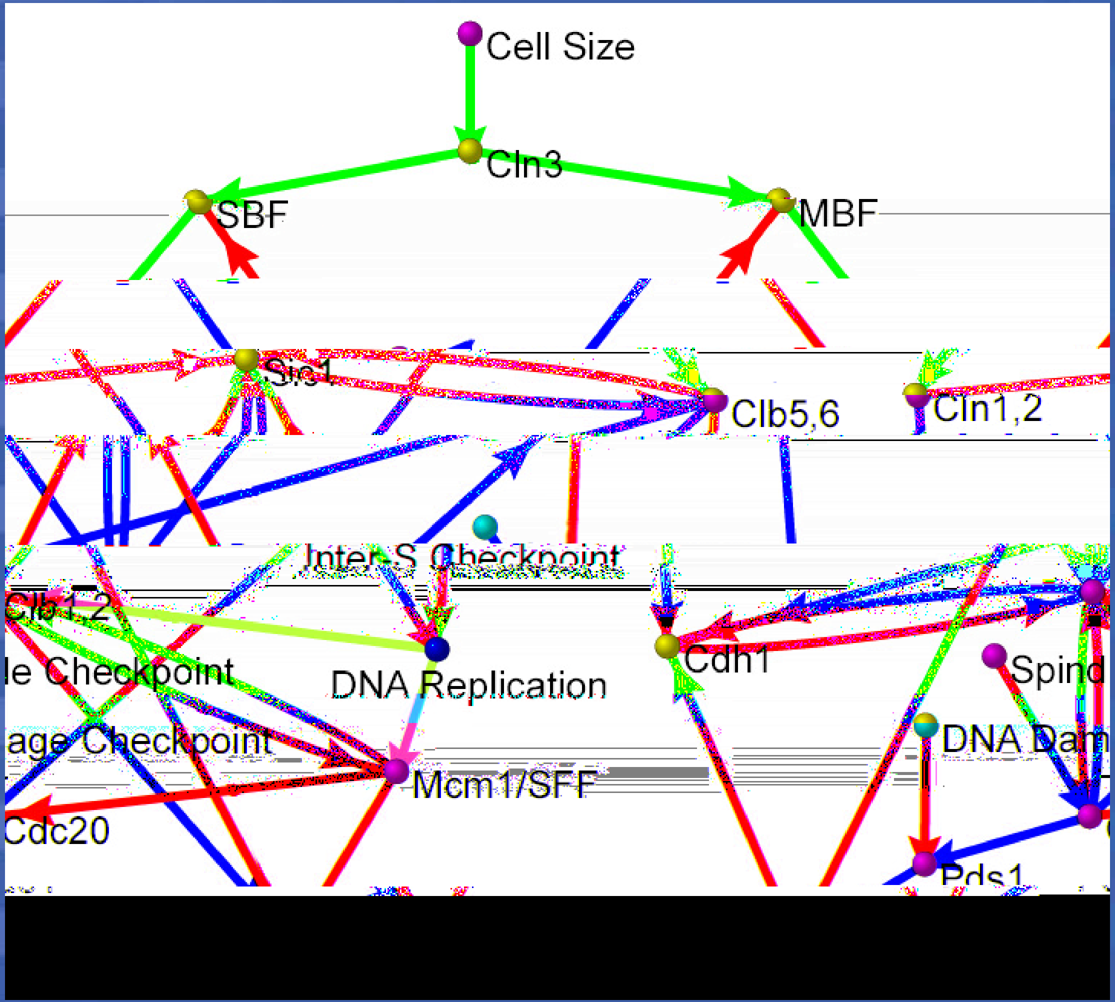


Cyclins Cycling

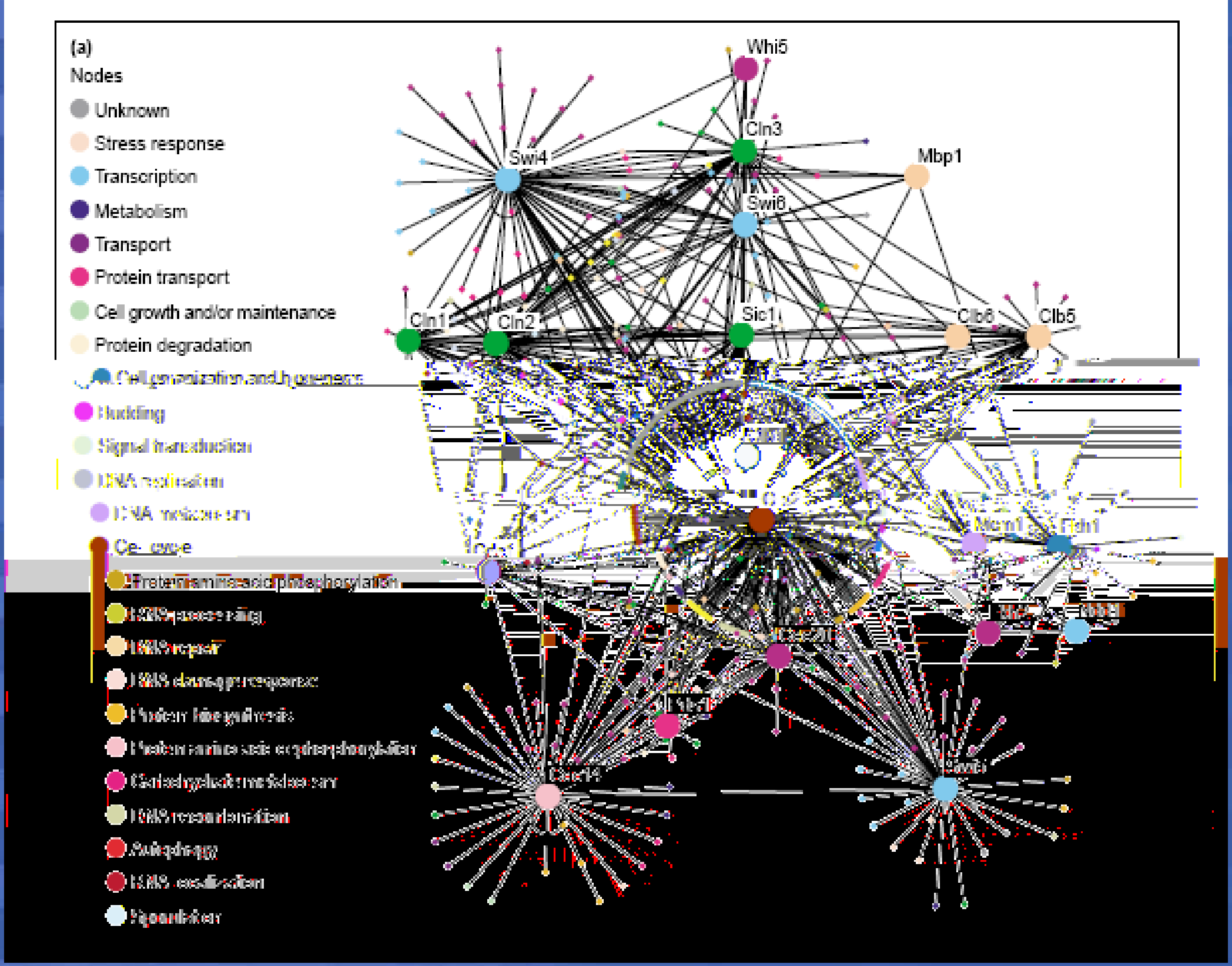
Cdc28/CDK

Regulatory Network of Yeast Cell Cycle





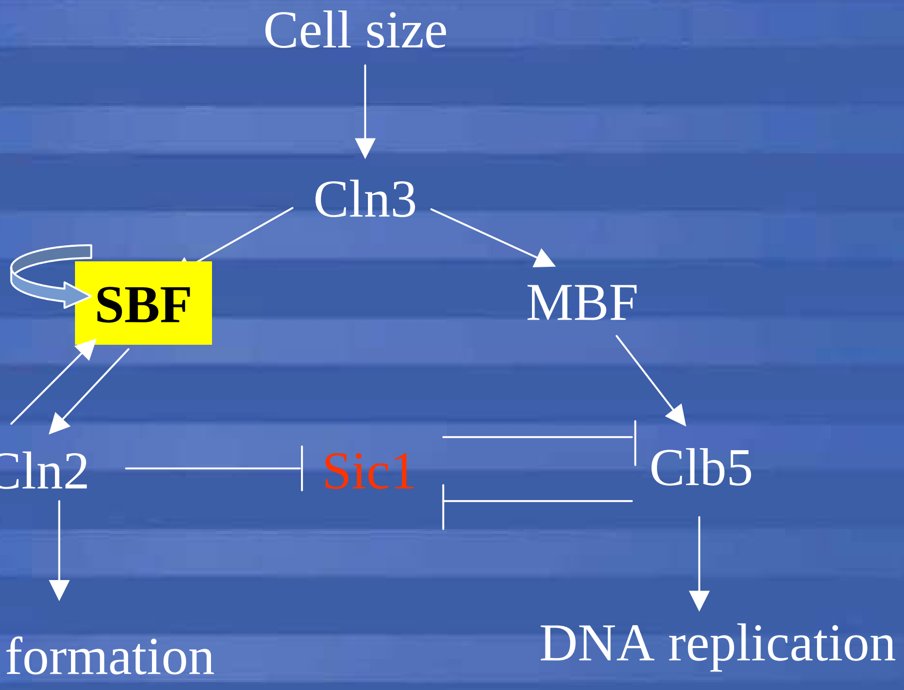
Breeden 2003 Current Biology
13: R31-R38



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



Cell size

Cln3

SBF

MBF

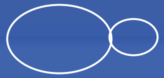
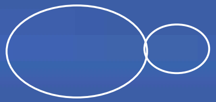
Cln2

