The cell cycle models in budding yeast

How to ensure a globally attractive cycle in a sequential-task biological process?

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2015，10

- **Quantitative biology in yeast cell cycle**

  The cell-cycle in budding yeast, modeling and quantitative experiment
- **3-node yeast cell cycle model**

  Feedbacks, checkpoints, a globally attractive trajectory…
- **How to ensure the stability of a multi-task process?**

- **Quantitative biology in yeast cell cycle**

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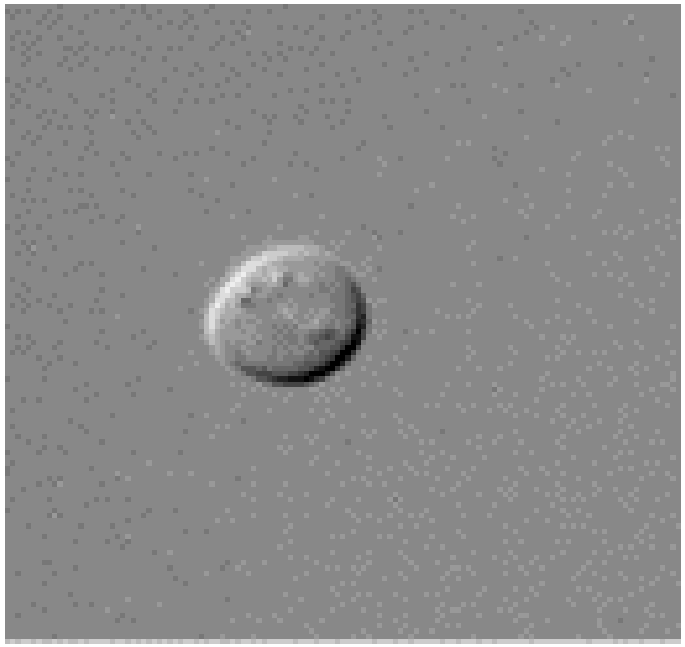
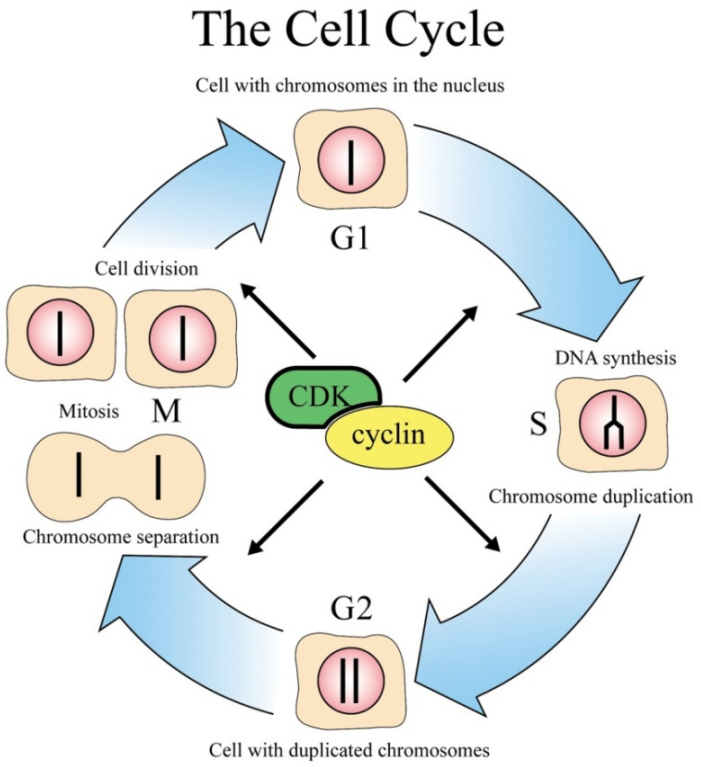
- **How to ensure the stability of a multi-task process?**

The cell cycle in budding yeast serves as a model system for quantitative biology

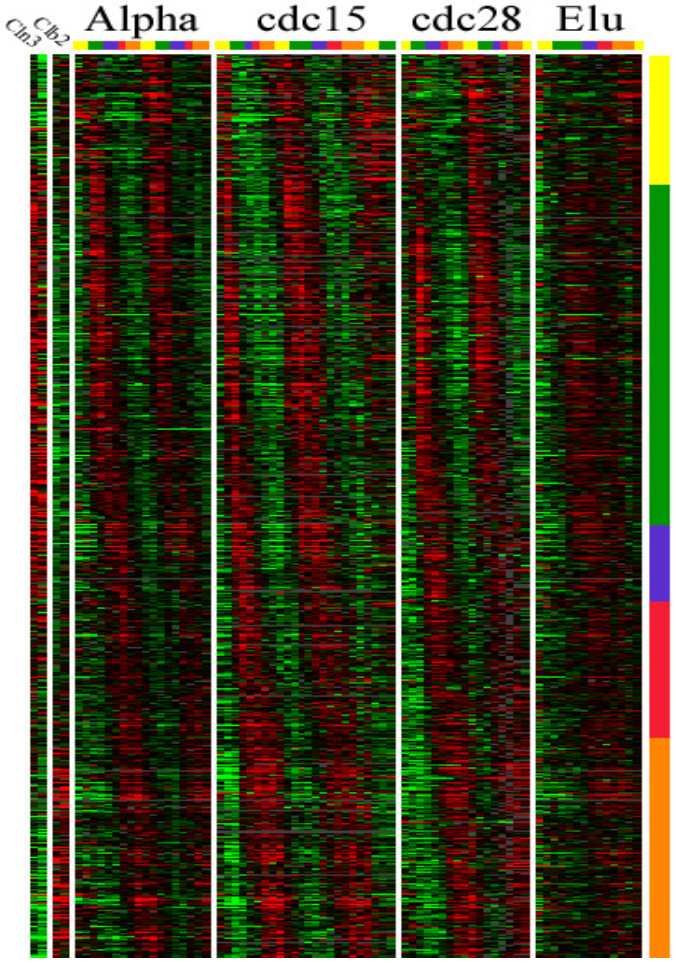




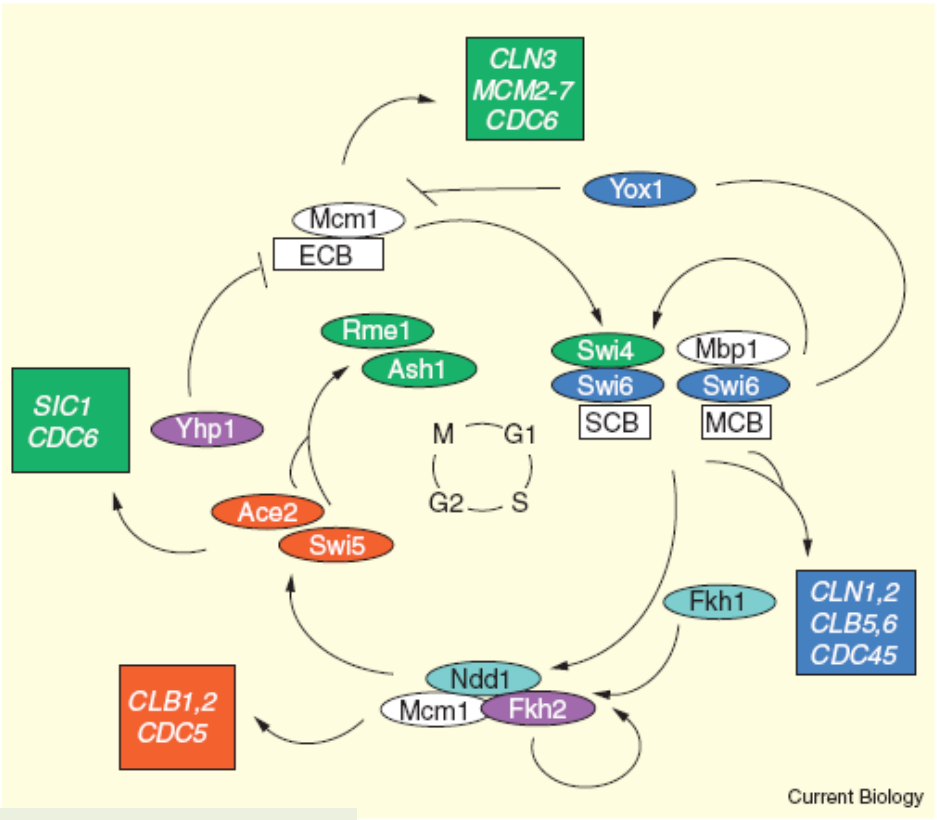
- **Cyclins, TF, inhibitors**
- **DNA replication checkpoint and spindle checkpoint**

Budding yeast cell-cycle

800 Genes involved in Budding Yeast Cell Cycle



Spellman, et al. (1998)



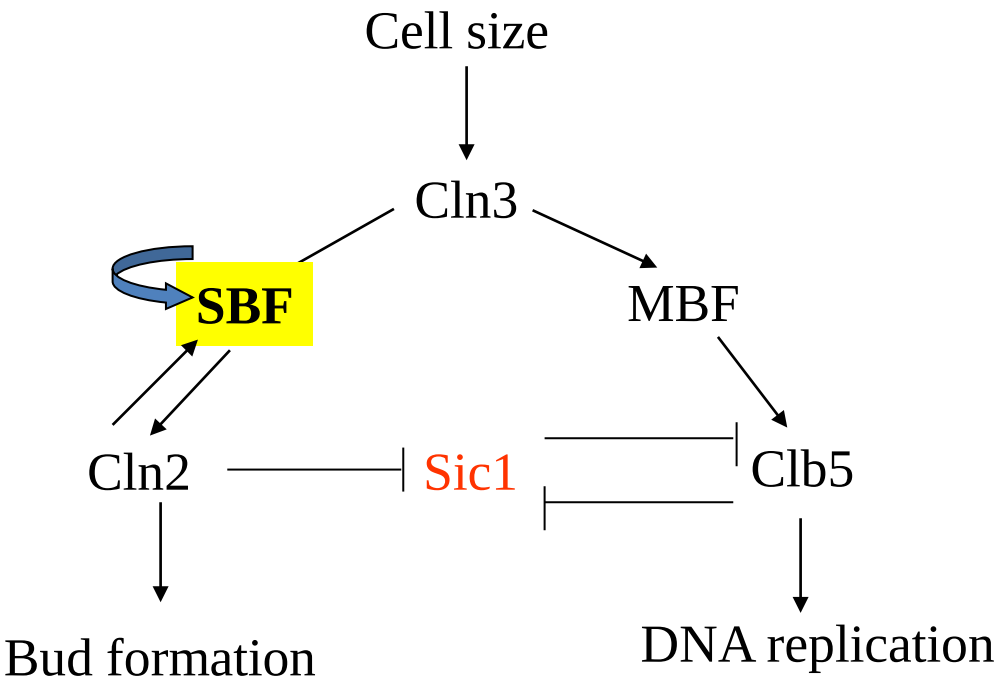
Spindle Checkpoints

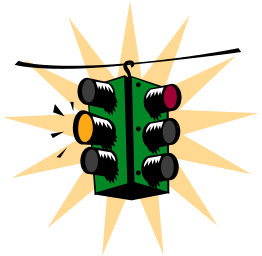
Current Biology, Vol. 13, R31–R38,

DNA Che

- **A vital process that is highly conserved in eukaryotes**

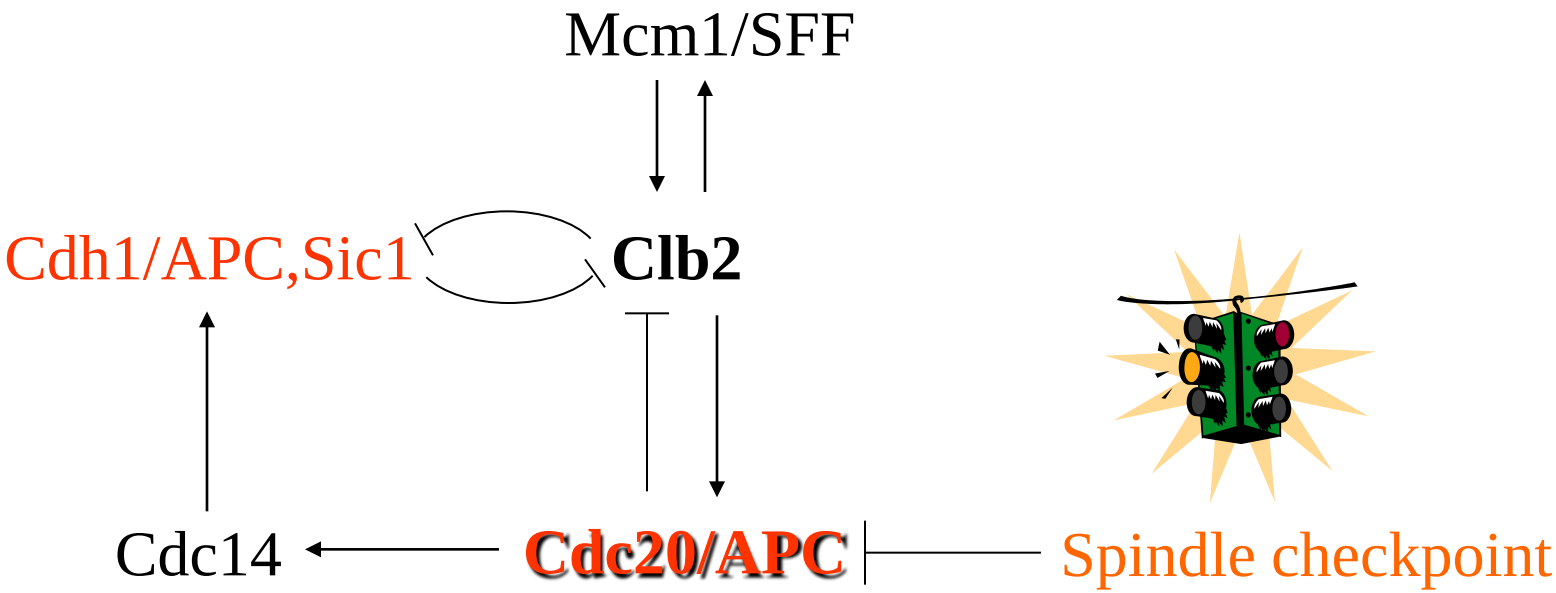
The START point and DNA replication checkpoint

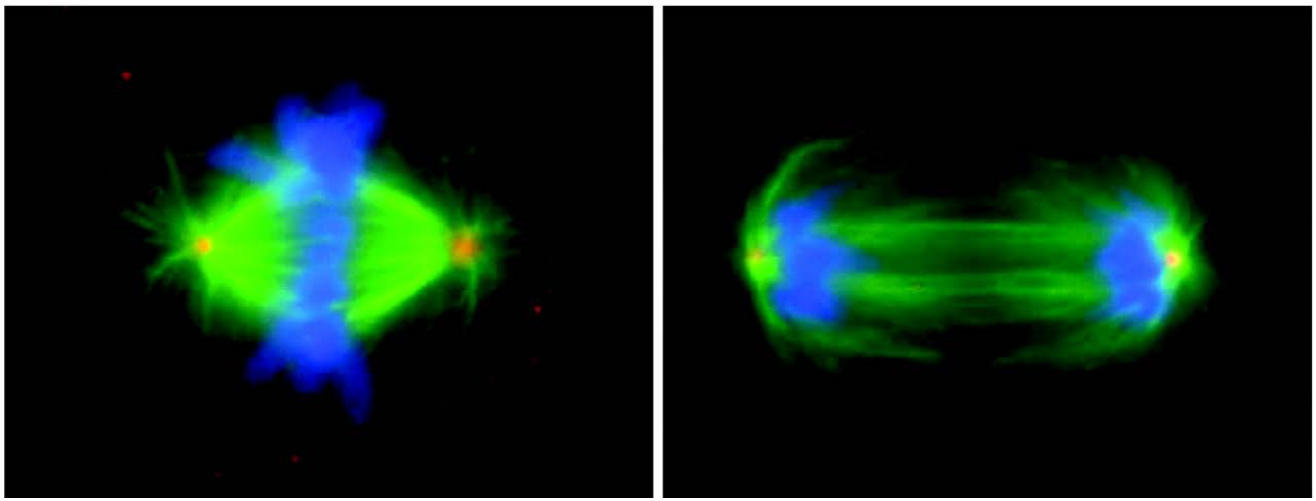




DNA replication checkpoint

G2/M transition and Mitosis





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.

