Landscape and Flux Quantifications of Nonequilibrium Biological Systems

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Content

Landscape and Flux Quantifications:

1. Non-Equilibrium Systems: Searching for Laws and principles

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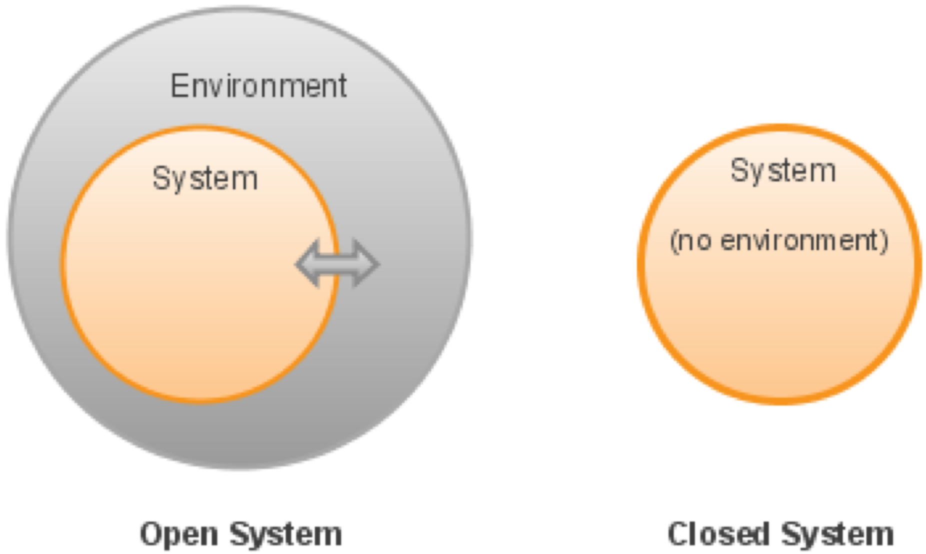
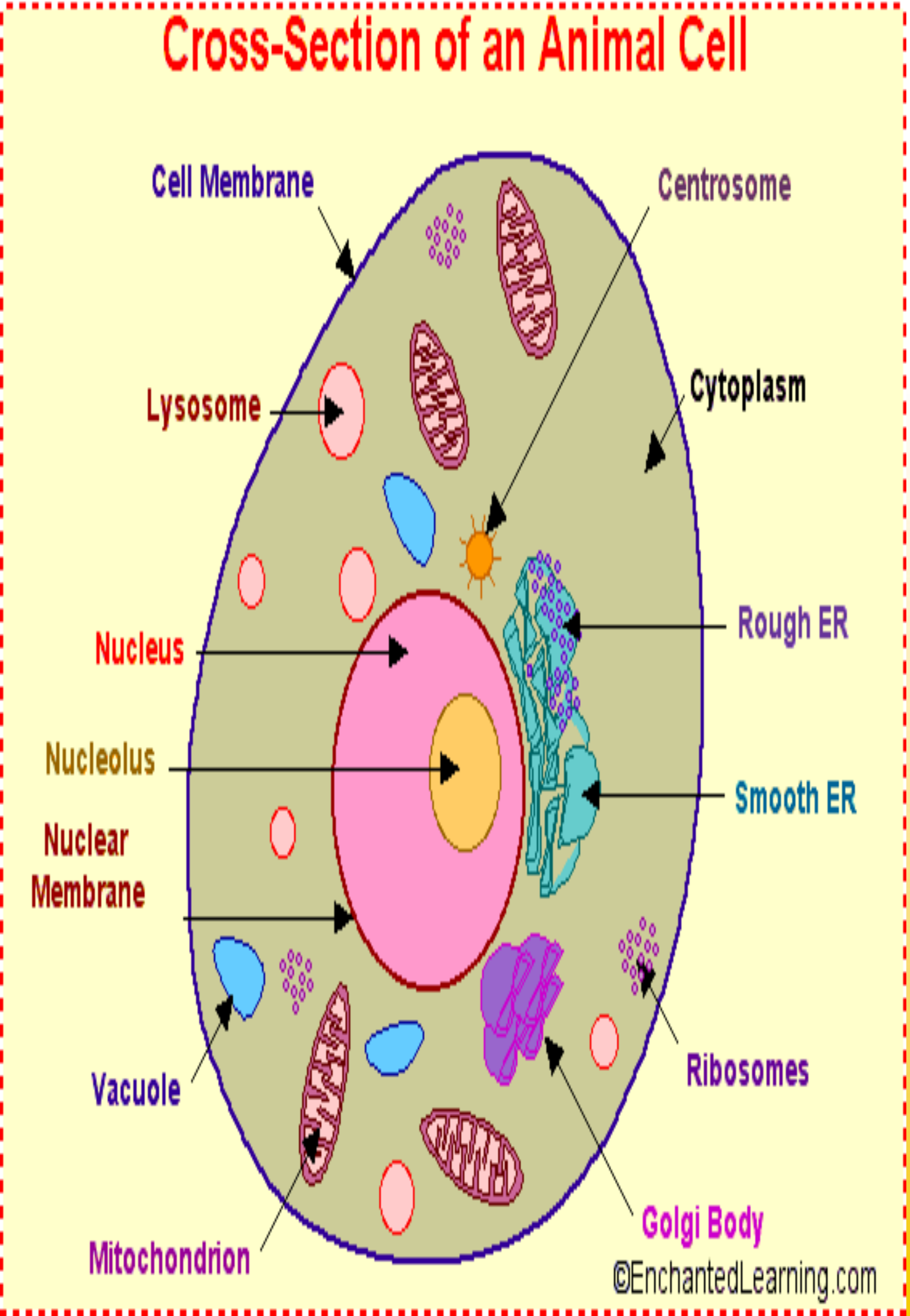