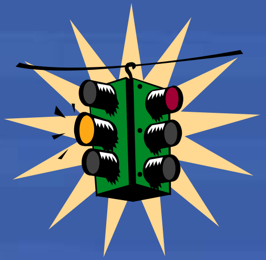
Sic1

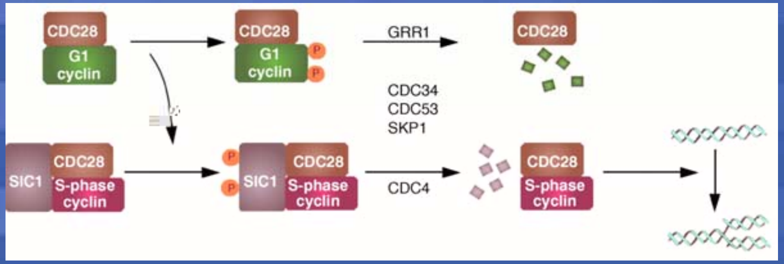
Clb5

Bud formation

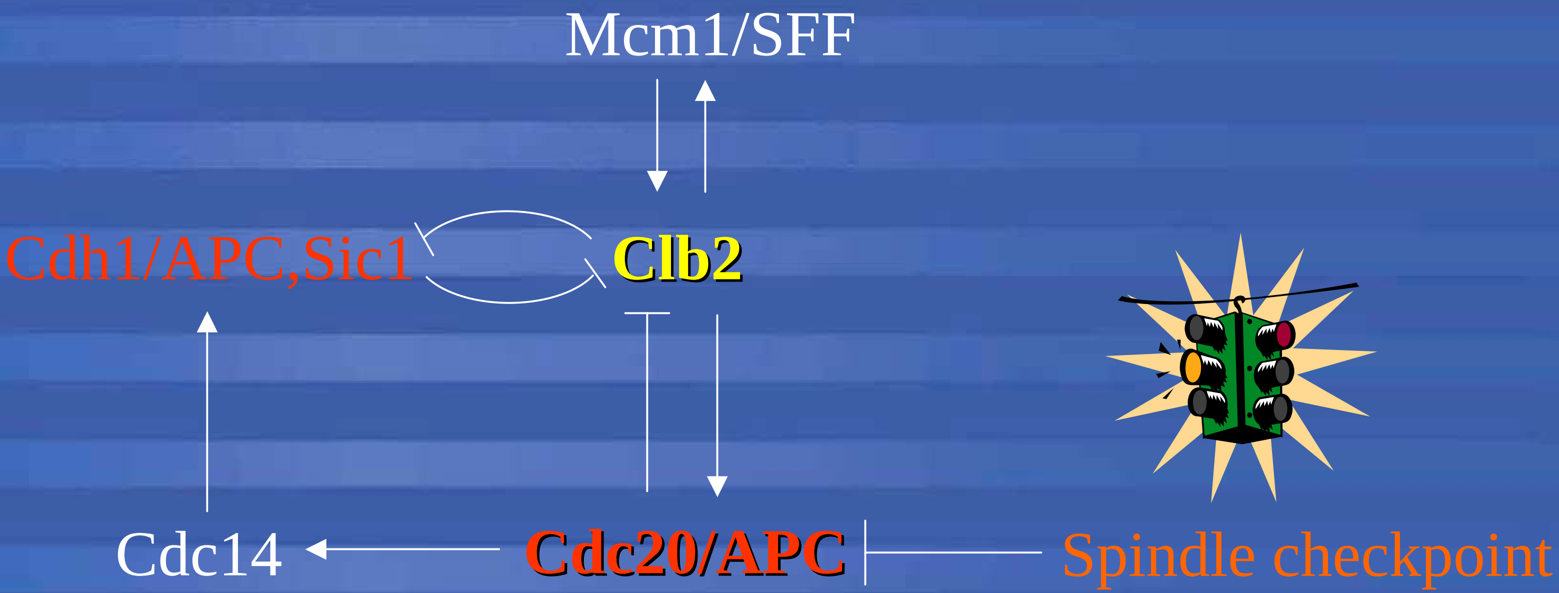
DNA replication

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





Mitosis



Mcm1/SFF