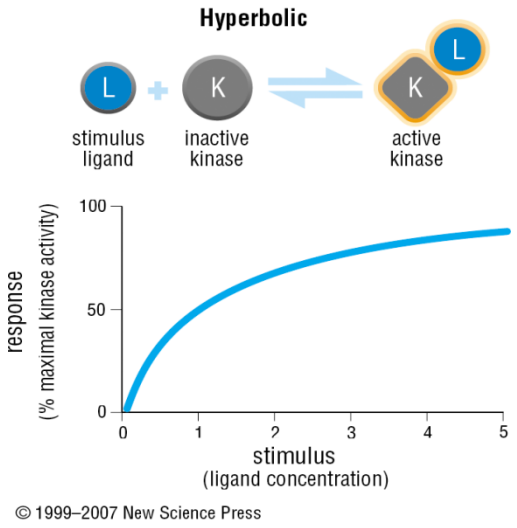
The Cell Cycle: Principles of Control

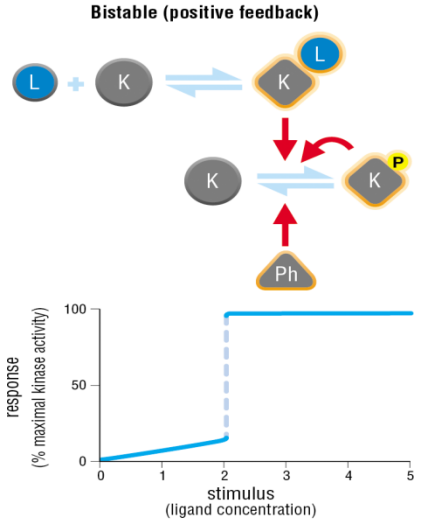
D. O. Morgan 2007

The cell-cycle control system generates robust, switch-like and adaptable changes in Cdk activity

Robust, noise, switch, bistablility, bifurcations, positive or negative feedbacks…

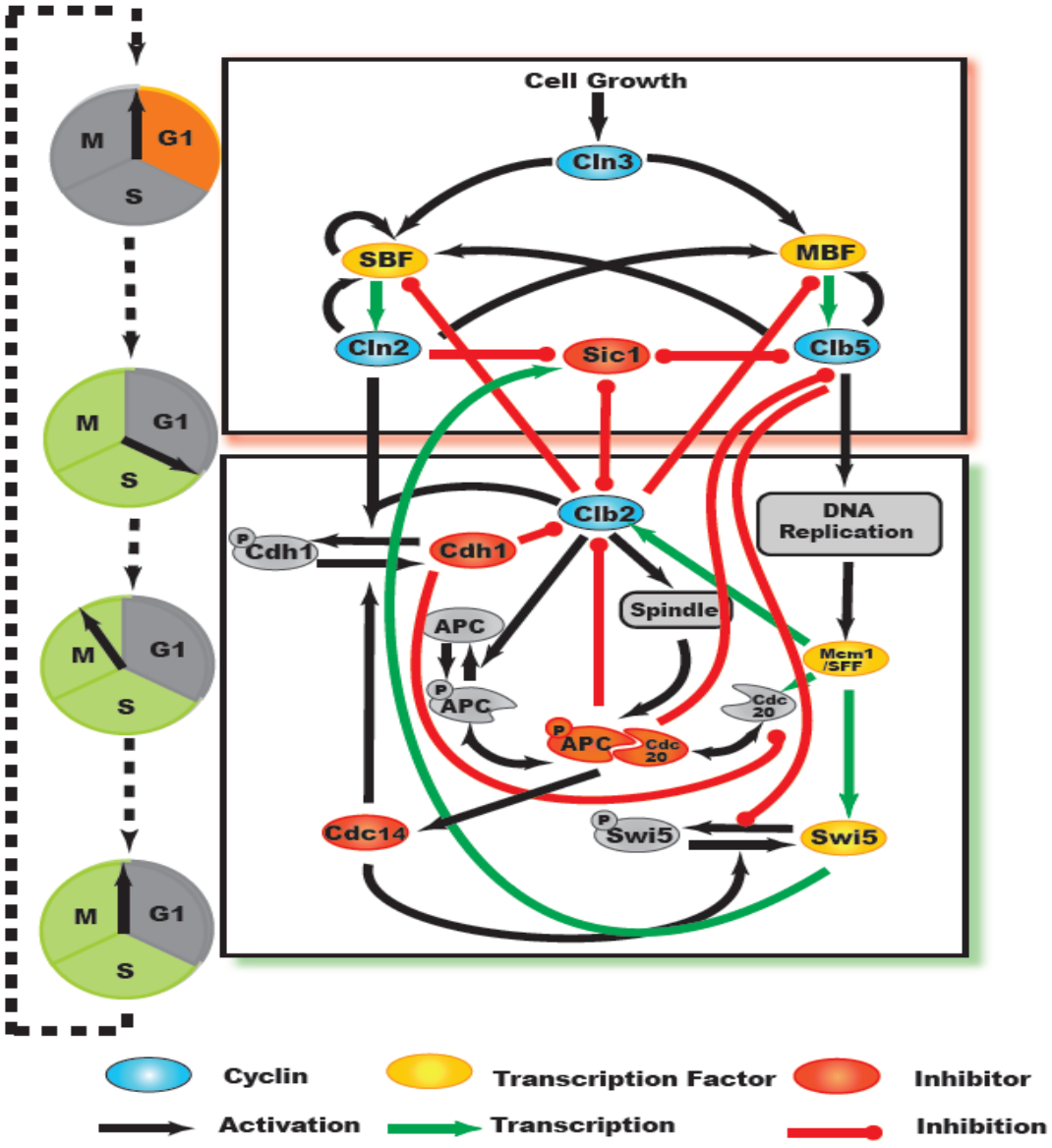
From **The Cell Cycle: Principles of Control**
by David O Morgan



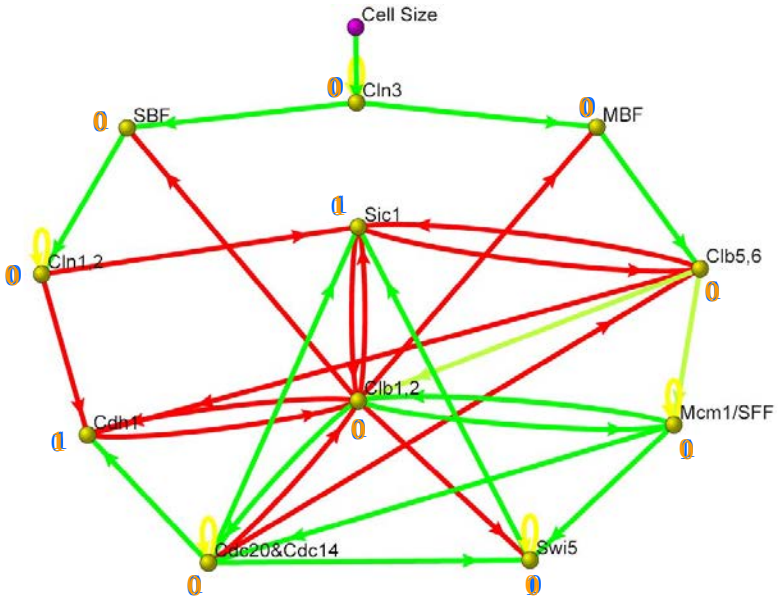


Fluctuations and noise inside and outside of CELL

The network of yeast cell cycle

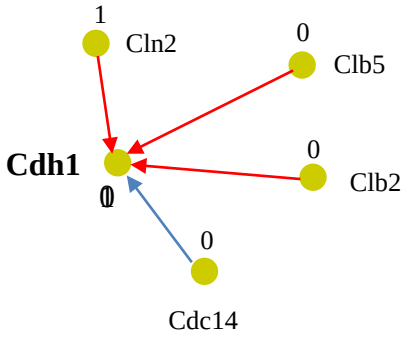


A Simple Boolean Model



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 Yeast 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

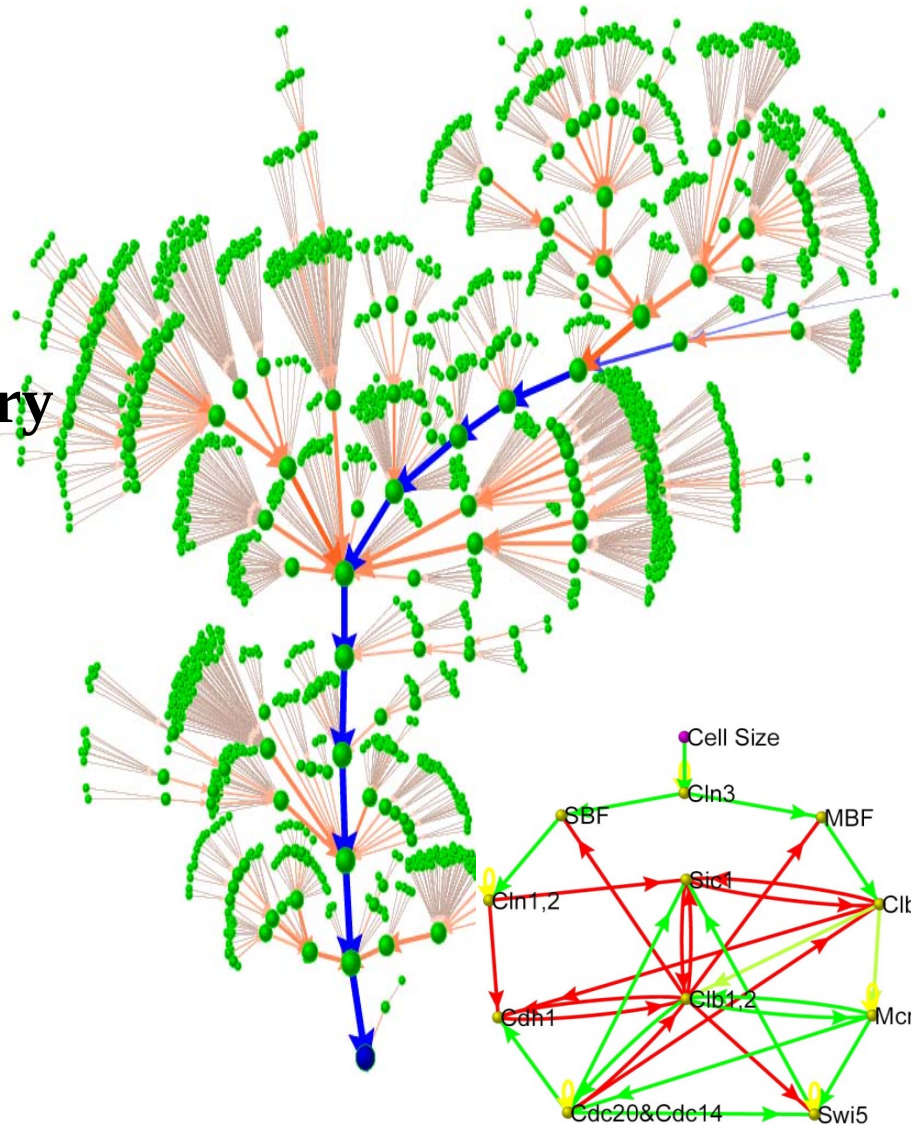
1764 of 2048 initial states (86%) evolve to G1 states. Making the **G1 state the only global attractor**.

The yeast cell-cycle network is robustly designed

PNAS 2004 101: 4781-4786

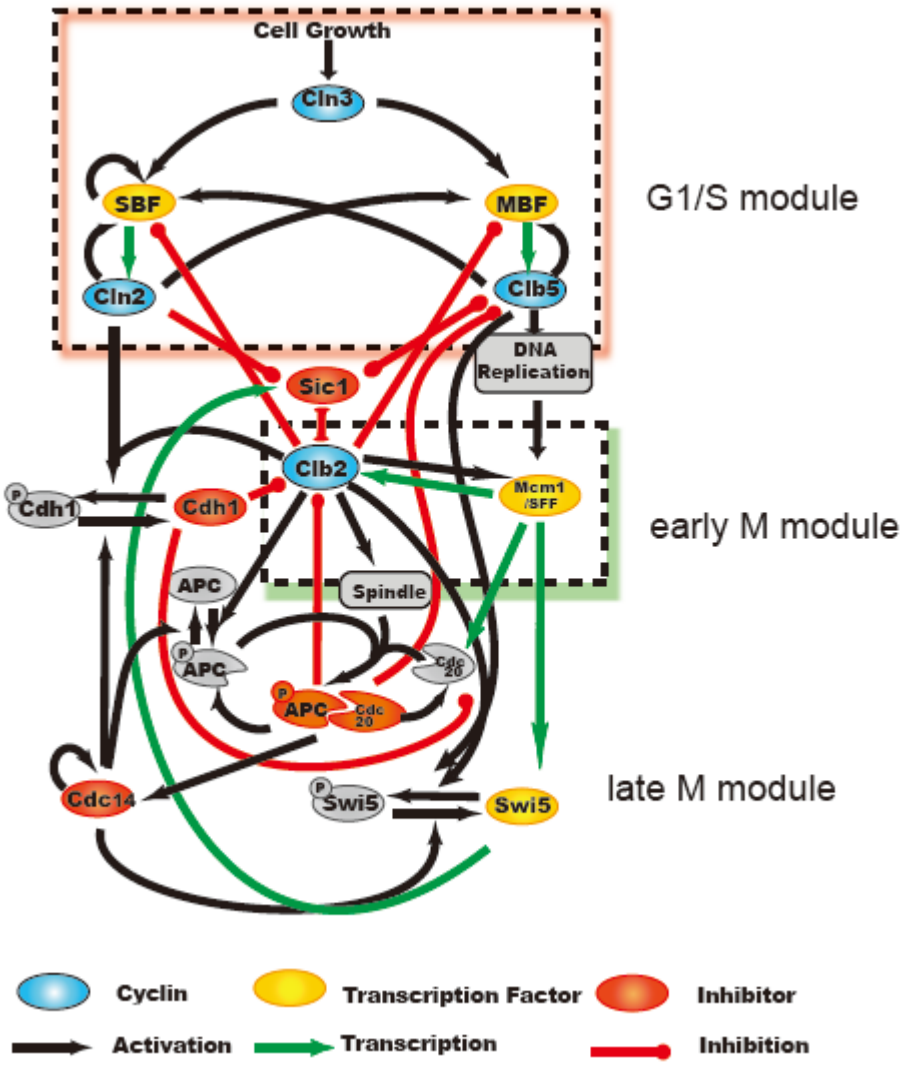
Dynamical Robustness

- ✓ **Global attractor**
- ✓ **Globally attracting trajectory**



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

The network of yeast cell cycle



Our ODE model…22 independent variables, 88 parameters

The 1st part, the equations governing cyclin-dependent kinases:

$$\frac{d[Cln3]}{dt} = -k_{d,n3}[Cln3],$$

$$\frac{d[Cln2]}{dt} = k'_{s,n2} + k''_{s,n2}[SBF] - k_{d,n2}[Cln2],$$

$$\frac{d[Clb5]_T}{dt} = k'_{s,b5} + k''_{s,b5}[MBF] - V_{d,b5}[Clb5]_T,\ V_{d,b5} = k'_{d,b5} + k''_{d,b5}[Cdc20],$$

$$\frac{d[Clb2]_T}{dt} = k'_{s,b2} + k''_{s,b2}[Mcm1] - V_{d,b2}[Clb2]_T,$$

$$V_{d,b2} = k_{d,b2} + k'_{d,b2}([Cdh1]_T - [Cdh1]) + k''_{d,b2}[Cdh1] + k''_{d,b2}[Cdc20],$$

$$[Clb5]_T = [Clb5] + [Clb5/Sic1] + [Clb5/Sic1\_P],$$

$$[Clb2]_T = [Clb2] + [Clb2/Sic1] + [Clb2/Sic1\_P],$$

$$[Sic1]_T = [Sic1]^T + [Sic1\_P]^T,$$

$$[Sic1]^T = [Sic1] + [Clb5/Sic1] + [Clb2/Sic1],$$

$$[Sic1\_P]^T = [Sic1\_P] + [Clb5/Sic1\_P] + [Clb2/Sic1\_P].$$

The 2nd part, the equations governing the inhibitors of cyclin-dependent kinases:

$$\frac{d[Sic1]^T}{dt} = k'_{s,c1} + k''_{s,c1}[Swi5] - k_{d1,c1}[Sic1]^T - V_{d2,c1}[Sic1]^T + V_{d2,c1p}[Sic1\_P]^T,$$

$$\frac{d[Sic1\_P]^T}{dt} = -k_{d1,c1p}[Sic1\_P]^T + V_{d2,c1}[Sic1]^T - V_{d2,c1p}[Sic1\_P]^T,$$

$$V_{d2,c1} = k_{d2,c1}(\varepsilon_{c1,n3}[Cln3] + \varepsilon_{c1,n2}[Cln2] + \varepsilon_{c1,b5}[Clb5] + \varepsilon_{c1,b2}[Clb2]),$$

$$V_{d2,c1p} = k_{a,c1,c14}[Cdc14]),\quad k_{d1,c1p} > k_{d1,c1},$$

$$\frac{d[Clb5/Sic1]}{dt} = k_{as,b5}[Clb5]\cdot[Sic1] - (k_{di,b5} + V_{d,b5} + k_{d1,c1} + V_{d2,c1})\cdot[Clb5/Sic1] + V_{d2,c1p}[Clb5/Sic1\_P],$$

$$\frac{d[Clb5/Sic1\_P]}{dt} = k_{as,b5}[Clb5]\cdot[Sic1\_P] - (k_{di,b5} + V_{d,b5} + k_{d1,c1p} + V_{d2,c1p})\cdot[Clb5/Sic1\_P] + V_{d2,c1}[Clb5/Sic1$$

$$\frac{d[Clb2/Sic1]}{dt} = k_{as,b5}[Clb2]\cdot[Sic1] - (k_{di,b2} + V_{d,b2} + k_{d1,c1} + V_{d2,c1})\cdot[Clb2/Sic1] + V_{d2,c1p}[Clb2/Sic1\_P],$$

$$\frac{d[Clb2/Sic1\_P]}{dt} = k_{as,b5}[Clb2]\cdot[Sic1\_P] - (k_{di,b2} + V_{d,b2} + k_{d1,c1p} + V_{d2,c1p})\cdot[Clb2/Sic1\_P] + V_{d2,c1}[Clb2/Sic1$$

$$\frac{d[Cdh1]}{dt} = (k'_{a,h1} + k''_{a,h1}[Cdc14])\cdot([Cdh1]_T - [Cdh1]) - V_{i,h1}[Cdh1],\qquad [Cdh1]_T = 1,$$

$$V_{i,h1} = k'_{i,h1} + k''_{i,h1}(\varepsilon_{i,h1,n3}[Cln3] + \varepsilon_{i,h1,n2}[Cln2] + \varepsilon_{i,h1,b5}[Clb5] + \varepsilon_{i,h1,b2}[Clb2]),$$

$$\frac{d[Cdc20]_T}{dt} = k'_{s,20} + k''_{s,20}[Mcm1] - (k_{d,20} + k'_{d,20}[Cdh1])\cdot[Cdc20]_T,$$

$$\frac{d[Cdc20]}{dt} = k_{a,20}[APC\_P]\cdot([Cdc20]_T - [Cdc20])\cdot[SP] - (k_{i,20} + k_{d,20} + k'_{d,20}[Cdh1])\cdot[Cdc20],$$

Equations governing transcription factors:

$$\frac{d[SBF]}{dt} = \frac{V_{a,sbf}\cdot([SBF]_T - [SBF])}{J_{a,sbf} + ([SBF]_T - [SBF])} - \frac{(k'_{i,sbf} + k''_{i,sbf}[Clb2])\cdot[SBF]}{J_{i,sbf} + [SBF]},$$

$$V_{a,sbf} = k_{a,sbf}(\varepsilon_{sbf,sbf}[SBF] + \varepsilon_{sbf,n2}[Cln2] + \varepsilon_{sbf,n3}[Cln3] + \varepsilon_{sbf,b5}[Clb5]),$$

$$\frac{d[MBF]}{dt} = \frac{V_{a,mbf}\cdot([MBF]_T - [MBF])}{J_{a,sbf} + ([MBF]_T - [MBF])} - \frac{(k'_{i,sbf} + k''_{i,sbf}[Clb2])\cdot[MBF]}{J_{i,sbf} + [MBF]},$$

$$V_{a,mbf} = k_{a,sbf}(\varepsilon_{sbf,n2}[Cln2] + \varepsilon_{sbf,n3}[Cln3] + \varepsilon_{sbf,b5}[Clb5]),$$

$$[SBF]_T = [MBF]_T = 1,$$

$$\frac{d[Mcm1]}{dt} = \frac{k_{a,mcm}([Clb2] + \varepsilon_{mcm,DNA}[DNA])\cdot([Mcm1]_T - [Mcm1])}{J_{a,mcm} + ([Mcm1]_T - [Mcm1])} - \frac{k_{i,mcm}\cdot[Mcm1]}{J_{i,mcm} + [Mcm1]},$$

$$[Mcm1]_T = 1,$$

$$\frac{d[Swi5]}{dt} = k'_{s,swi} + k''_{s,swi}[Mcm1] + (k'_{a,swi} + k''_{a,swi}[Cdc14])\cdot[Swi5\_P] - (k'_{d,swi} + k'_{i,swi}[Clb5] + k''_{i,swi}[Clb2])\cdot[Swi5],$$

$$\frac{d[Swi5\_P]}{dt} = (k'_{i,swi}[Clb5] + k''_{i,swi}[Clb2])\cdot[Swi5] - (k''_{d,swi} + k'_{a,swi} + k''_{a,swi}[Cdc14])\cdot[Swi5\_P],$$

Others:

$$\frac{d[DNA]}{dt} = \frac{k_{s,DNA}[Clb5]^{n_{DNA}}}{J^{n_{DNA}}_{a,DNA} + [Clb5]^{n_{DNA}}} - k_{d,DNA}[DNA],$$

$$\frac{d[SP]}{dt} = \frac{k_{s,SP}[Clb2]^{n_{SP}}}{J^{n_{SP}}_{a,SP} + [Clb2]^{n_{SP}}} - k_{d,SP}[SP],$$

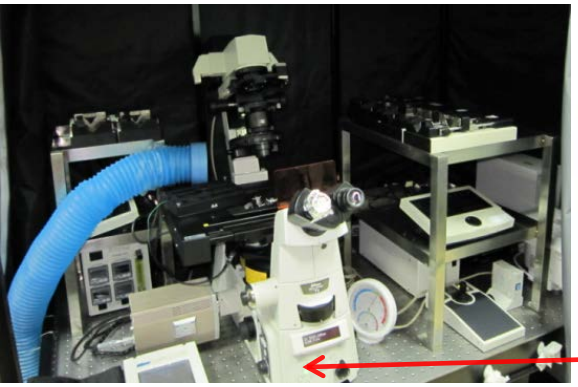
$$\frac{d[APC\_P]}{dt} = (k'_{a,apc} + k''_{a,apc}[Clb2])\cdot[APC] - k_{a,20}[APC\_P]\cdot([Cdc20]_T - [Cdc20])\cdot[SP]$$
$$+ (k_{i,20} + k_{d,20} + k'_{d,20}[Cdh1])\cdot[Cdc20] - k_{i,apc}[APC\_P],$$

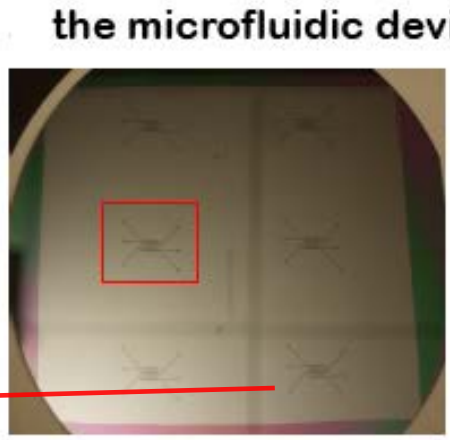
$$[APC]_T = [APC] + [APC\_P] = \text{constant} = 1,$$

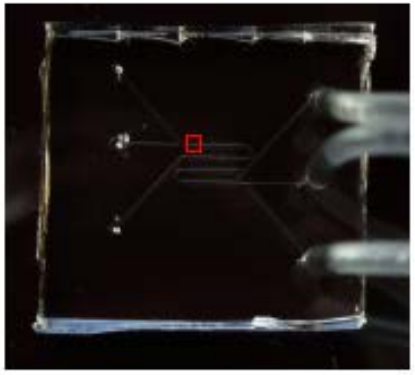
$$\frac{d[Cdc14]}{dt} = k_{a,14} + \frac{k'_{a,14}[Cdc20]^{n_{14}}}{J^{n_{14}}_{a,14} + [Cdc20]^{n_{14}}} - k_{d,14}[Cdc14].$$

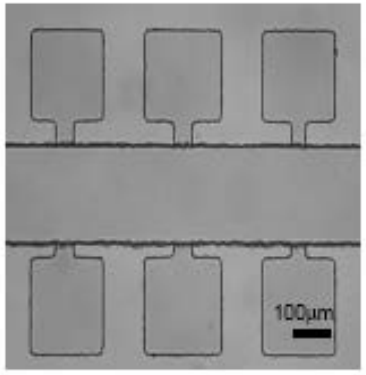
Observing a yeast cell

Automatic scanning microscope system with microfluidic device





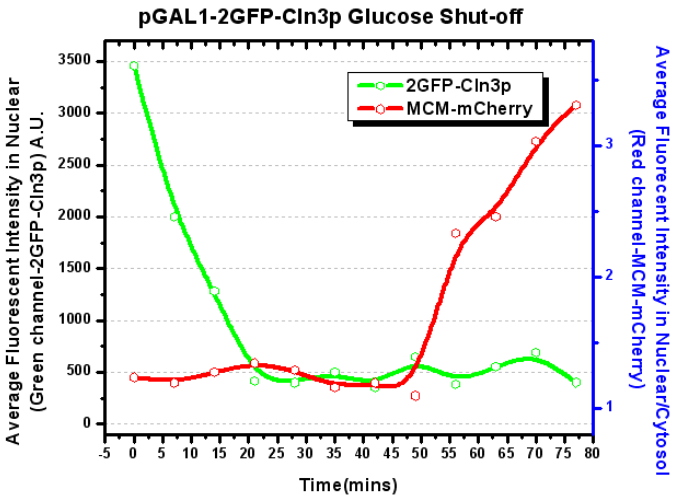


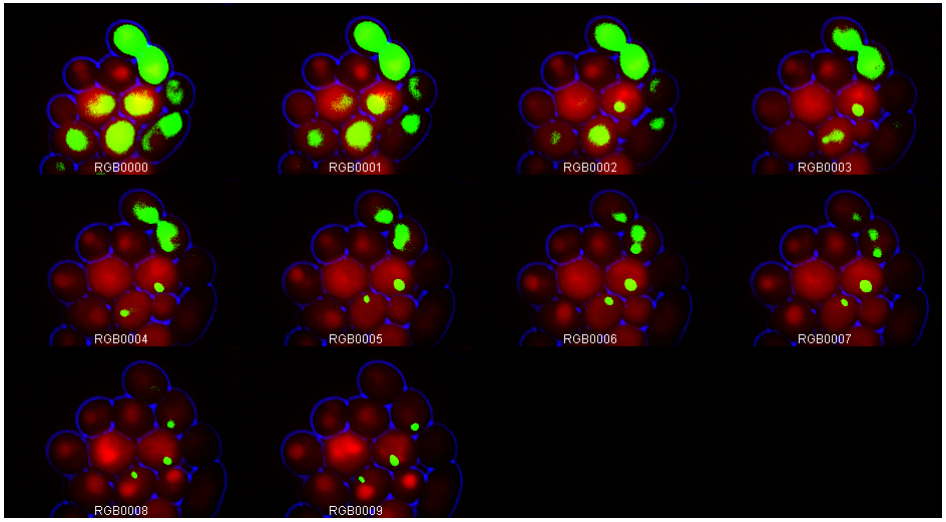


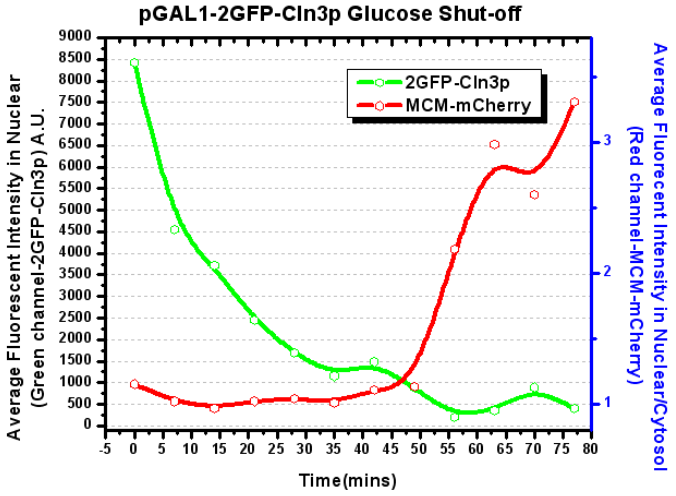
- Construct the fluorescent protein reporter for the key regulators in cell cycle
- Observing the key regulator level in each yeast cell
- Comparing with the theoretical model

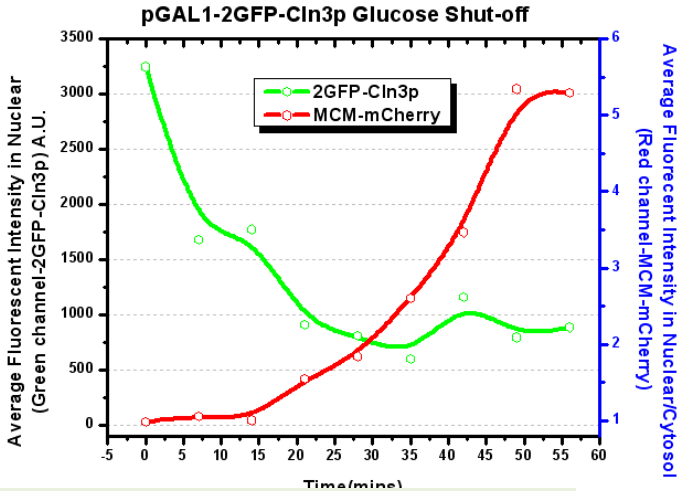
The kinetics of G1/S transition (with an GFP tagged Cln3p as the signal and S phase markers.) -----*MAT a cln3::LEU2 bck2::NAT pGAL1-2GFP-CLN3 pADH1-MCM-mCherry* S288c background

- **Glucose shut-off**









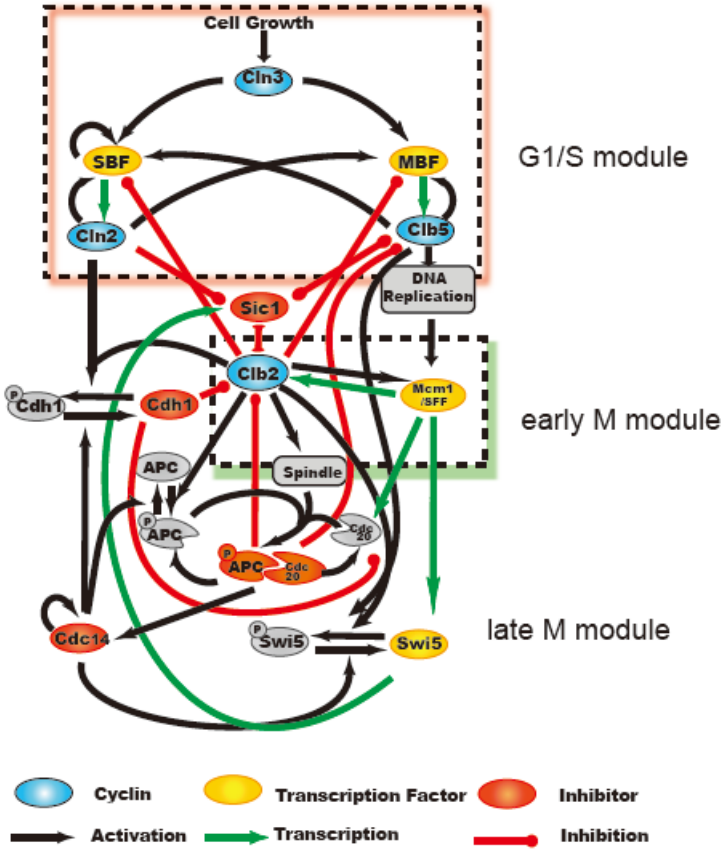
Yang et. al. PLoS Biol. (2012) 11: e1001673

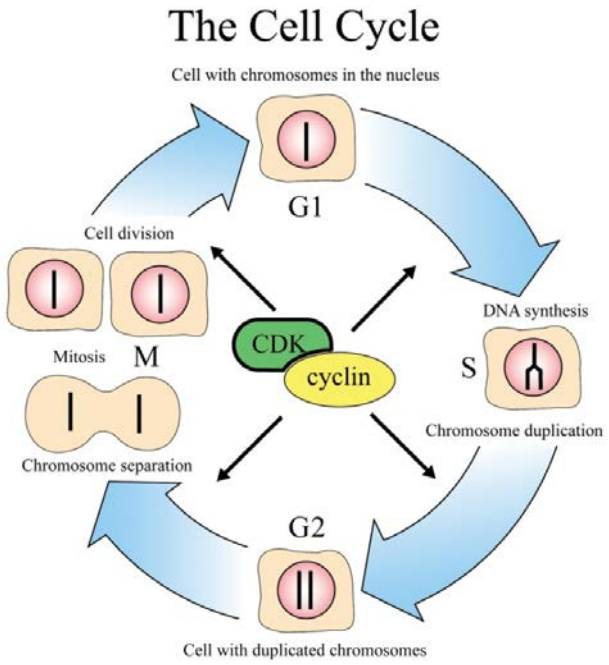
- **Quantitative biology in yeast cell cycle**

  The cell-cycle in budding yeast , modeling and quantitative experiment
- **3-node yeast cell cycle model**