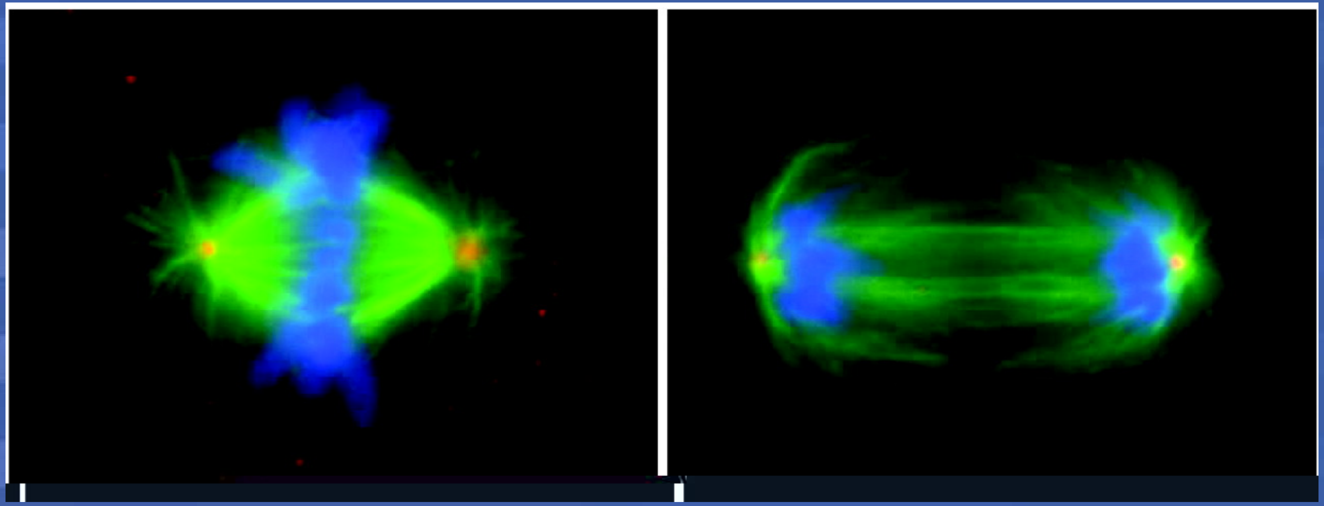
Cdh1/APC,Sic1

Clb2

Cdc14

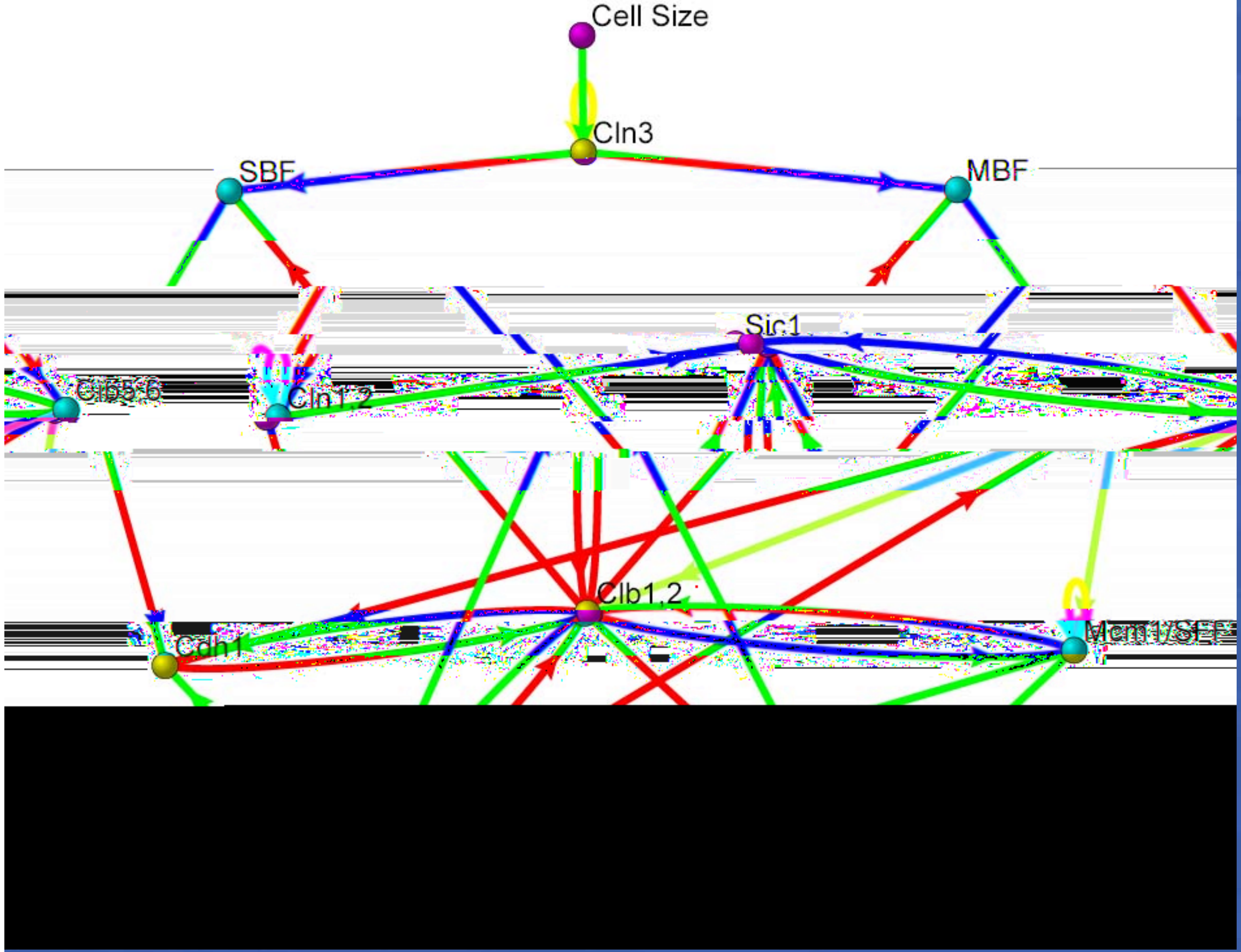
Cdc20/APC

Spindle checkpoint



Movie

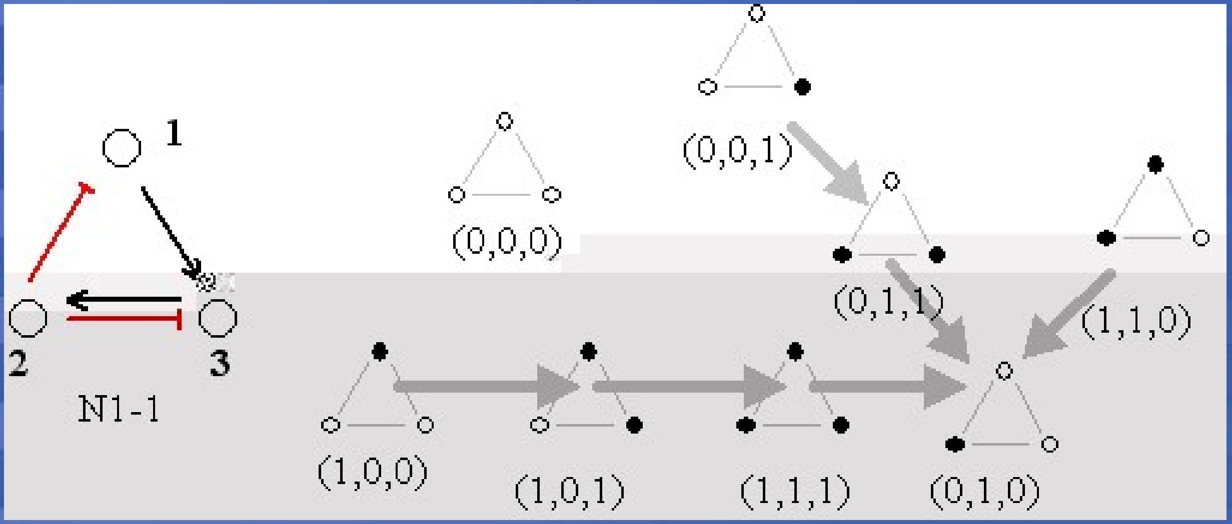
Simplified cell-cycle network and Boolean network model