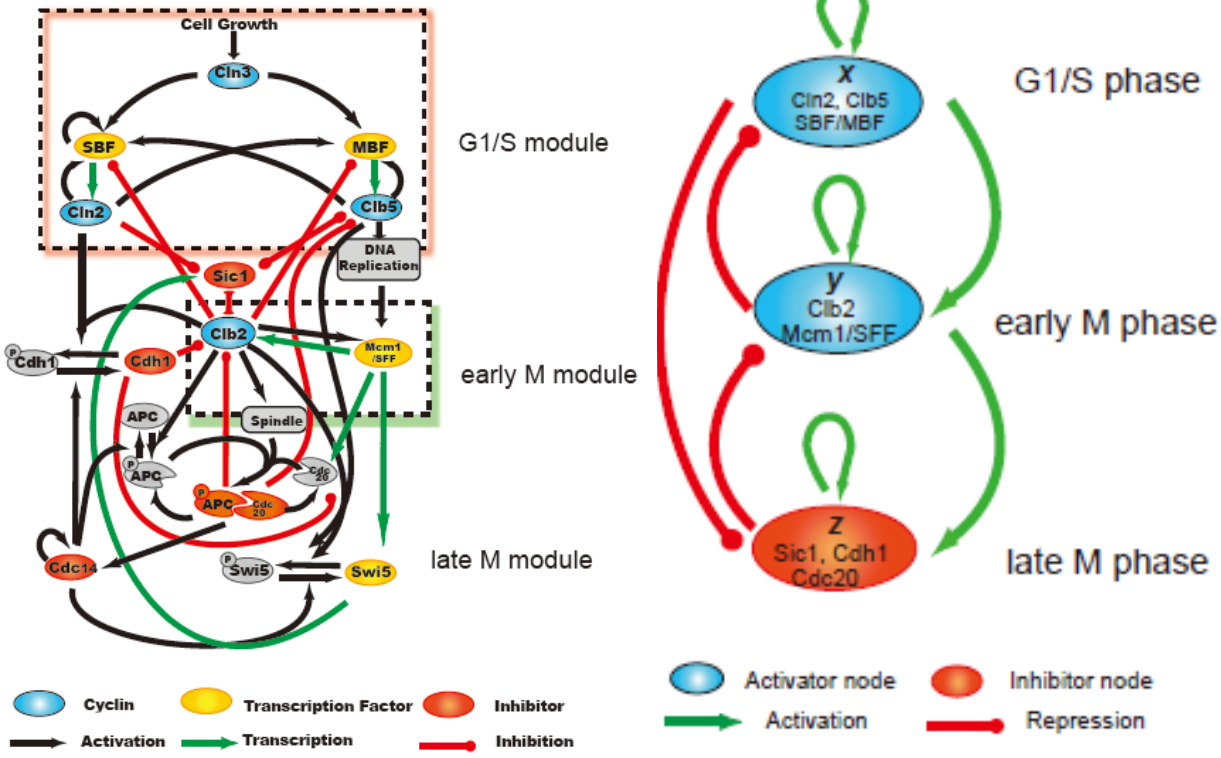
  Feedbacks, checkpoints, a globally attractive trajectory…
- **How to ensure the stability of a multi-task process?**

Abstract architecture and functions coarse-graining view of cell cycle





3-node yeast cell cycle network



- **The multi-task process:**
  DNA replication and mitosis, X (S phase) → Y (M phase)
- **Robustness, stability, and modularity**

1. Genetic switches controlled saddle-node bifurcations
2. Sensitive parameters are related to feedbacks loops

3-node yeast cell cycle model

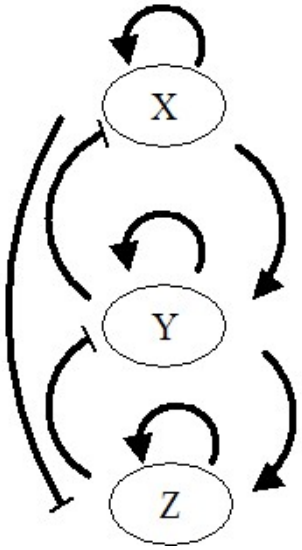
- assumptions, variables, parameters

- Assumptions and equations

$$\frac{dX}{dt} = \frac{K_1 \cdot X^2}{J_1^2 + X^2} - X - K_3 \cdot X \cdot Y,$$

$$\frac{dY}{dt} = K_4 \cdot X + \frac{K_5 \cdot Y^2}{J_2^2 + Y^2} - K_6 \cdot Y - K_7 \cdot Y \cdot Z,$$

$$\frac{dZ}{dt} = K_8 \cdot Y - K_9 \cdot Z - K_{10} \cdot X \cdot Z + \frac{K_{11} \cdot Z^2}{J_3^2 + Z^2},$$



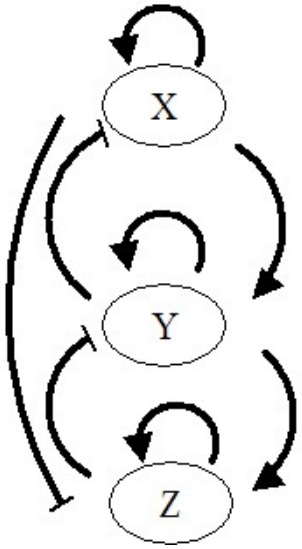
variables	X	Y	Z
modules	G1/S	G2/early M	late M
Key proteins	Cln2, Clb5, SBF/MBF	Clb2, Mcm1	Sic1, Cdh1, Cdc20

3-node yeast cell cycle model

$$\frac{dx}{dt} = \frac{x^2}{j_1^2 + x^2} - k_1 \cdot x - x \cdot y,$$

$$\frac{dy}{dt} = k_{a1} \cdot x + \frac{y^2}{j_2^2 + y^2} - k_2 \cdot y - y \cdot z,$$

$$\frac{dz}{dt} = k_{a2} \cdot y + \frac{k_s \cdot z^2}{j_3^2 + z^2} - k_3 \cdot z - k_i \cdot z \cdot x,$$



$$k_1 = K_2 T = \frac{K_2}{\sqrt{K_3 K_5}} \qquad k_2 = K_6 T = \frac{K_6}{\sqrt{K_3 K_5}} \qquad k_3 = K_9 T = \frac{K_9}{\sqrt{K_3 K_5}}$$

$$j_1 = \frac{J_1}{X_0} \qquad j_2 = \frac{J_2}{Y_0} \qquad j_3 = \frac{J_3}{Z_0}$$

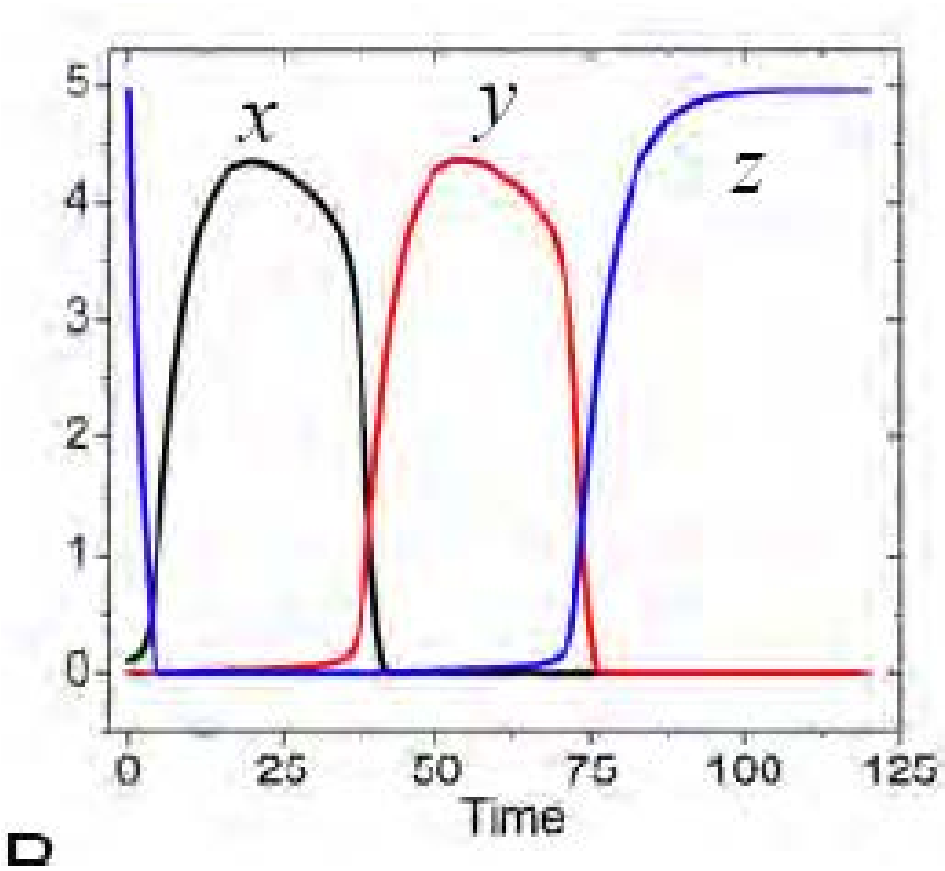
$$k_{a1} = \frac{K_1 K_4}{K_5} \frac{1}{\sqrt{K_3 K_5}} \qquad k_{a2} = \frac{K_8 K_7}{K_3} \frac{1}{\sqrt{K_3 K_5}}$$

$$k_i = \frac{K_1 K_{10}}{K_3 K_5} \qquad k_s = \frac{K_7 K_{11}}{K_3 K_5}$$

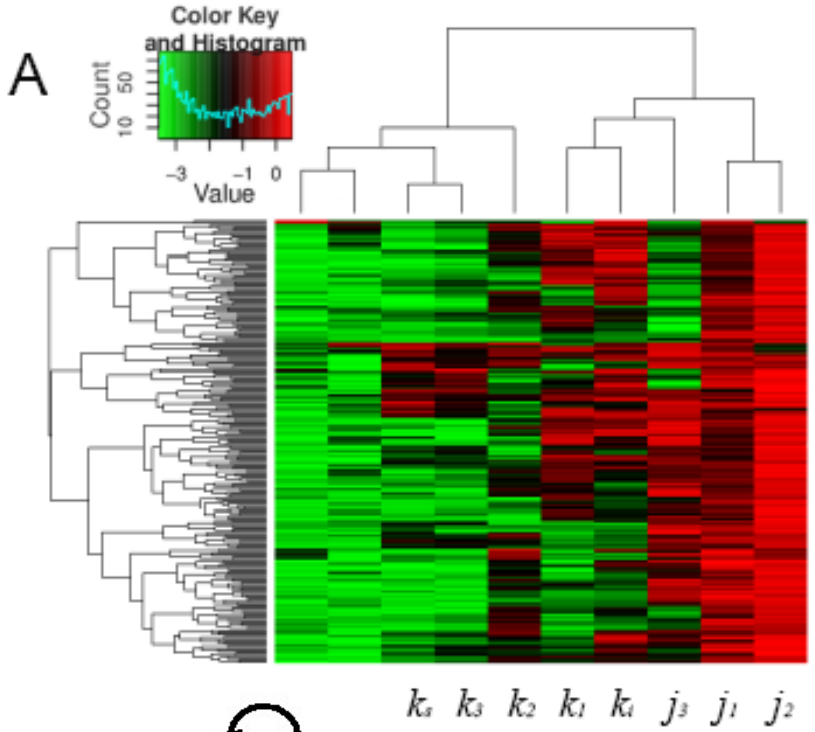
j1 and k1: activation of x;
j2 and k2: activation of y;
J3, k3, ks: activation of x;
ka1: x→ y;
ka2: y→ z;
ki: x--| z

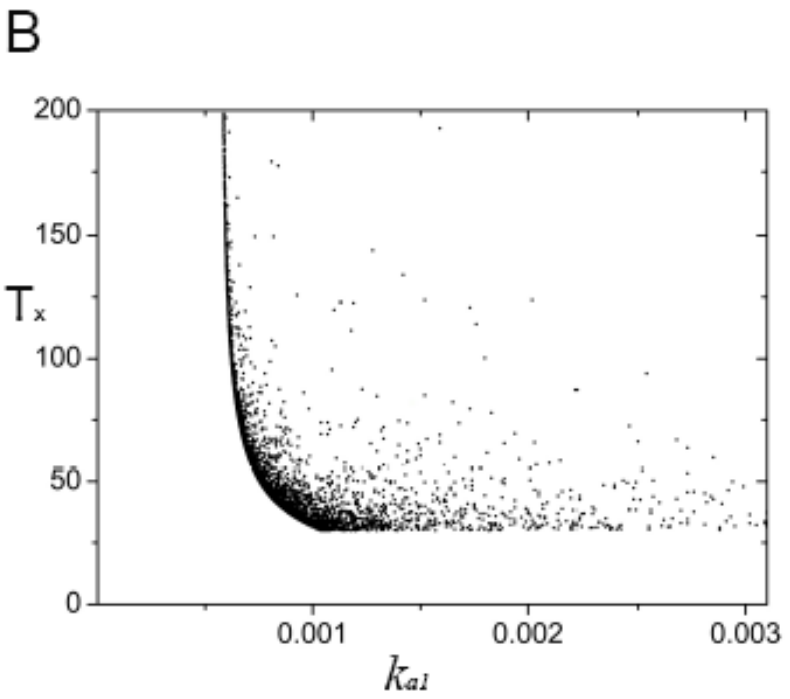
How to select the ‘prefect’ parameters for the yeast cell-cycle?

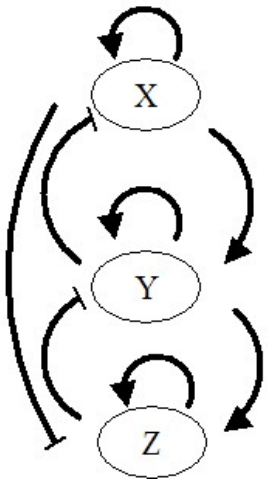
- Events order (DNA replication, mitosis);
- Duration for x wave (DNA replication in S phase) → y wave (mitosis in M phase)



The duration of G1/S and early M phases is controlled the activation rates k_{a1} and k_{a2}.







$\leftarrow k_{a1}x$

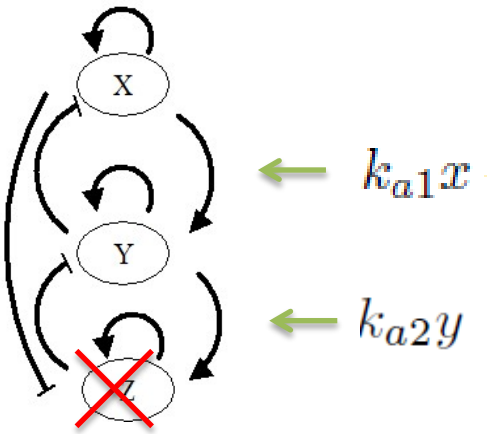
$\leftarrow k_{a2}y$

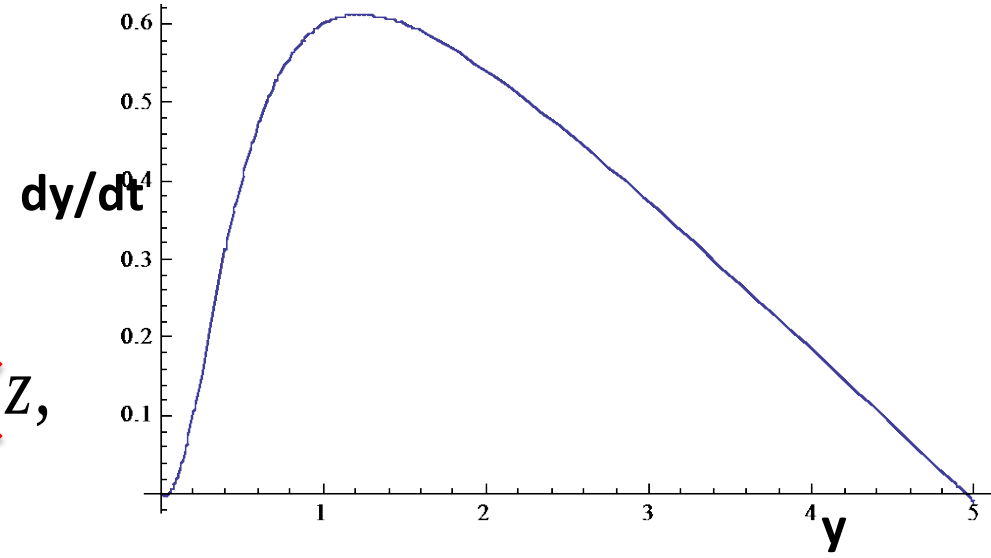
$$T_x = \frac{\pi}{\sqrt{c(k_{a1} - k_{a1}^c)x^{(3)}}}.$$

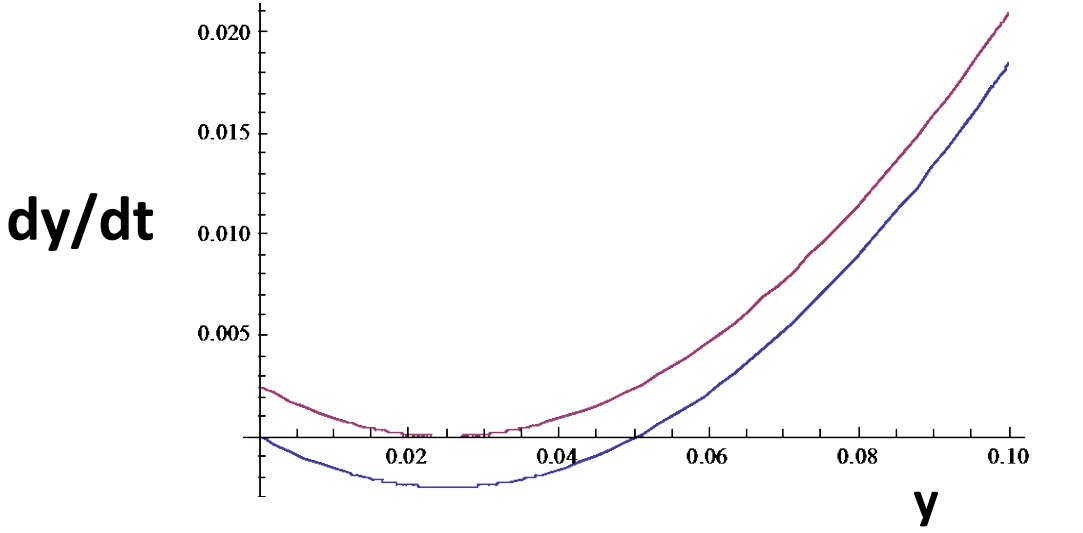
How does the activated x wave triggers the y wave?

$$\frac{dx}{dt} = \frac{x^2}{j_1^2 + x^2} - k_1 \cdot x - x \cdot y,$$

$$\frac{dy}{dt} = k_{a1} \cdot x + \frac{y^2}{j_2^2 + y^2} - k_2 \cdot y - y \cdot z,$$







Near the bifurcation:
Ghost effects and Bottlenecks

$$\dot{x} = r + x^2$$

where r is proportional to the distance from the bifurcation, and $0 < r << 1$. The graph of $\dot{x}$ is shown in Figure 4.3.7.