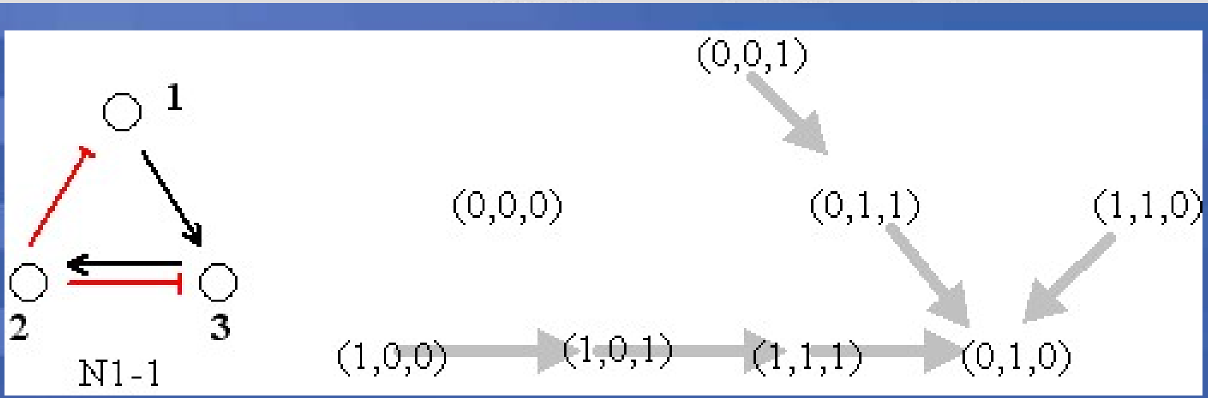


11Nodes; 16 Green lines; 13 Red lines; 5 Yellow lines

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…

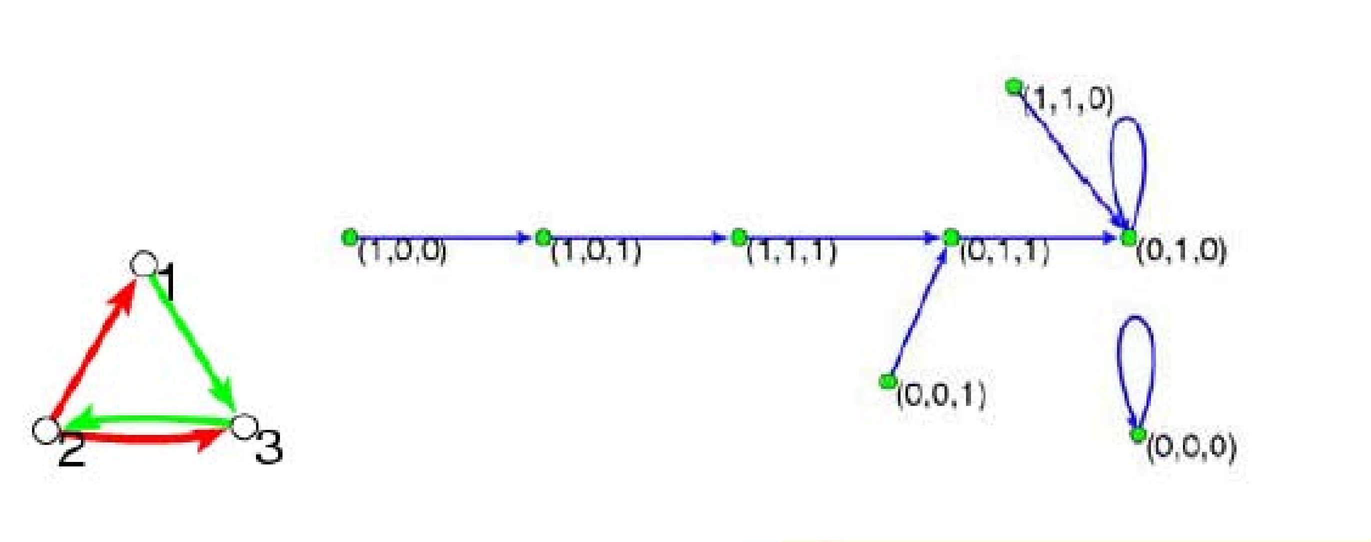
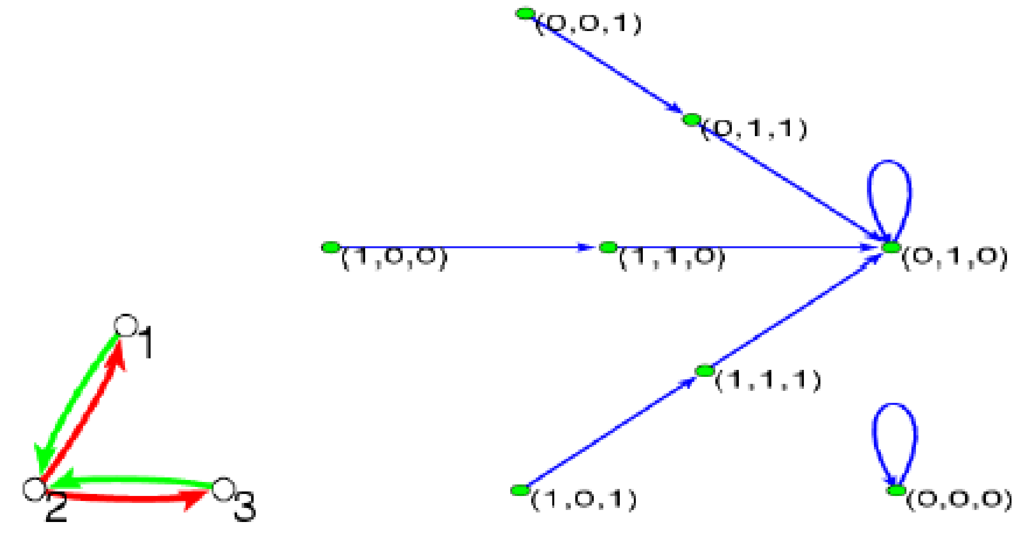
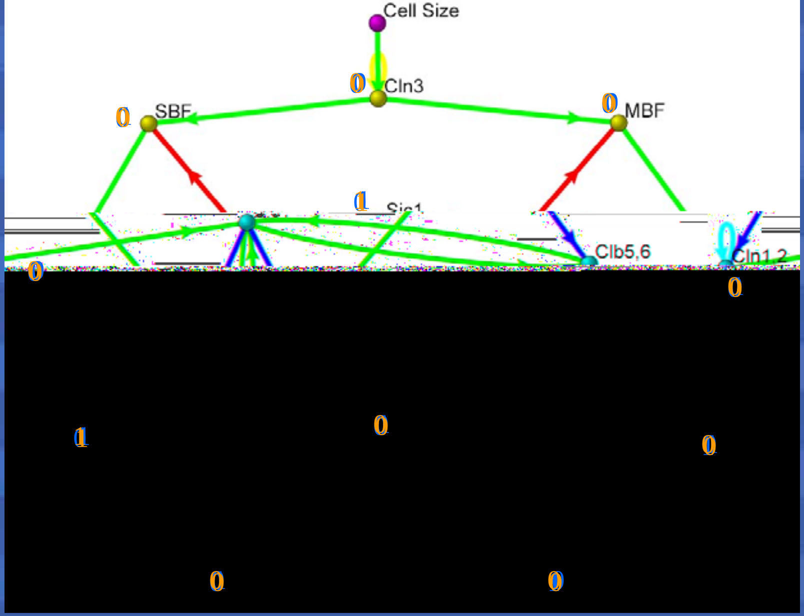


Figure [The network N2-1 and its dynam[illegible] trajectory under rule2]



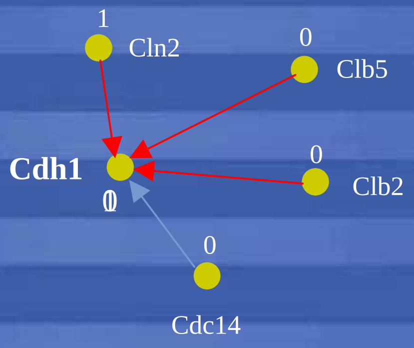
a_{ij} (green) = 1,
a_{ij} (red) = -1

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	G_1
3	0	1	1	1	1	0	0	0	1	0	0	
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	M
8	0	0	0	0	0	1	1	0	0	1	1	
9	0	0	0	0	0	1	1	0	1	1	1	
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

[redacted] states

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	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