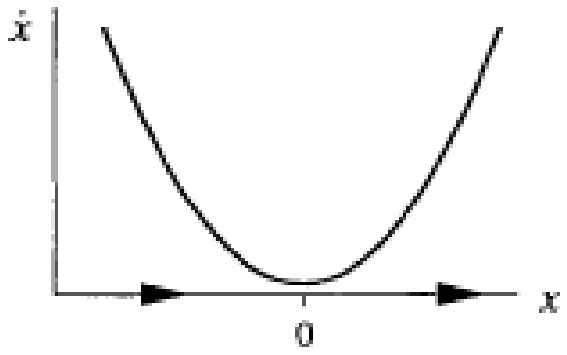
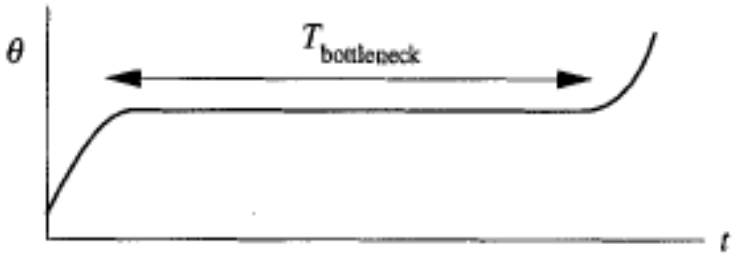


Figure 4.3.7

To estimate the time spent in the bottleneck, we calculate the time taken for x to go from $-\infty$ (all the way on one side of the other side). The result is



$$T_{\text{bottleneck}} \approx \int_{-\infty}^{\infty} \frac{dx}{r + x^2} = \frac{\pi}{\sqrt{r}},$$

Steven H. Strogatz. 1994. Nonlinear dynamics and chaos. p99

Duration of G1/S is controlled by strength of activation from x wave to y wave

During the late S phase and early M phase, x is almost fully activated and has repressed z to zero,

$$\frac{dx}{dt} = \frac{x^2}{j_1^2 + x^2} - k_1 x - xy = G(x, j_1, k_1) - xy,$$

$$\frac{dy}{dt} = k_{a1} x + \frac{y^2}{j_2^2 + y^2} - k_2 y = k_{a1} x + H(y, j_2, k_2).$$

$$k_{a1}^c \equiv |H(y^*)|/x^{(3)},$$

Furthermore, if $0 < (k_{a1} - k_{a1}^c) \ll 1$, then just after the bifurcation we have $x \simeq x^{(3)}$, $y \simeq y^* \simeq y^{(1)}$, and $z \simeq 0$, so

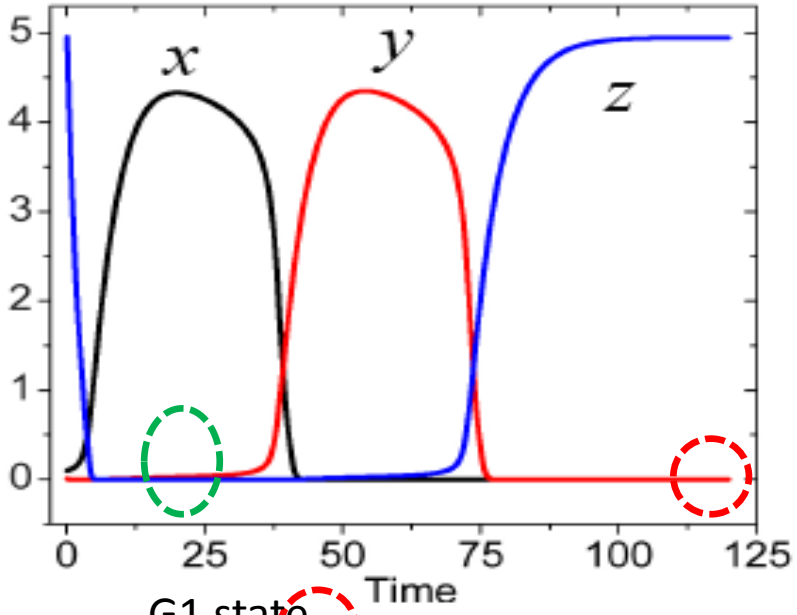
$$\frac{\mathrm{d}y}{\mathrm{d}t} = k_{a1} x + H(y, j_2, k_2) \simeq (k_{a1} - k_{a1}^c) x^{(3)} + c(y - y^{(1)})^2 \ll 1.$$

We have

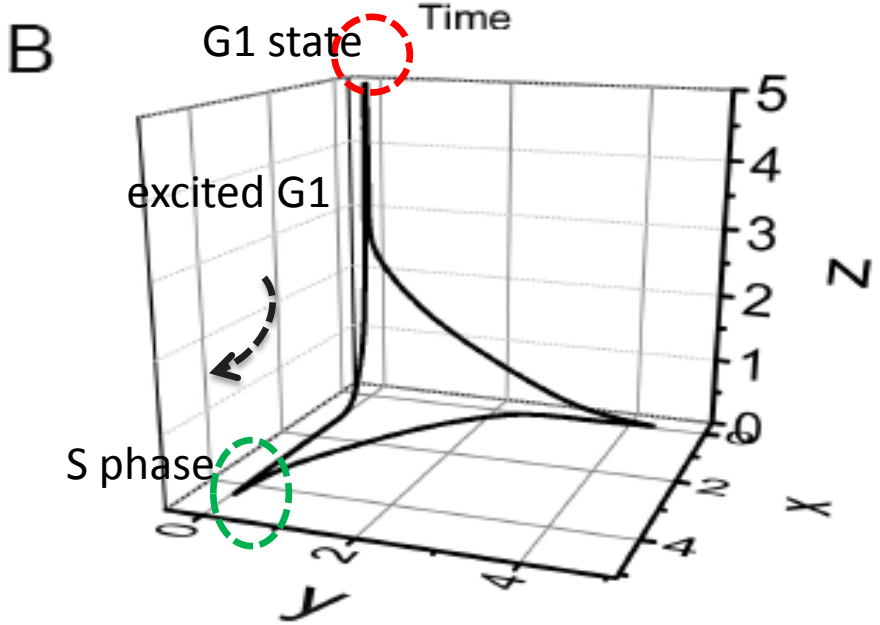
$$T_x = \int_0^\infty \frac{dy}{(k_{a1} - k_{a1}^c) x^{(3)} + c(y - y^{(1)})^2} = \frac{\pi}{\sqrt{c(k_{a1} - k_{a1}^c) x^{(3)}}}.$$

The “perfect” yeast cell-cycle trajectory

A



B

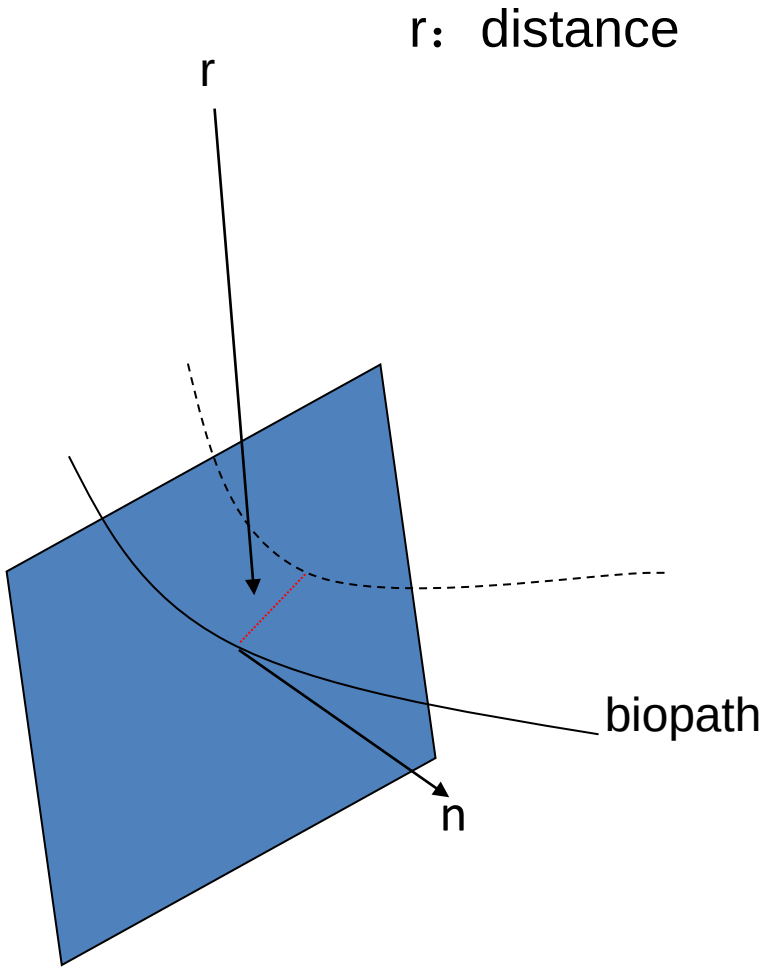


j1=0.5, j2=0.5,
k1=0.2,
k2=0.2, j3=0.5,
k3=0.2, ki=5.0,
ks=1;

Ka1= ka2=0.001

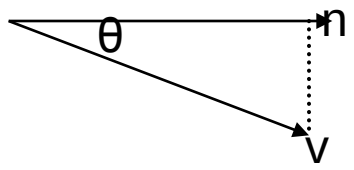
Dynamical analysis of the trajectories
1. Initial normal plane ball

- Different initial states lead to different trajectories.
- Using the bio-pathway as a standard, one direct way to examine the variation between trajectories is to measure the distance on each normal plane of bio-pathway.
- Small perturbations are added near excited G1 as a initial ball.

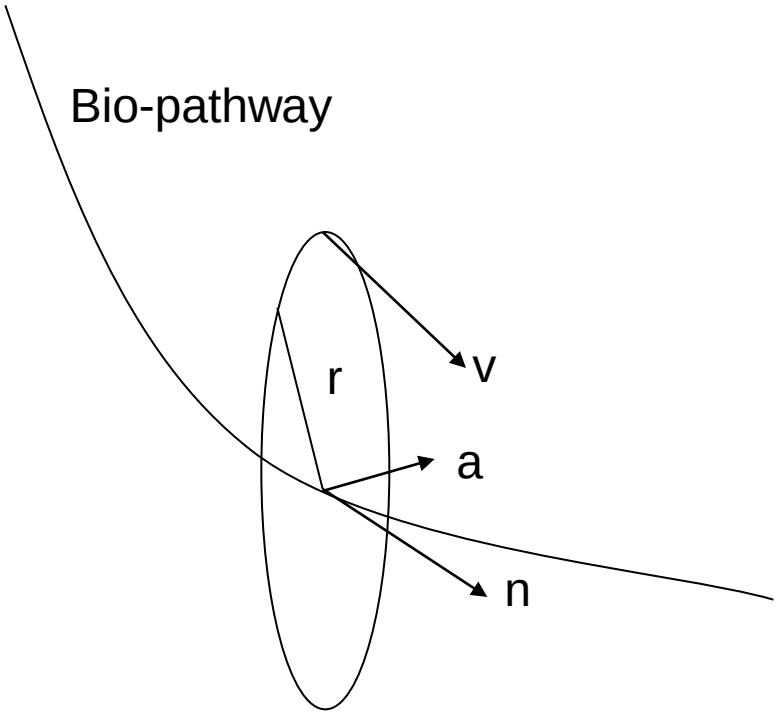


Dynamical analysis of the trajectories
2. Local manifolds

Same perturbation is added on each point of bio-pathway.



Bio-pathway



$\sin\theta$

Normalize n and v

$$v_p = \vec{v} \cdot \vec{n} = \cos\theta$$

$$v_n = \left|\vec{v} - (\vec{v} \cdot \vec{n})\vec{n}\right| = \sin\theta$$

We record 3 variables:

|v|, $\cos\theta$,

Dynamical analysis of the trajectories
3. Jacobian matrix

$$(x(t), y(t), z(t)) \xrightarrow{F=(f_1, f_2, f_3)} \vec{v} = (\dot{x}, \dot{y}, \dot{z})$$

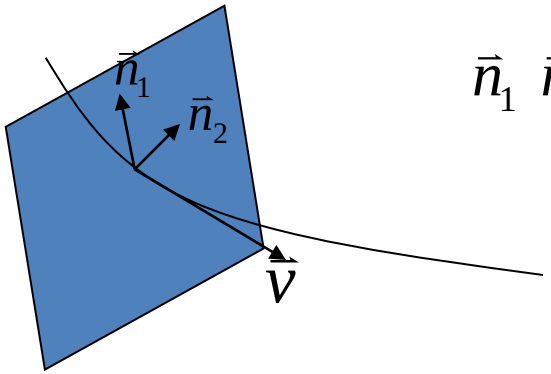
$$|J| \equiv \begin{pmatrix} \frac{\partial f_1}{\partial x} & \frac{\partial f_1}{\partial y} & \frac{\partial f_1}{\partial z} \\ \frac{\partial f_2}{\partial x} & \frac{\partial f_2}{\partial y} & \frac{\partial f_2}{\partial z} \\ \frac{\partial f_3}{\partial x} & \frac{\partial f_3}{\partial y} & \frac{\partial f_3}{\partial z} \end{pmatrix} \Rightarrow \lambda_1, \lambda_2, \lambda_3 \Downarrow \vec{r}_1, \vec{r}_2, \vec{r}_3$$

$If, \lambda_i < 0$

Then the point is stable in the direction of $\vec{r}_i$.

Vice versa.

Local Jacobian matrix

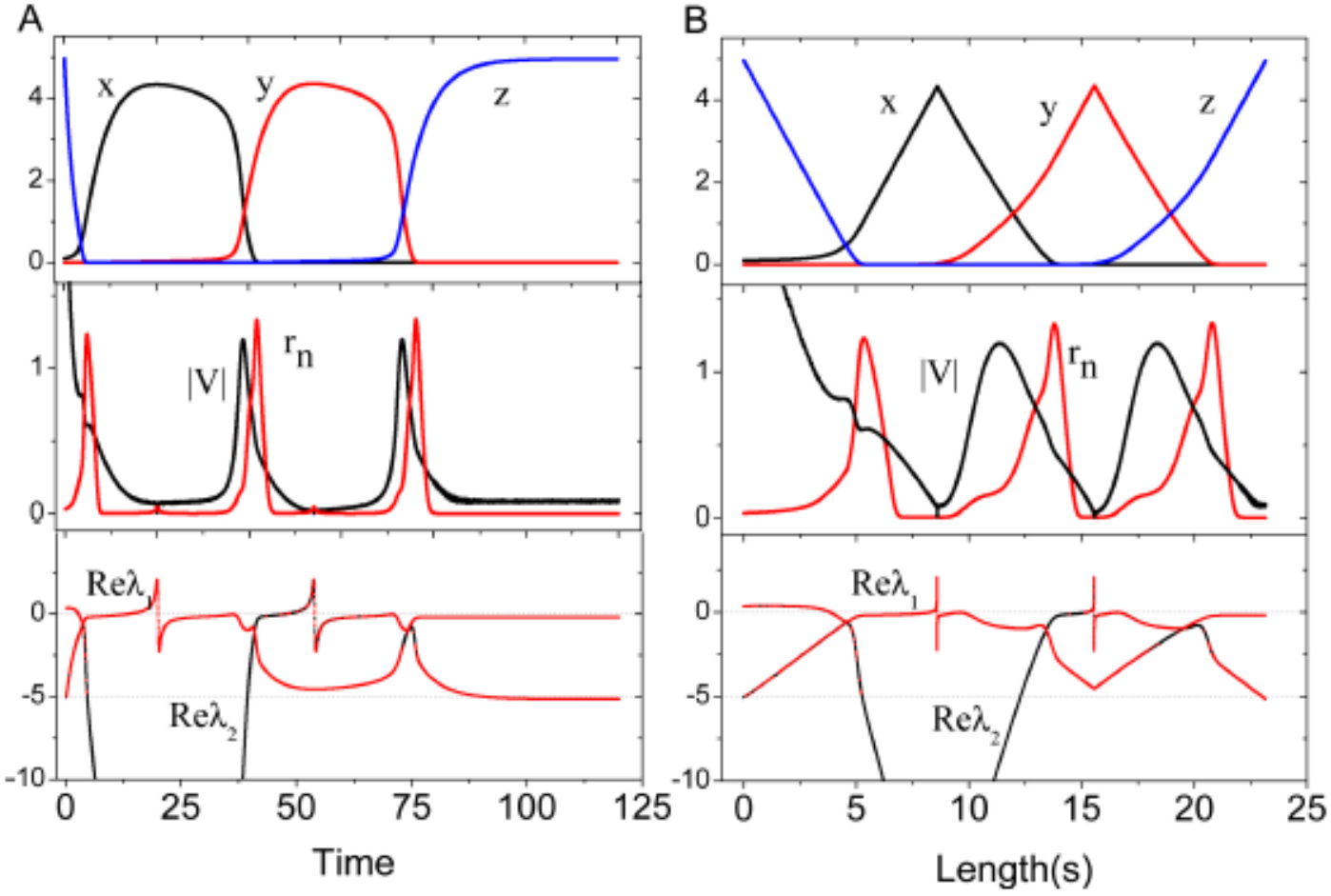


$\vec{n}_1$ $\vec{n}_2$ are a pair of normed unit vectors in normal plane.