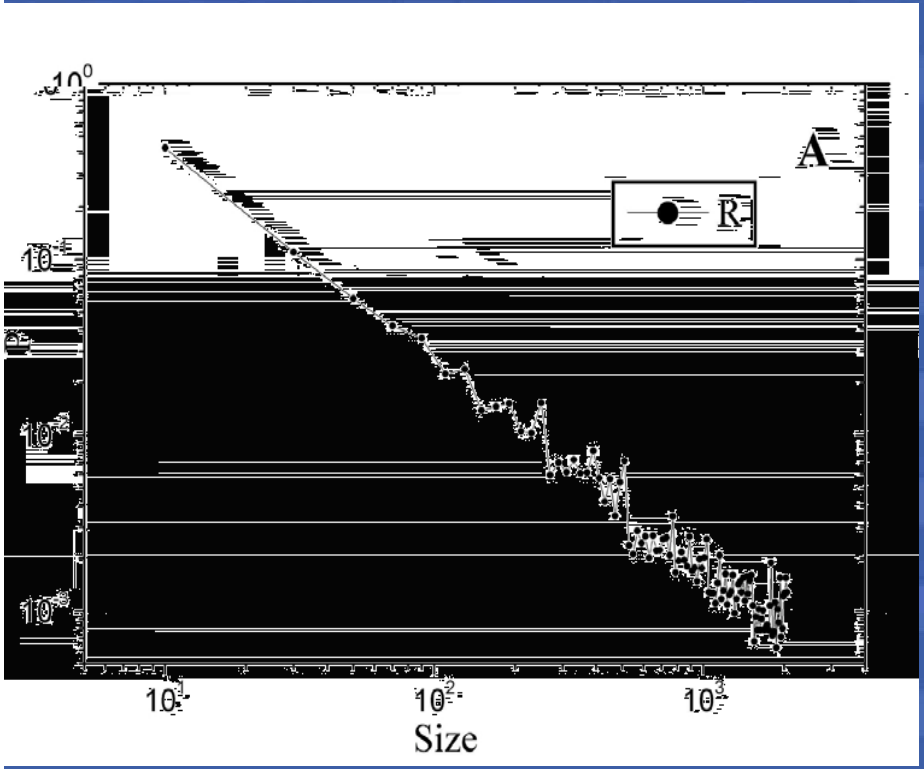
(2) Evolution Trajectory (using W value)

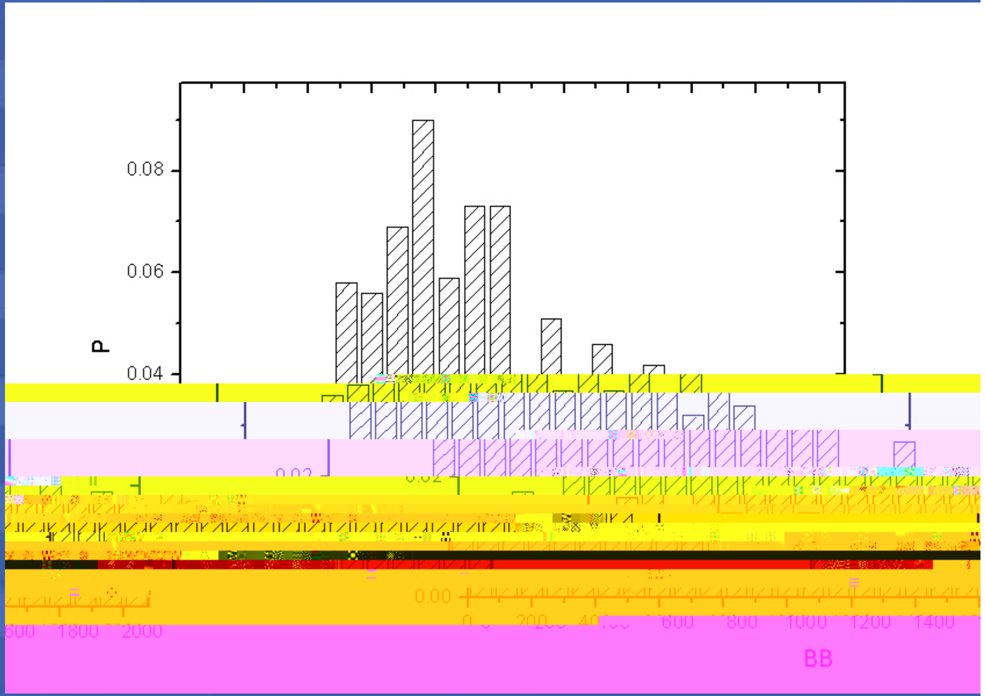
$$W_i = \frac{\sum \text{weight-of-every-step}}{\text{step-length}}$$