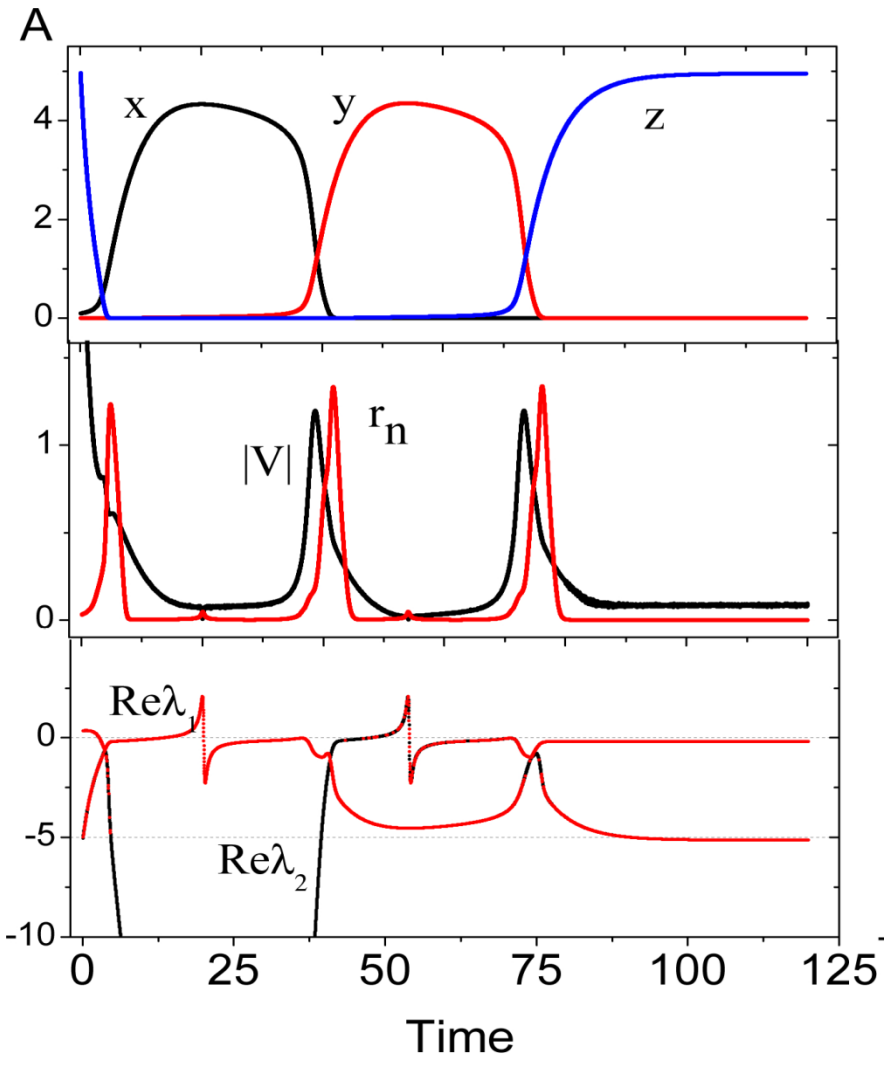
$$\underline{\underline{P}} = \begin{pmatrix} \vec{n}_1 \\ \vec{n}_2 \\ 0 \end{pmatrix}$$

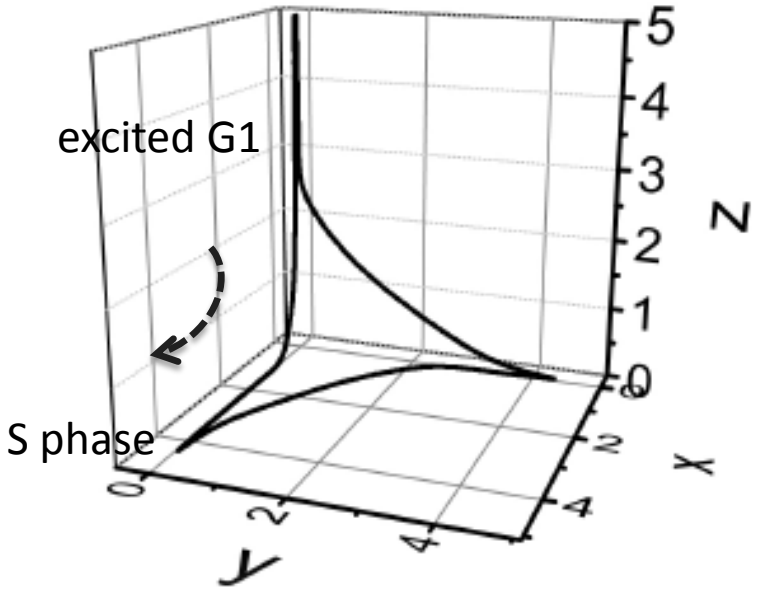
$$\begin{pmatrix} \vec{n}_1 \\ \vec{n}_2 \\ 0 \end{pmatrix} \begin{pmatrix} \frac{\partial f_1}{\partial x} & \frac{\partial f_1}{\partial y} & \frac{\partial f_1}{\partial z} \\ \frac{\partial f_2}{\partial x} & \frac{\partial f_2}{\partial y} & \frac{\partial f_2}{\partial z} \\ \frac{\partial f_3}{\partial x} & \frac{\partial f_3}{\partial y} & \frac{\partial f_3}{\partial z} \end{pmatrix} \begin{pmatrix} \vec{n}_1' & \vec{n}_2' & 0 \end{pmatrix} = \begin{pmatrix} j_{11} & j_{12} & 0 \\ j_{21} & j_{22} & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

The “perfect” yeast cell-cycle trajectory



The ‘perfect’ yeast cell-cycle trajectory containing ghost effects





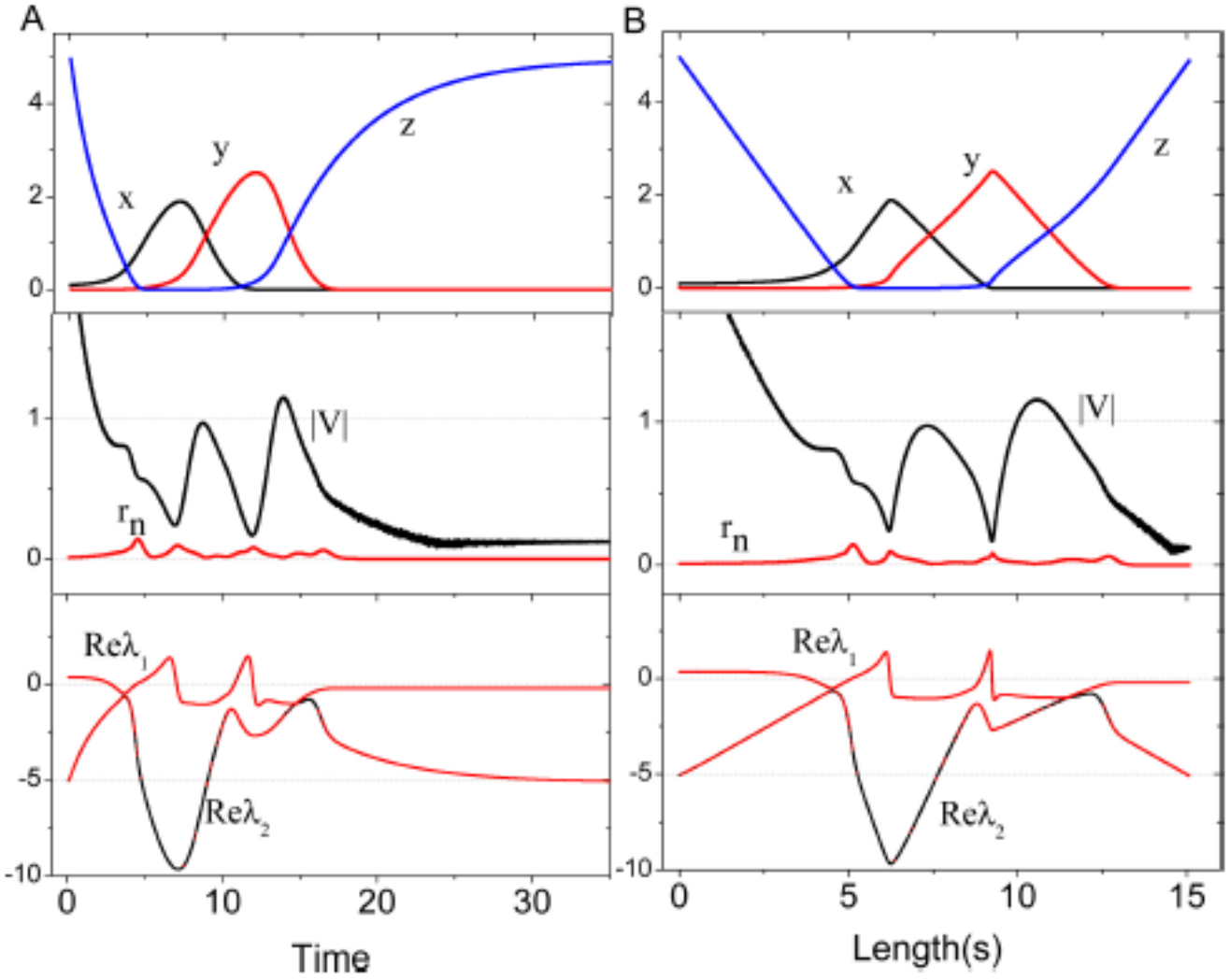
- The durations of x and y waves
- The expansive and convergent manifold
- Modularity of state/parameter space
- Checkpoints at the vertices

The manifolds diverge and converge, wave after wave, cycle in cycle out…

A dynamical view of yeast cell cycle process:

Suppose that the states (activities of the key regulators) of yeast cells can be dynamically observed, if a group of yeast cells start from different excited G1 states with fluctuations of biochemical parameters that tend to vary from cell to cell, how do the yeast cells evolve during the whole cell cycle process?

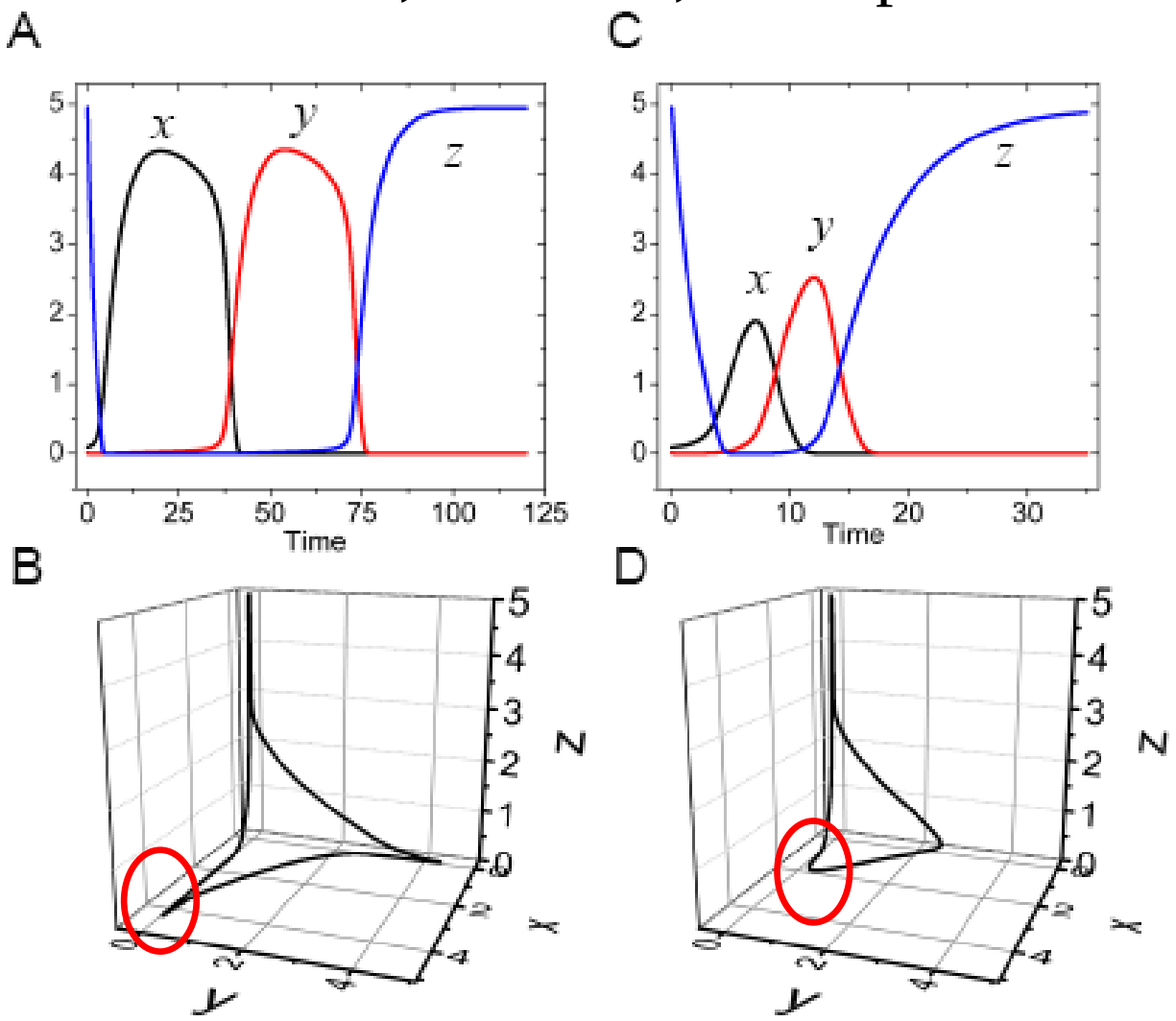
A “imperfect” yeast cell-cycle process



j1=0.5, j2=0.5, k1=0.2, k2=0.2, j3=0.5, k3=0.2,

ka1=0.04, ka2=0.04, ki=5.0, ks=1;

A ‘perfect’ and ‘imperfect’ cell-cycle trajectory manifold, duration, checkpoints



j1=0.5, j2=0.5, k1=0.2, k2=0.2, j3=0.5, k3=0.2, ki=5.0, ks=1;

Ka1= ka2=0.001, (A & B) vs. **ka1= ka2=0.04** (C & D)

The "perfect" yeast cell-cycle with inhibitor

We have the following equations:

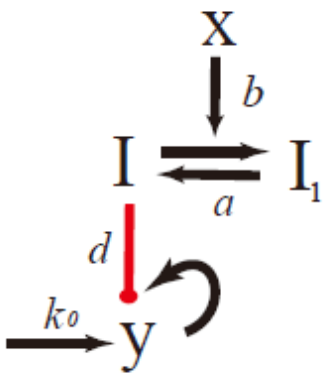
$$\frac{\mathrm{d}x}{\mathrm{d}t} = \frac{x^2}{j_1^2 + x^2} - k_1 x - yx,$$

$$\frac{\mathrm{d}y}{\mathrm{d}t} = (k_0 + \frac{y^2}{j_2^2 + y^2}) \cdot \frac{d}{K + I} - k_2 y \qquad \text{Case 1}$$

$$\frac{\mathrm{d}y}{\mathrm{d}t} = k_0 + \frac{y^2}{j_2^2 + y^2} \cdot \frac{d}{K + I} - k_2 y. \qquad \text{Case 2}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = -bxI + a(I_{tot} - I),$$

$$\frac{\mathrm{d}z}{\mathrm{d}t} = k_{a2} y + \frac{k_s z^2}{j_3^2 + z^2} - k_3 z - k_i xz.$$



Case 1 $T_x \simeq \frac{\pi}{\sqrt{B(Ak_0 - k_0^c)}}.$ where $A \equiv \frac{d}{K+I} = \frac{d}{K + I_{tot}\frac{a}{a+bx}},$

$$H(y) \equiv \frac{y^2}{j_2^2 + y^2} \cdot A - k_2 y,$$

Case 2 $T_x \simeq \frac{\pi}{\sqrt{B(k_0 - k_0^c)}}.$ $H(y^*)$ is the minimum of $H(y)$. $B \equiv \frac{\partial^2 H(y)}{\partial y^2}|_{y^*}.$

Energy Landscape Reveals That the Budding Yeast Cell Cycle Is a Robust and Adaptive Multi-stage Process

Cheng Lv[1], Xiaoguang Li[2], Fangting Li[1,3]*, Tiejun Li[2]*

$$S(\mathbf{x}) \propto -\ln P(\mathbf{x})$$

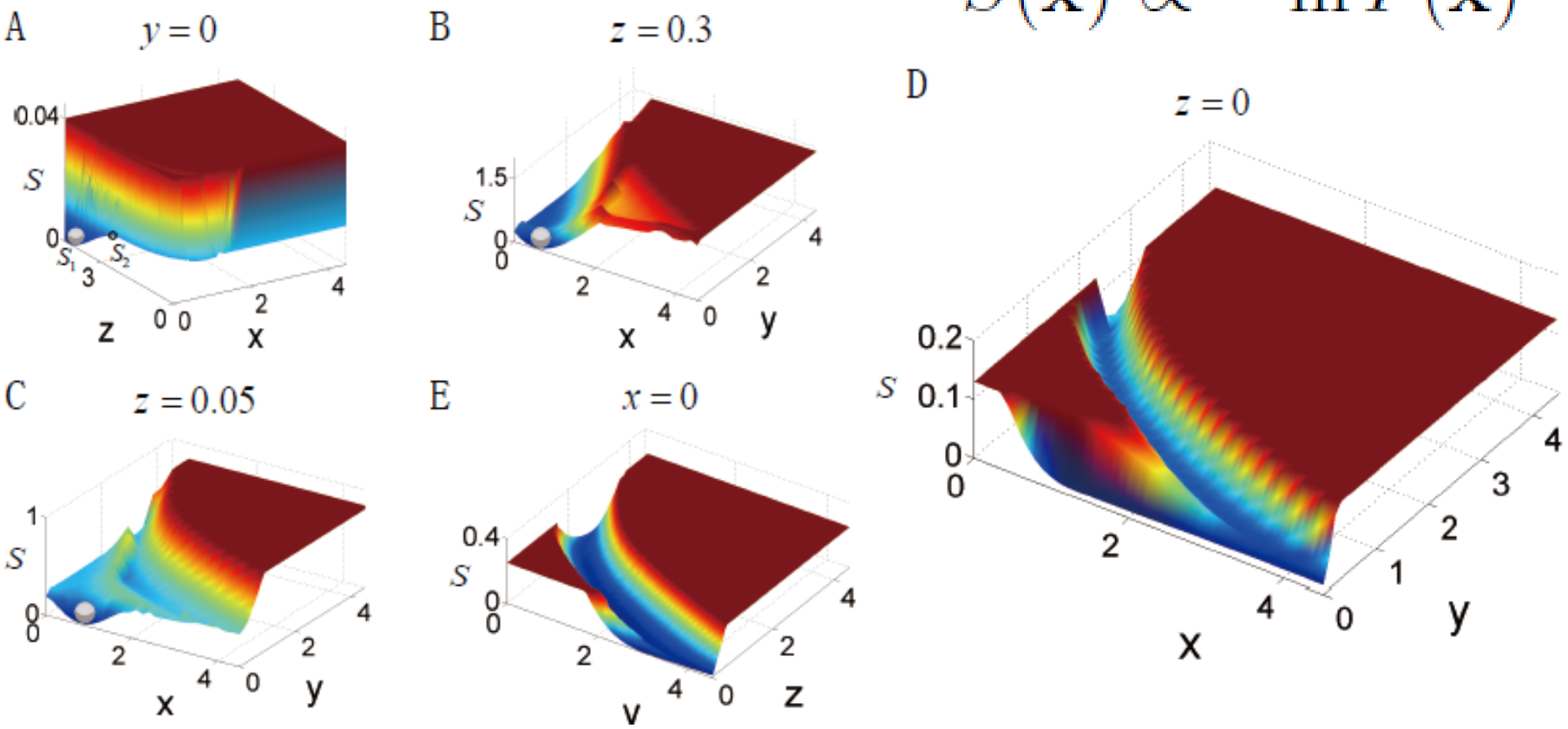


Fig. 2. Global quasi-potential energy landscape of the three-variable yeast cell-cycle network. (A) The x-z plane where $y = 0$, corresponds to the G1/S transition and G2 stages. (B), (C) The x-y plane where $z = 0.3$ and 0.05, respectively, correspond to the late G2 stage. (D) The x-y plane where $z = 0$, corresponds to the G2 and early M stage. (E) The y-z plane where $x = 0$, corresponds to the late M stage.

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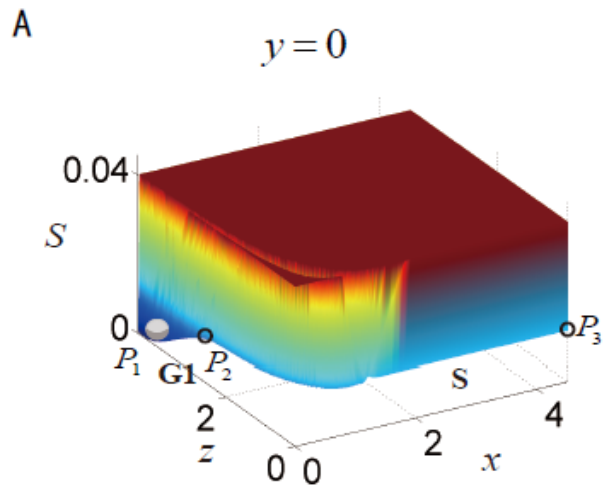
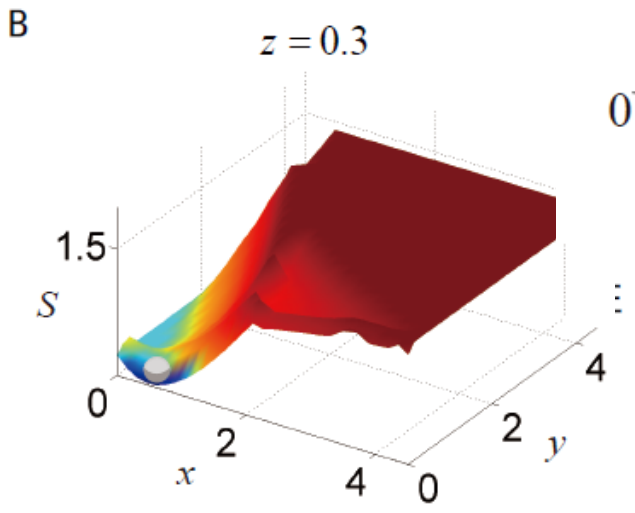
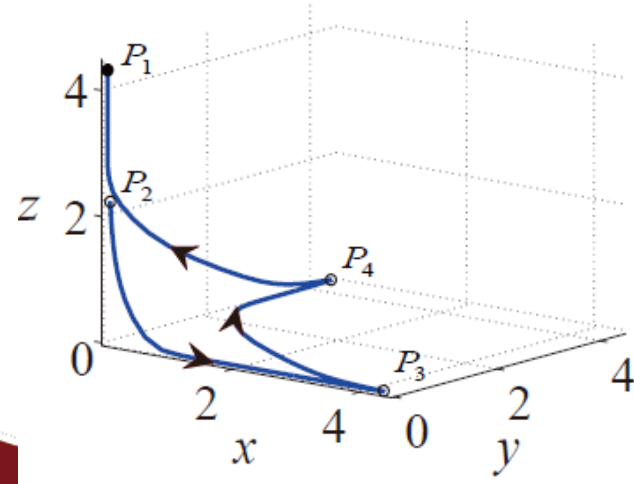
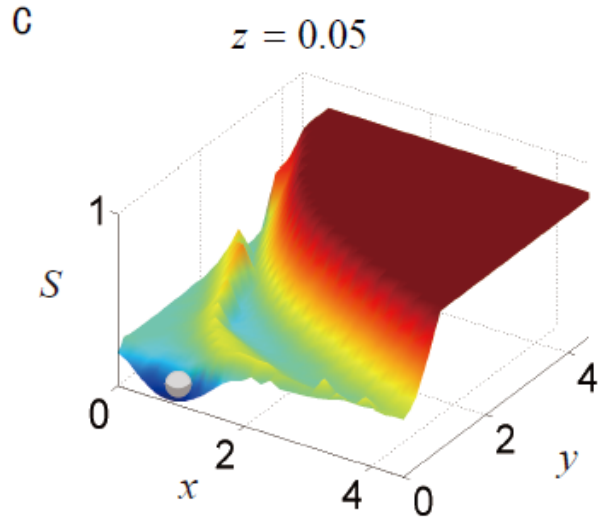
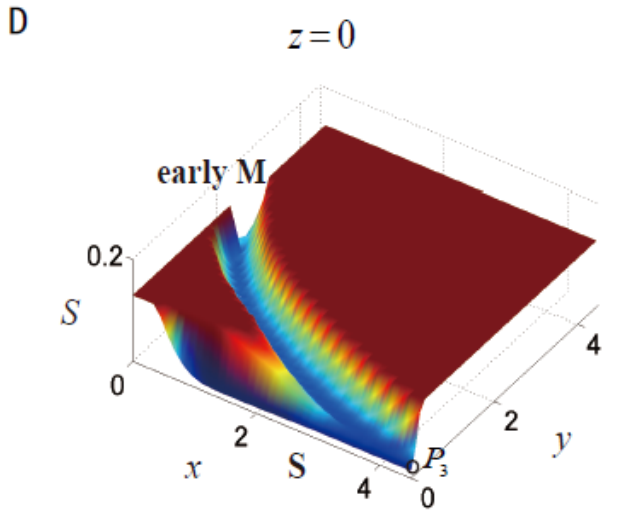
The landscape of perfect cell cycle

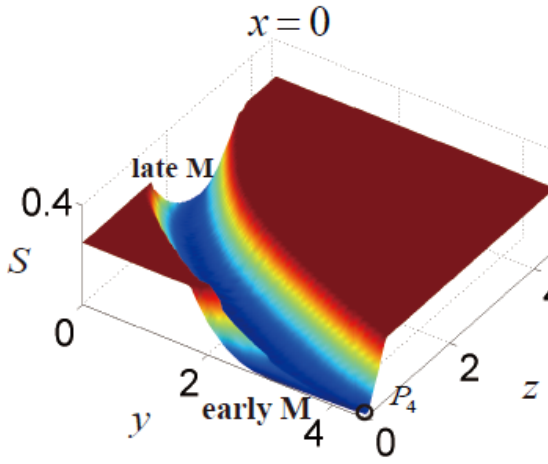




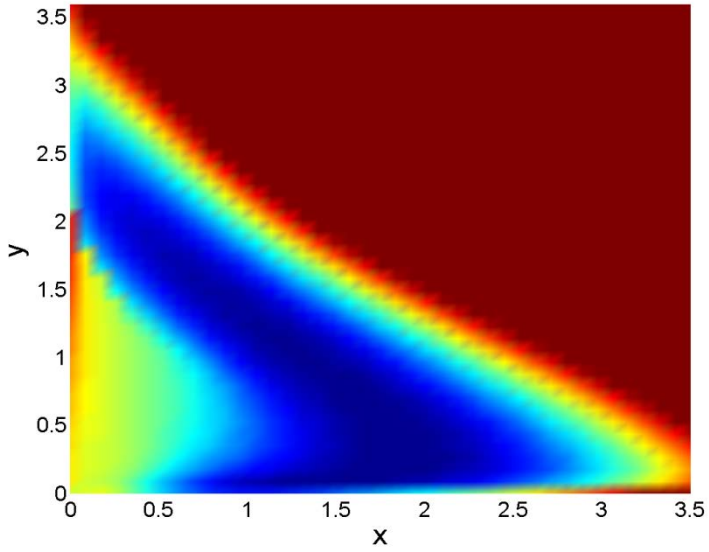


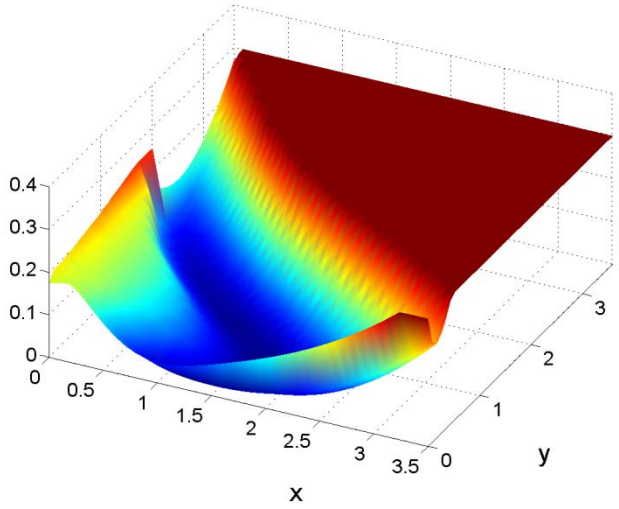


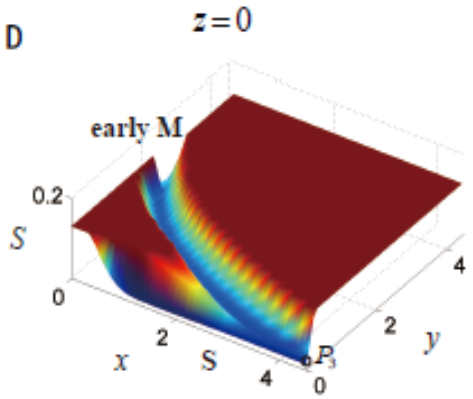




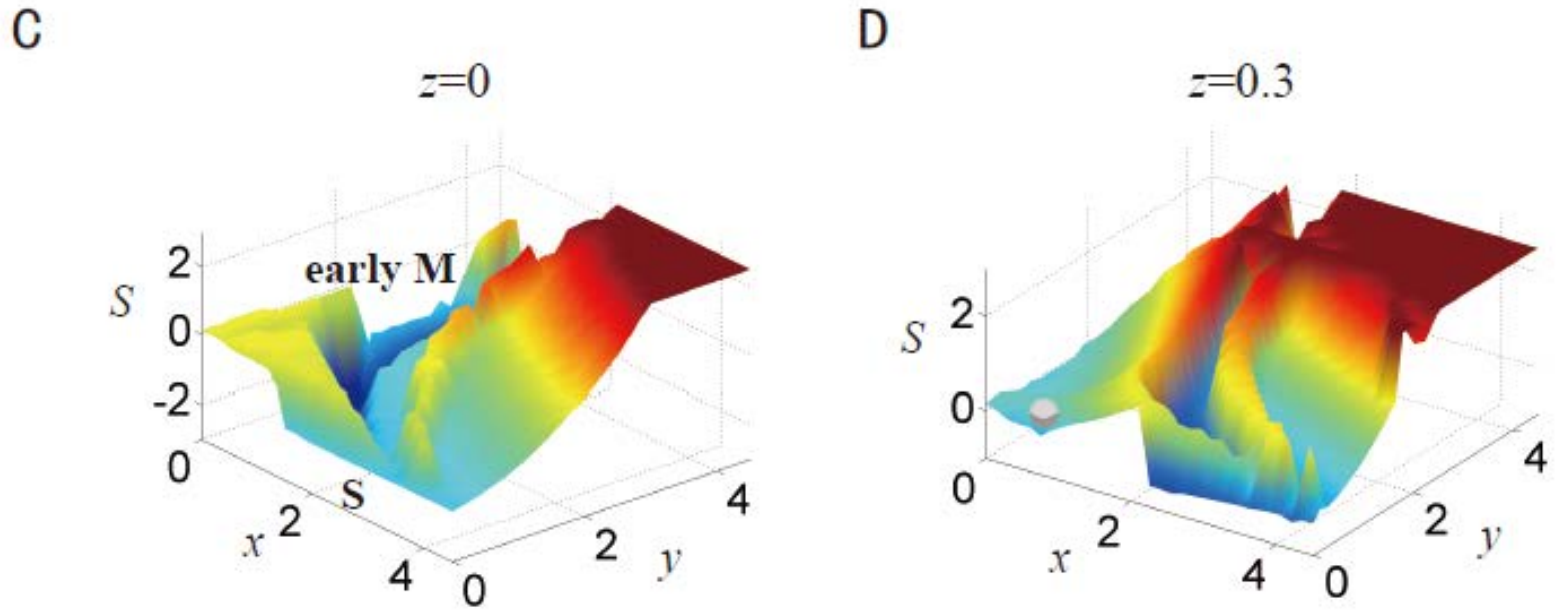
The landscape of imperfect cell cycle





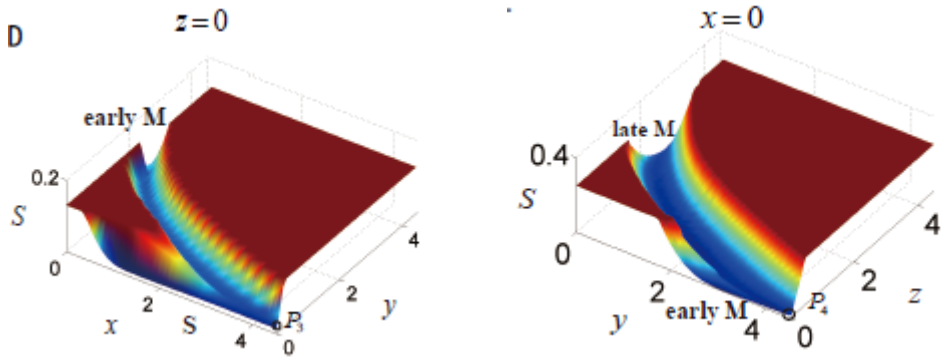


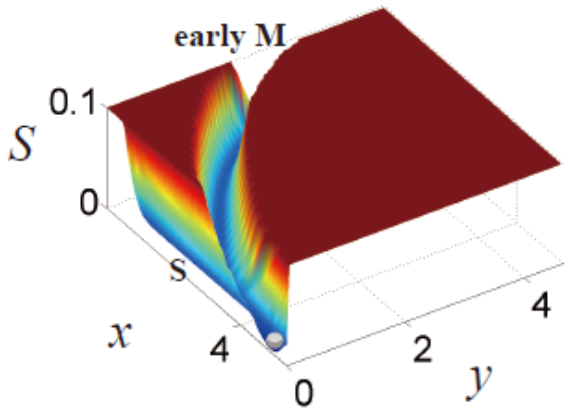
The pseudo energy landscape on the x-y plane with z=0 (C) and z=0:3 (D).