$$W = \langle W_i \rangle$$

(3) Stability against different perturbations

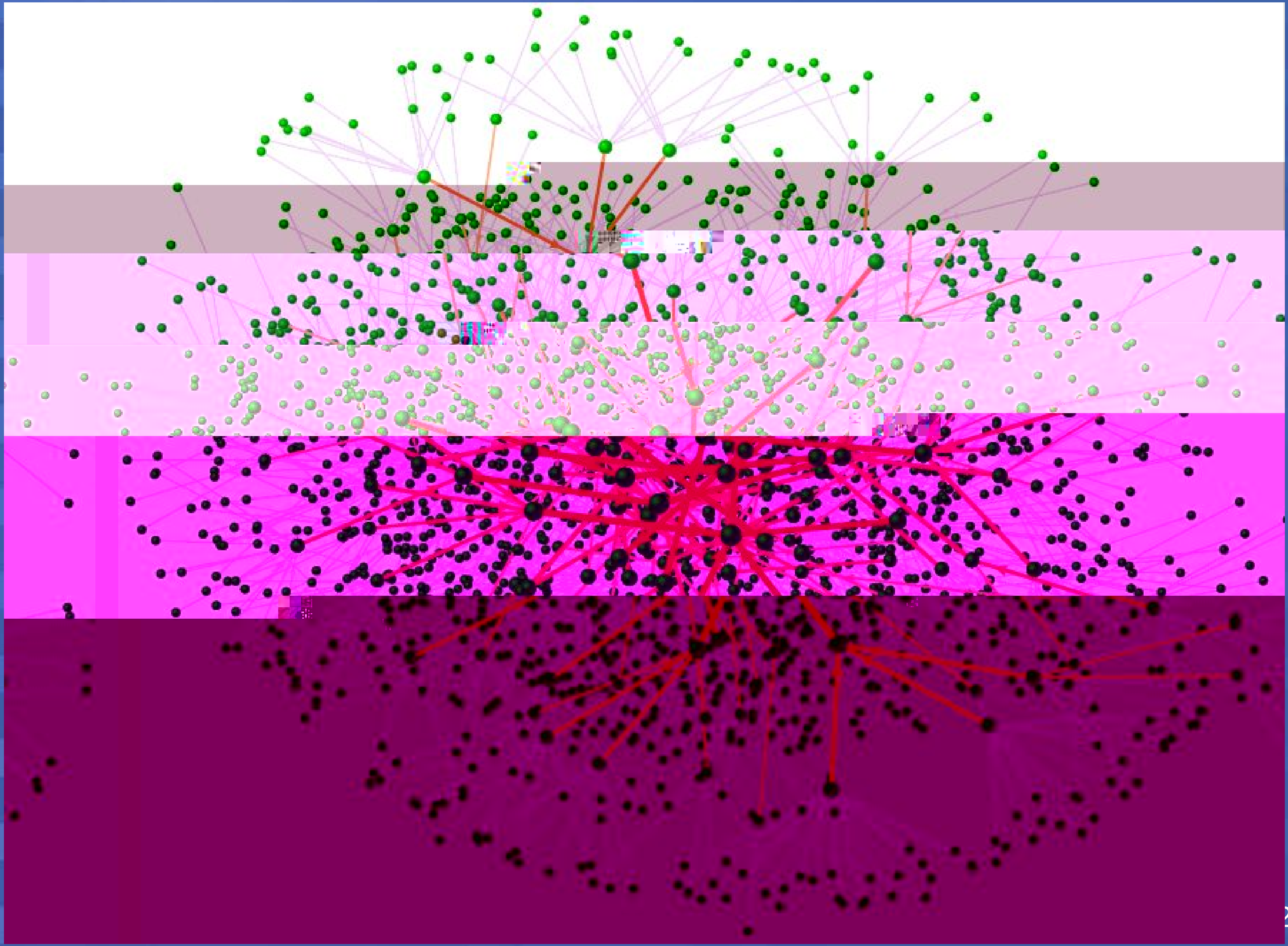
Attractor size distribution



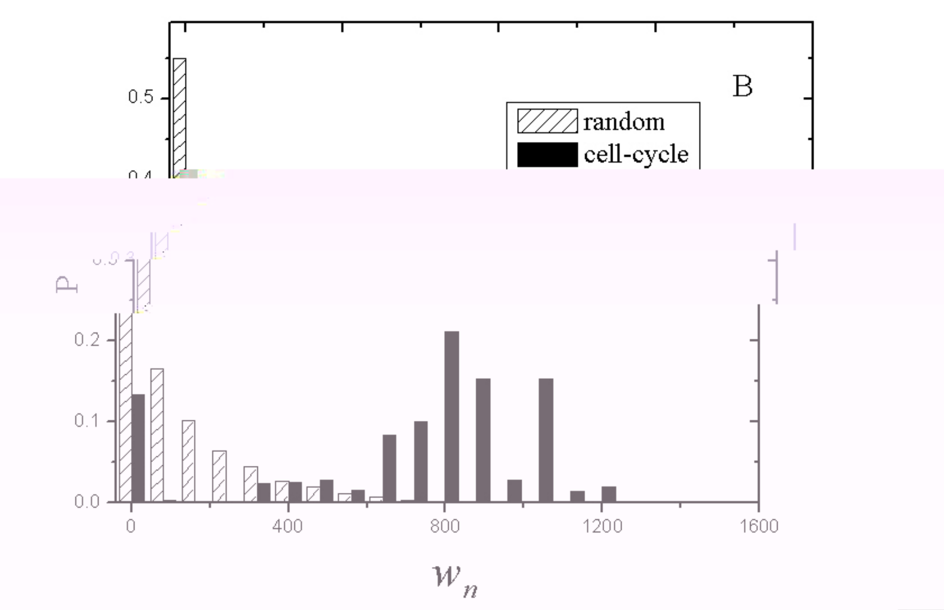


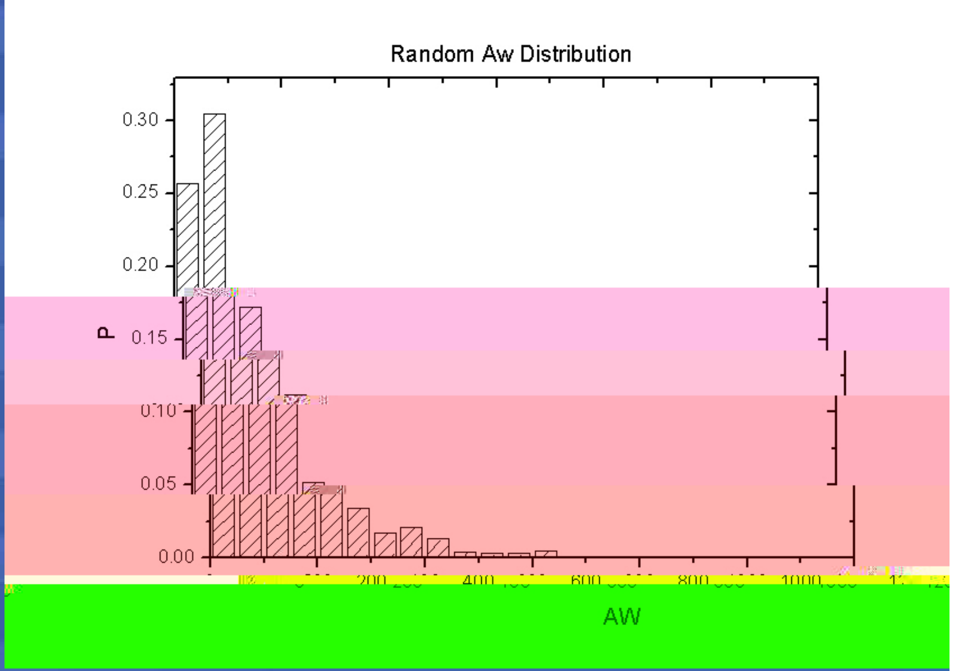
P(BB>1764) = 0.1

Flow diagram of random networks



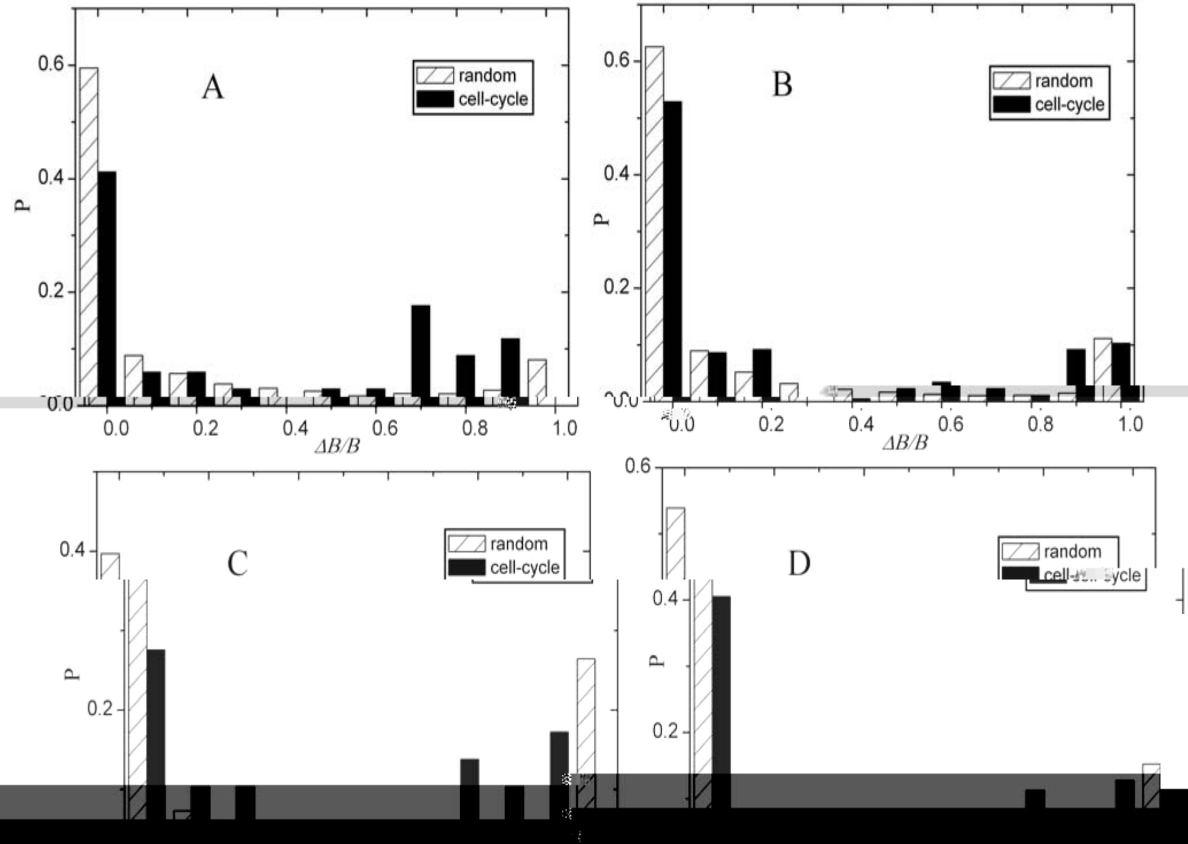
Distribution of W

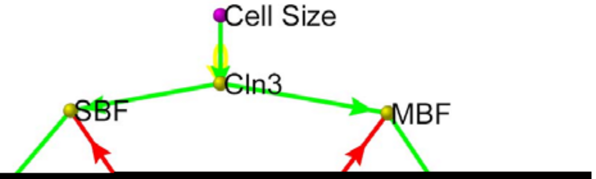




P(AW>743)=0.0025

Stability analysis (I)