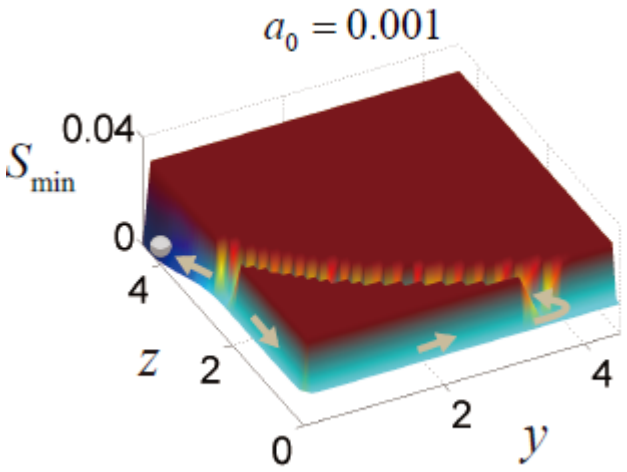
Difference from Langivan method: local pseudo energy Irreversibility, **sliding board** (滑梯模型)

The energy landscape in response to external signals

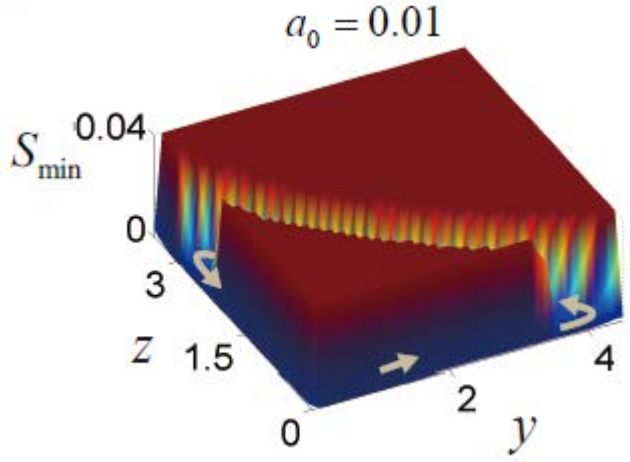




DNA checkpoint ON (ka1=0)

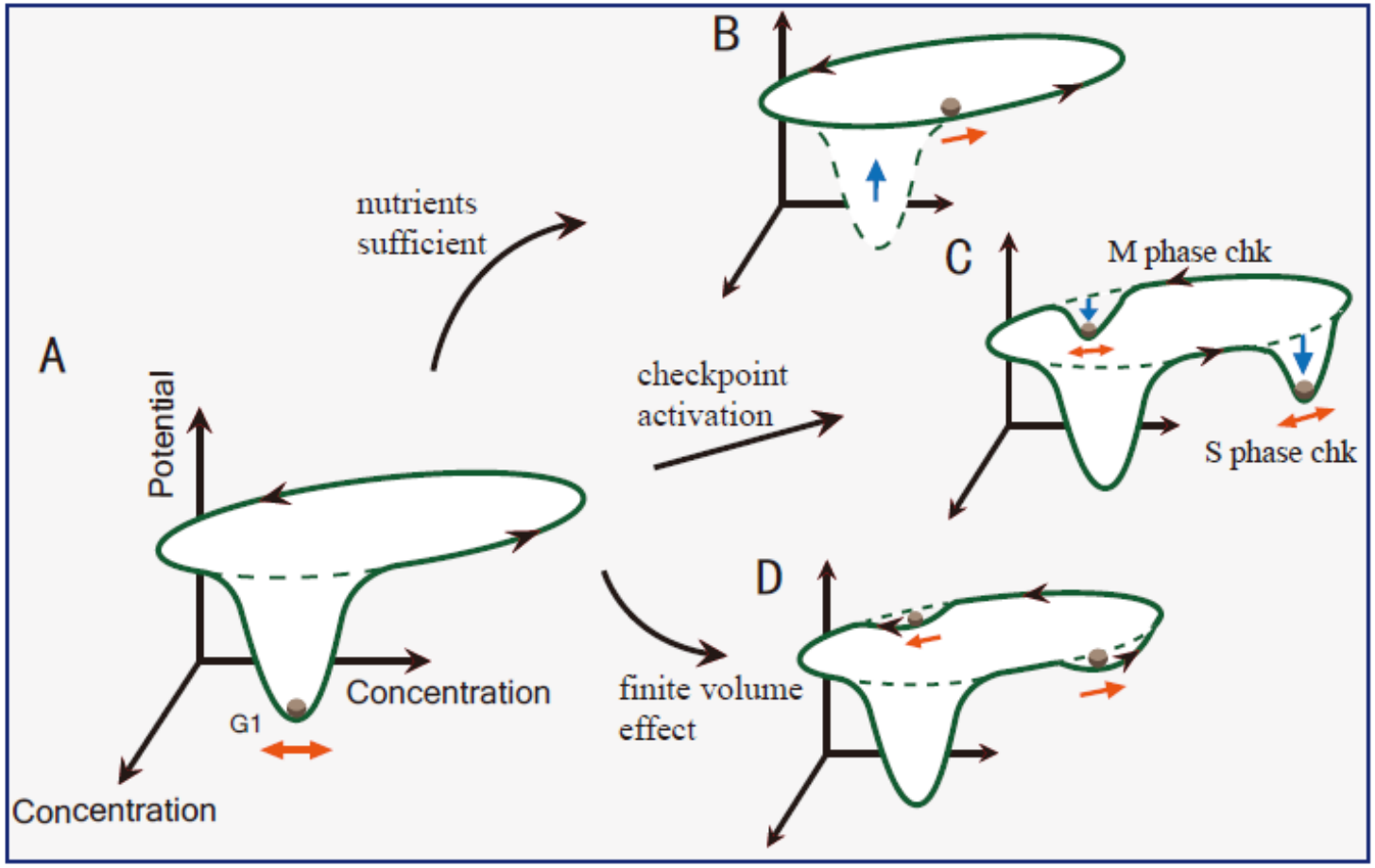


A excitable system under insufficient nutrients



Limit cycle under rich nutrient (a0=0.01)

The schematic quasi-potential energy landscape for the yeast cell cycle network



- **Quantitative biology in yeast cell cycle**

  The cell-cycle in budding yeast, modeling and quantitative experiment
- **3-node yeast cell cycle model**

  Feedbacks, checkpoints, a globally attractive trajectory…
- **How to ensure the stability of a multi-task process?**

Experimental testing?

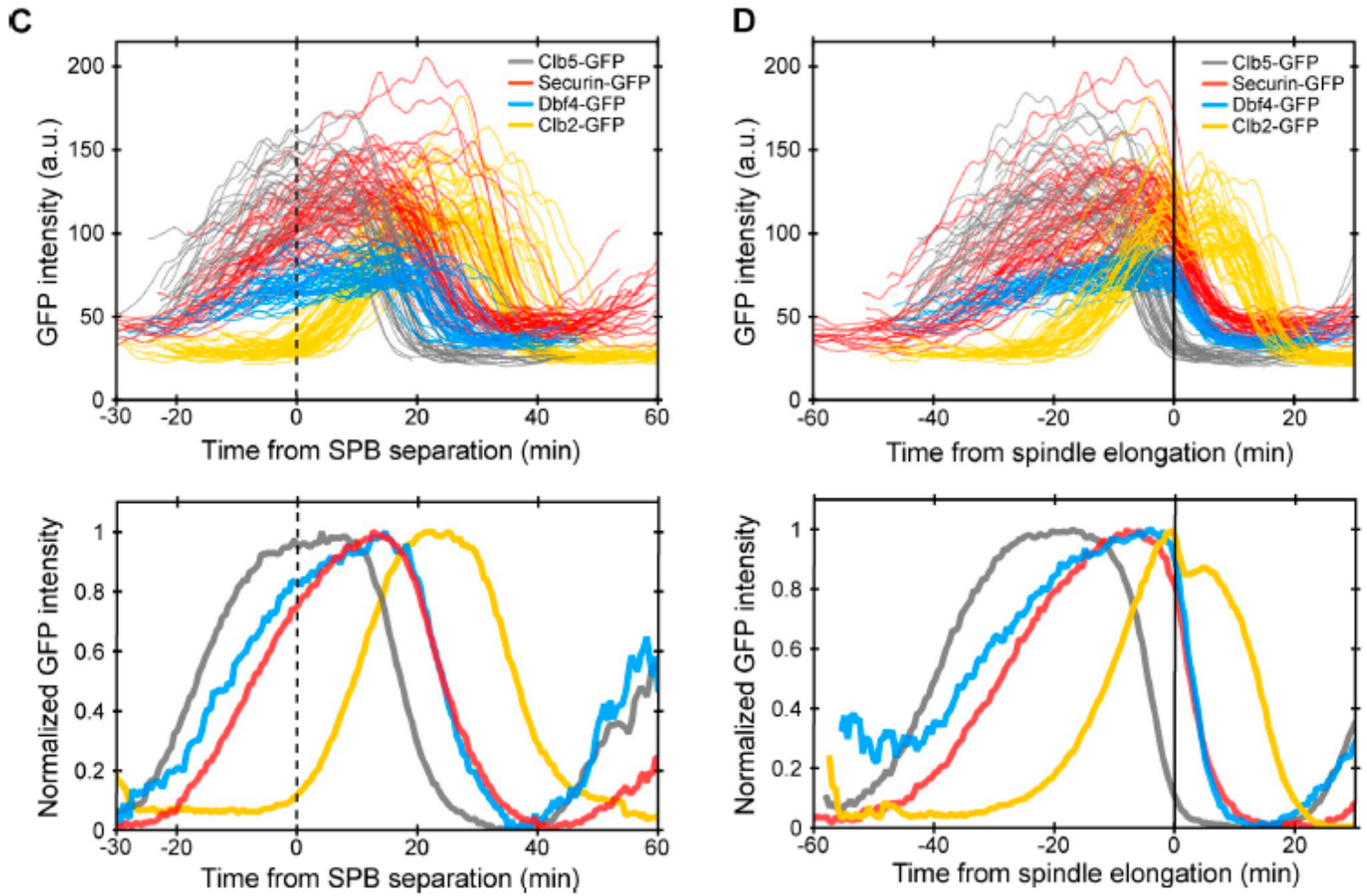


Figure 2. **Timing and dynamics of APC/C^{Cdc20} substrate degradation.** (A) Time from SPB separation to spindle elongation in individual cells with GFP tags on APC/C substrates. Each dot represents a single cell. Starting from the left, sample sizes are: *n* = 49, 90, 121, 82, and 77 cells. For each strain, the middle bar indicates the median value and error bars indicate the 25th and 75th percentiles. (B) GFP intensity of representative individual cells with tagged APC/C^{Cdc20} substrates (from the cell populations analyzed in A). Underlying black lines show the original data, and the colored lines are smoothed traces. The timing of SPB separation and spindle elongation are marked with broken and solid lines, respectively. (C and D) Comparison of different GFP-tagged

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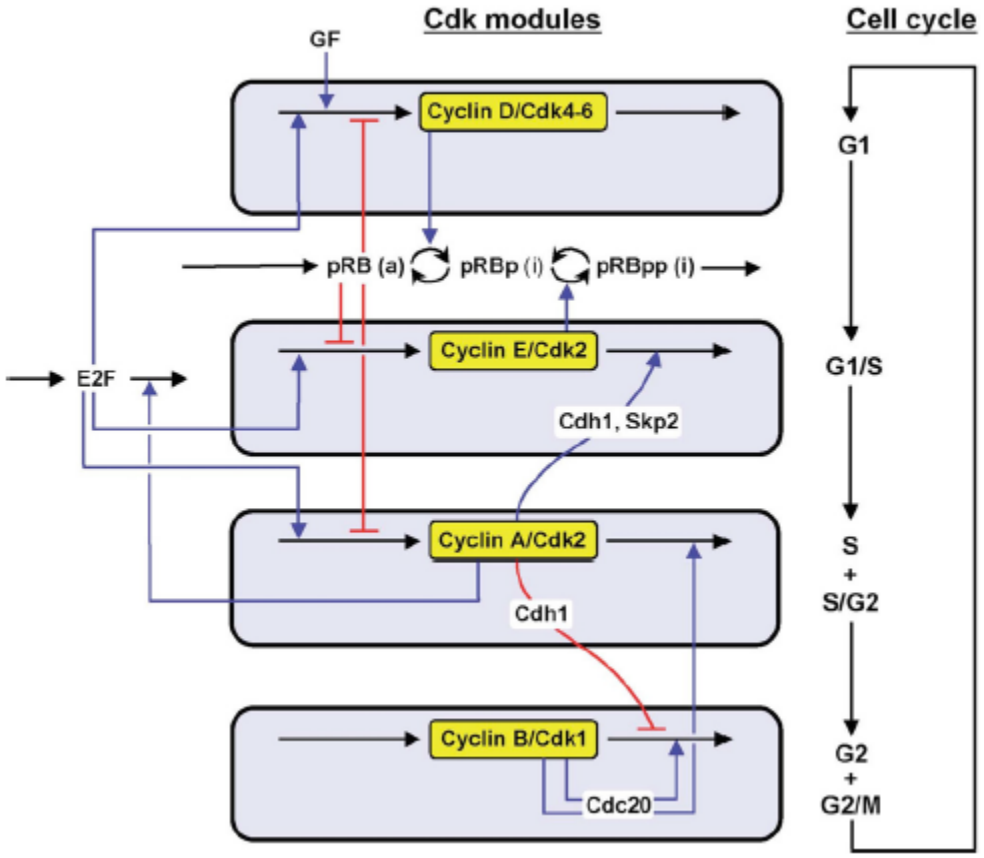
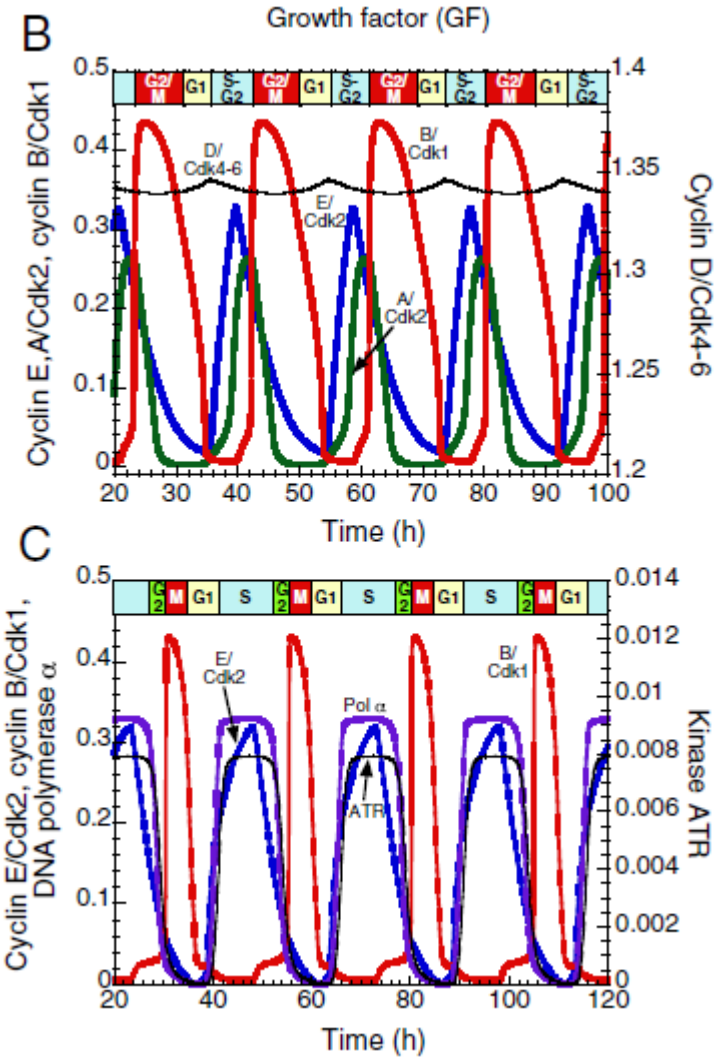
Temporal self-organization of the cyclin/Cdk network driving the mammalian cell cycle



39 variables
~150 parameters



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A globally attractive cycle in a 3-node yeast cell-cycle model

- A globally attractive cycle is driven by sequential saddle-node bifurcations containing ghost effects
- The vertices with convergent manifold correspond to the cell cycle checkpoints
- Modularity of state/parameter space
- The “ideal” yeast cell cycle trajectory and the cell cycle checkpoints

A possible synthetic network design for executing orderly multi-task processes

- Each event is controlled by the different key regulators, and the duration of each event regulated by the activation rates between successive waves
- Introducing an inhibitor with multi-phosphorylation into the activation of successive waves largely reduces duration sensitivity to relative changes in kinetic parameters

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Thanks!

谢谢！