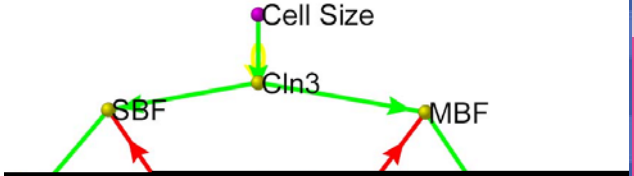


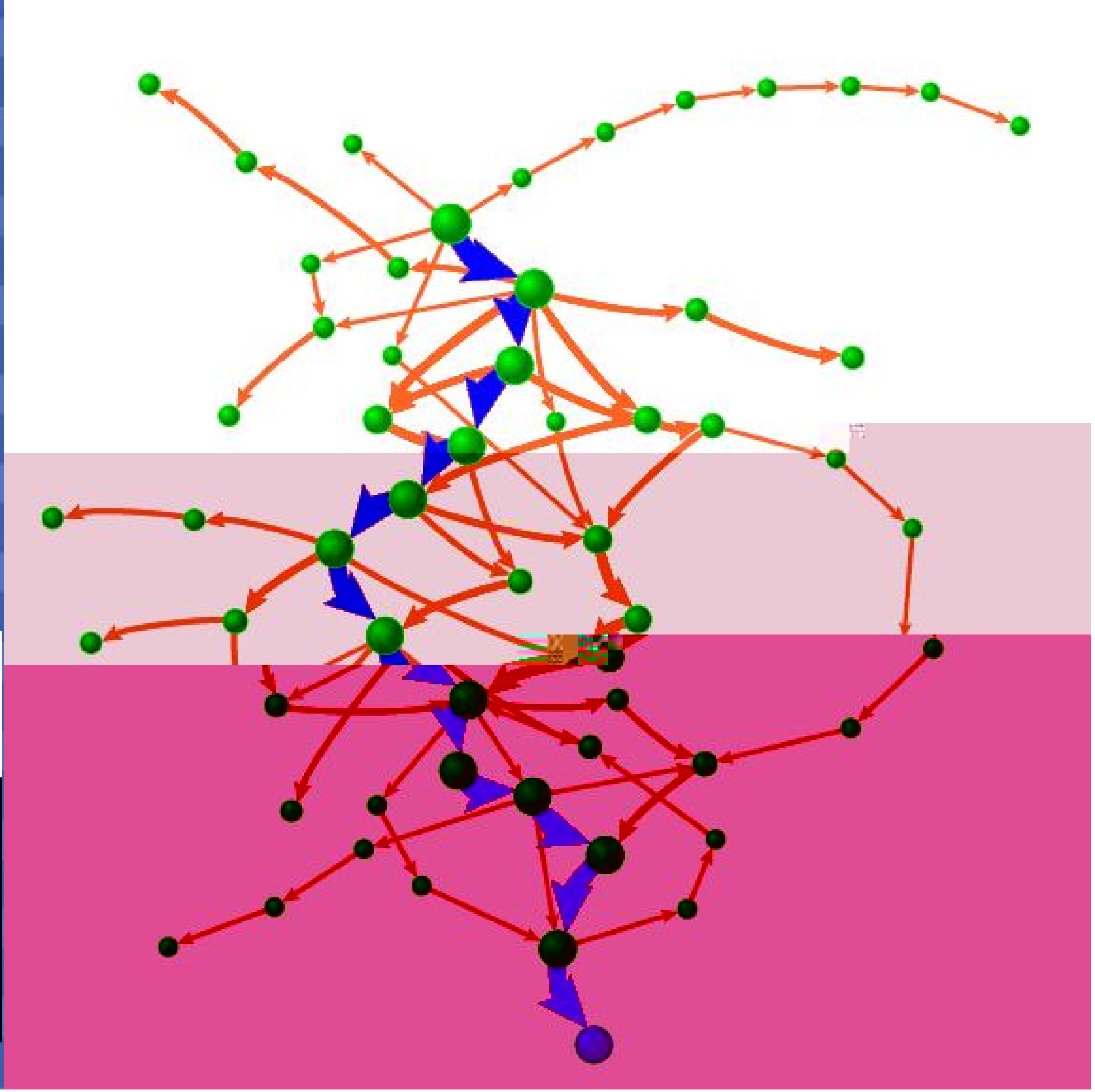
Color switches

Average

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

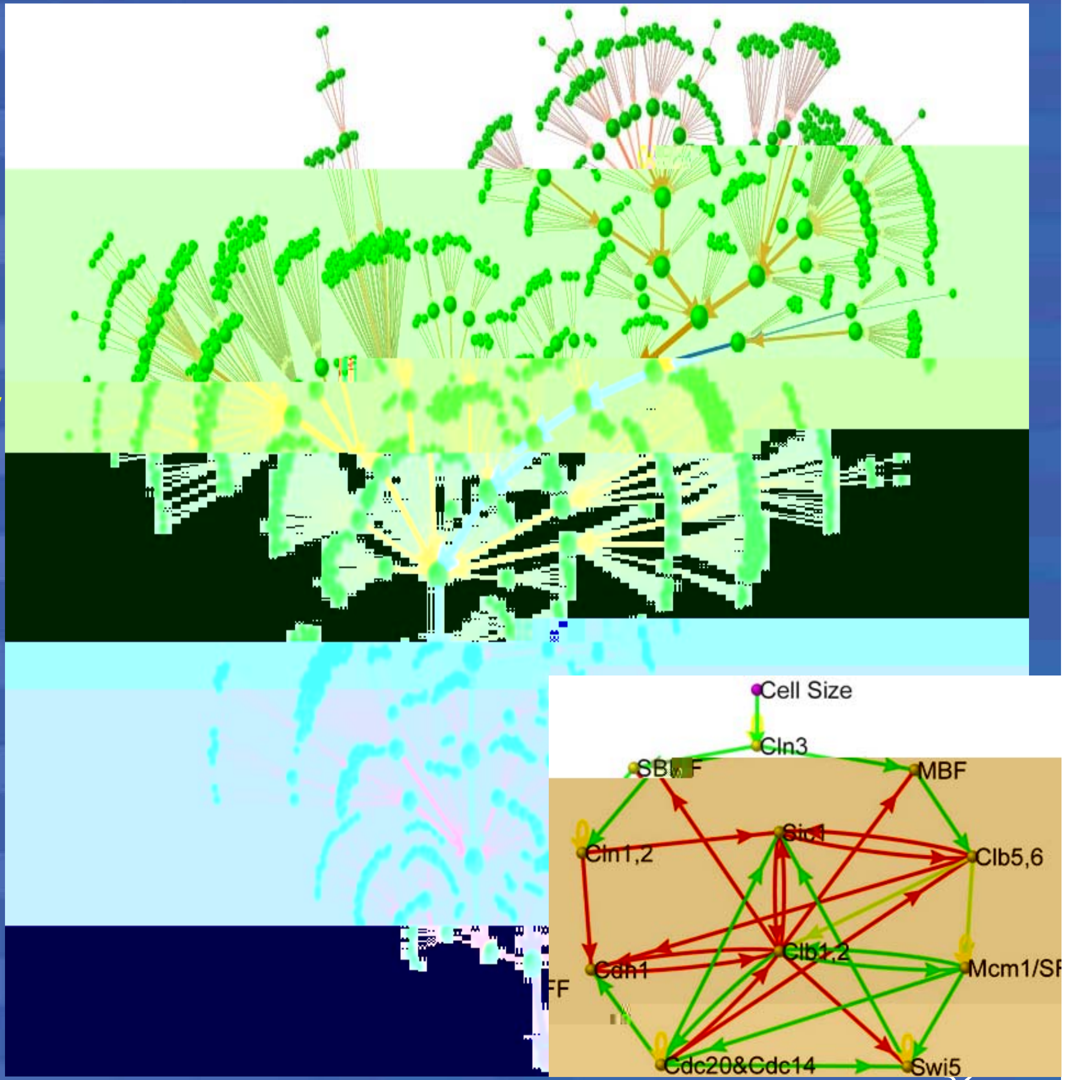
- Dynamical Robustness

  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.

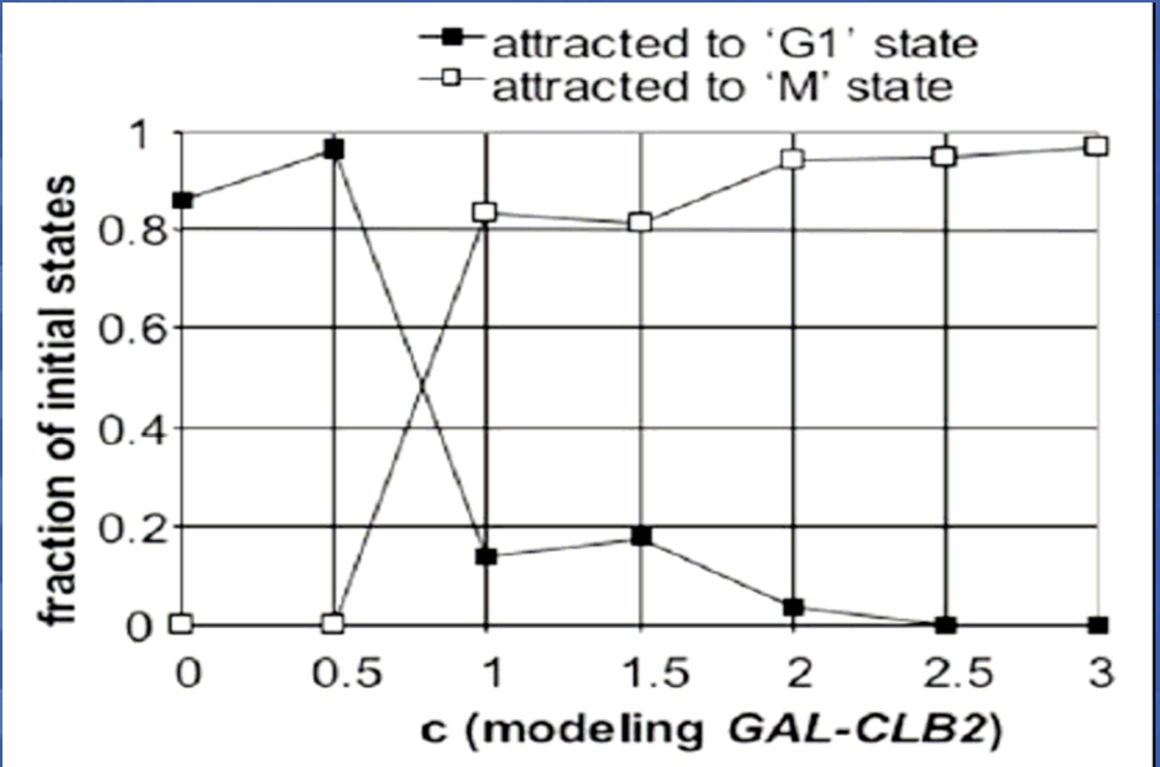


Figure 7. Boolean network predictions. The model of Li *et al.* (2004) was implemented using [illegible] by adding a constant c to the Σ(aij*Sj(t)) term for the Clb2 node (j = 10). This has the effect of adding a fixed positive input to the Clb2 node. For the indicated values of c, the 2048 distinct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

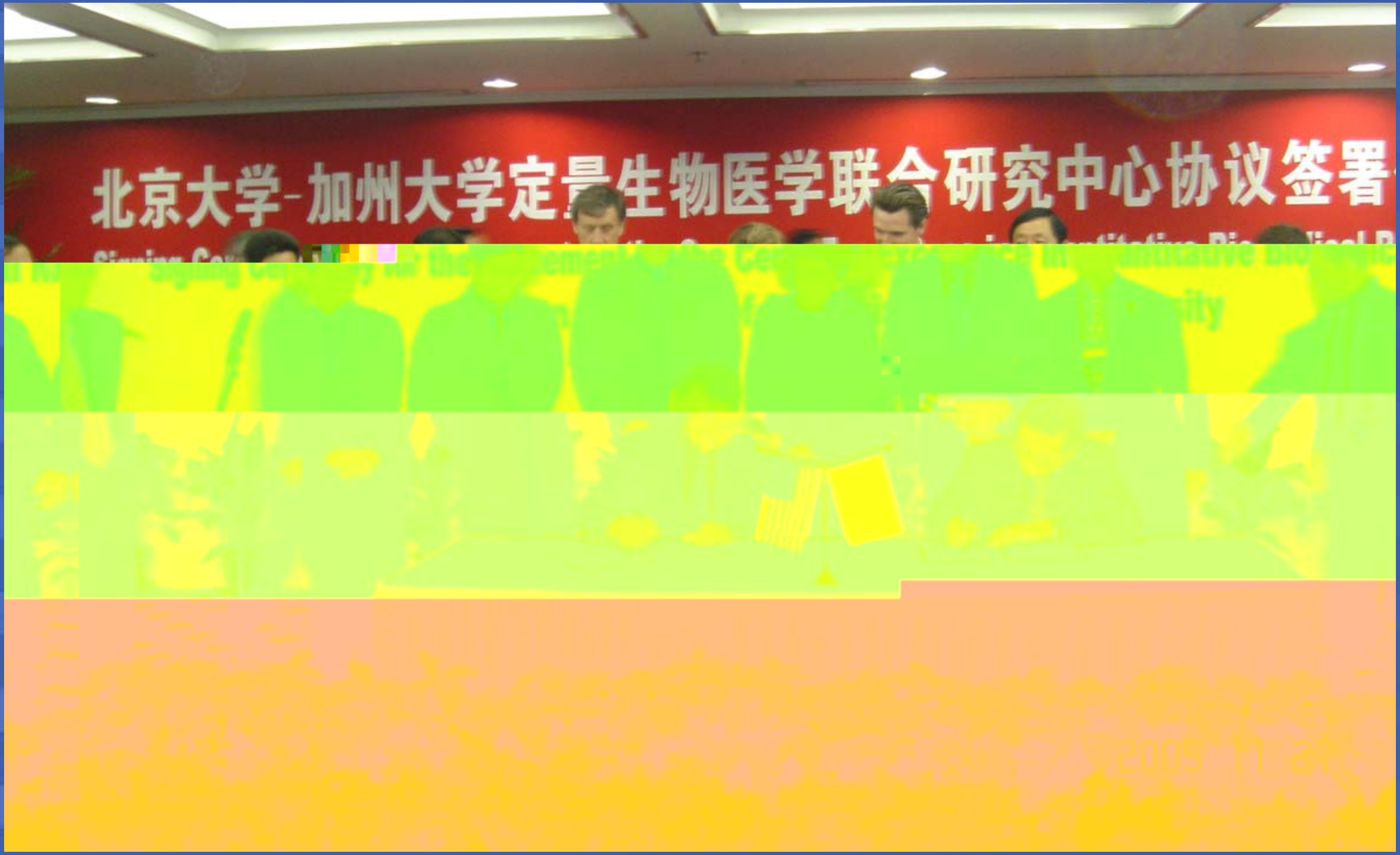
北京大学理论生物学中心

中心主任：汤超教授
副主任：来鲁华教授，欧阳颀教授

北京大学理论生物学中心在李政道先生及北京大学有关领导的倡导和大力支持下，于1999年开始筹建，2001年9月17日在北京大学正式成立。

北京大学理论生物学中心与美国加州大学旧金山分校于2005年成立联合研究中心

中心主任：汤超，副主任：欧阳颀，李浩



Acknowledgement

Directors:

OUYANG Qi 欧阳颀 *TANG Chao* 汤超

Major contributors:

吕莹 龙涛 贾珣 钟鸣远

杨晓静

谭宁

感谢马文喆、倪鸣等 Network 讨论小组的成员们！

Thank you!