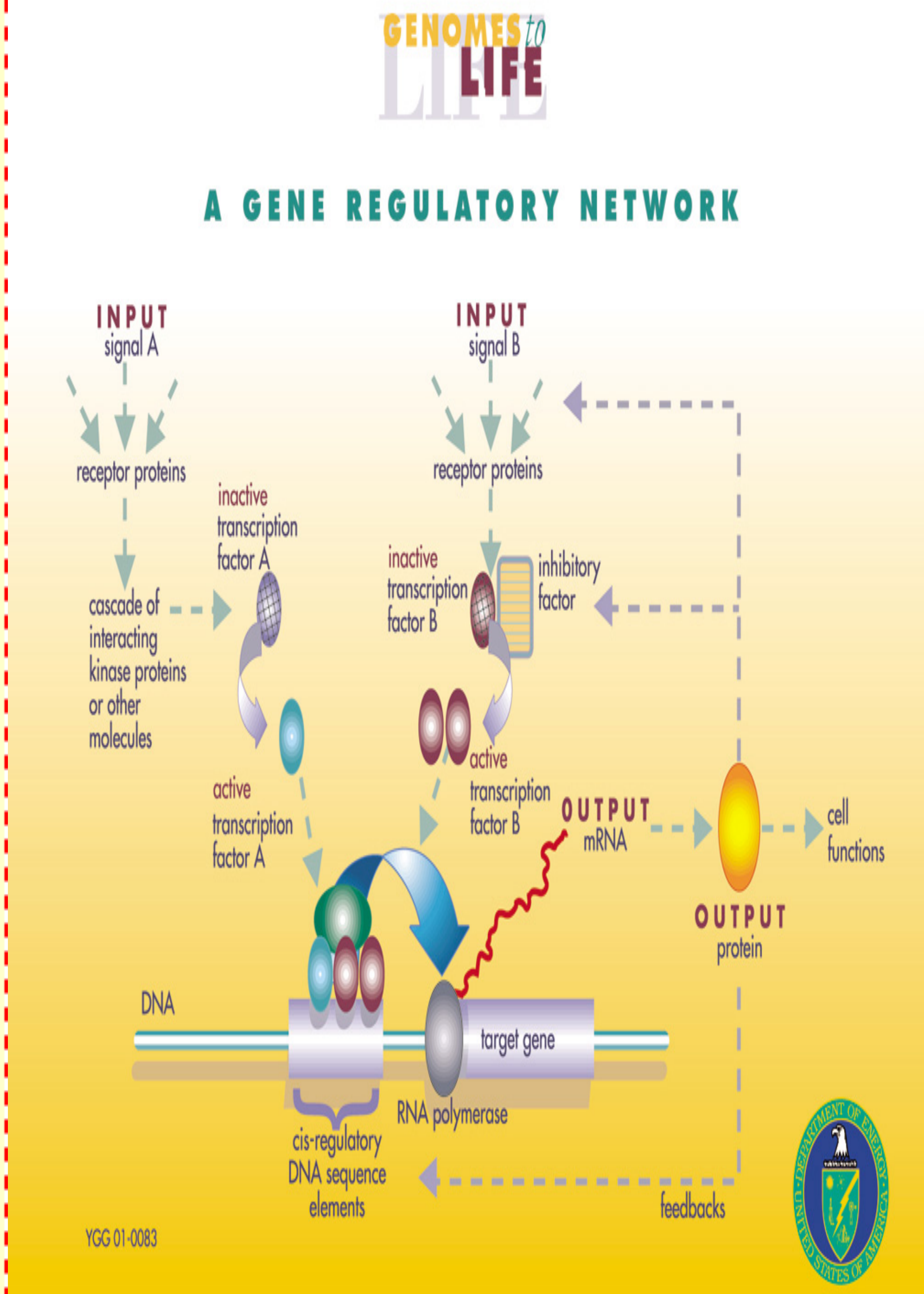
1. Open nonequilibrium systems: energy, matter and information exchange with outside environments:

   Earth, galaxies, ocean, plant, atmosphere, animals, society, economy, evolution, ecology, humans, brains, organs, cells, cellular networks.

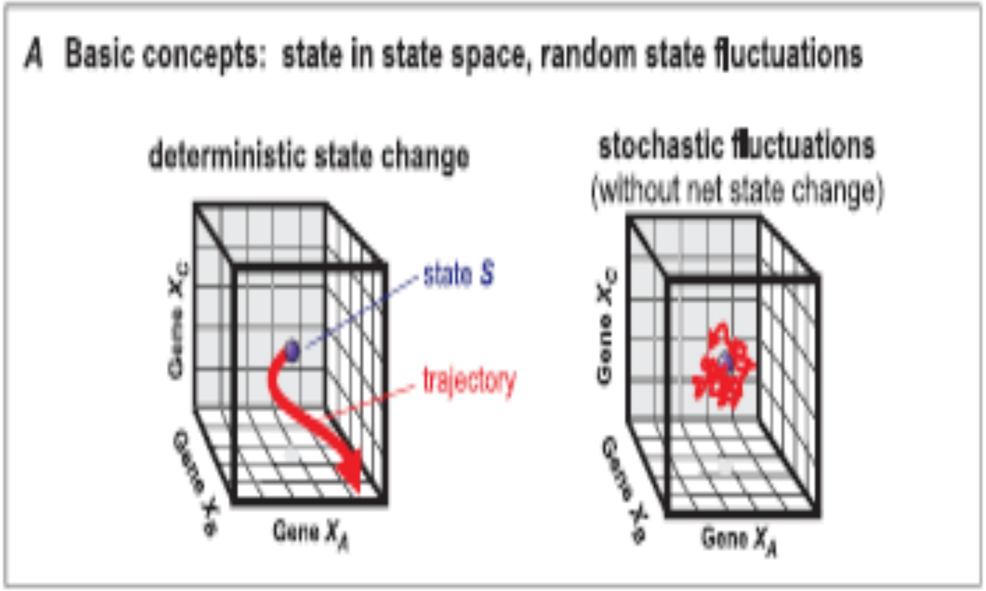
2. Quantitative descriptions of closed equilibrium systems: Newton and Boltzman

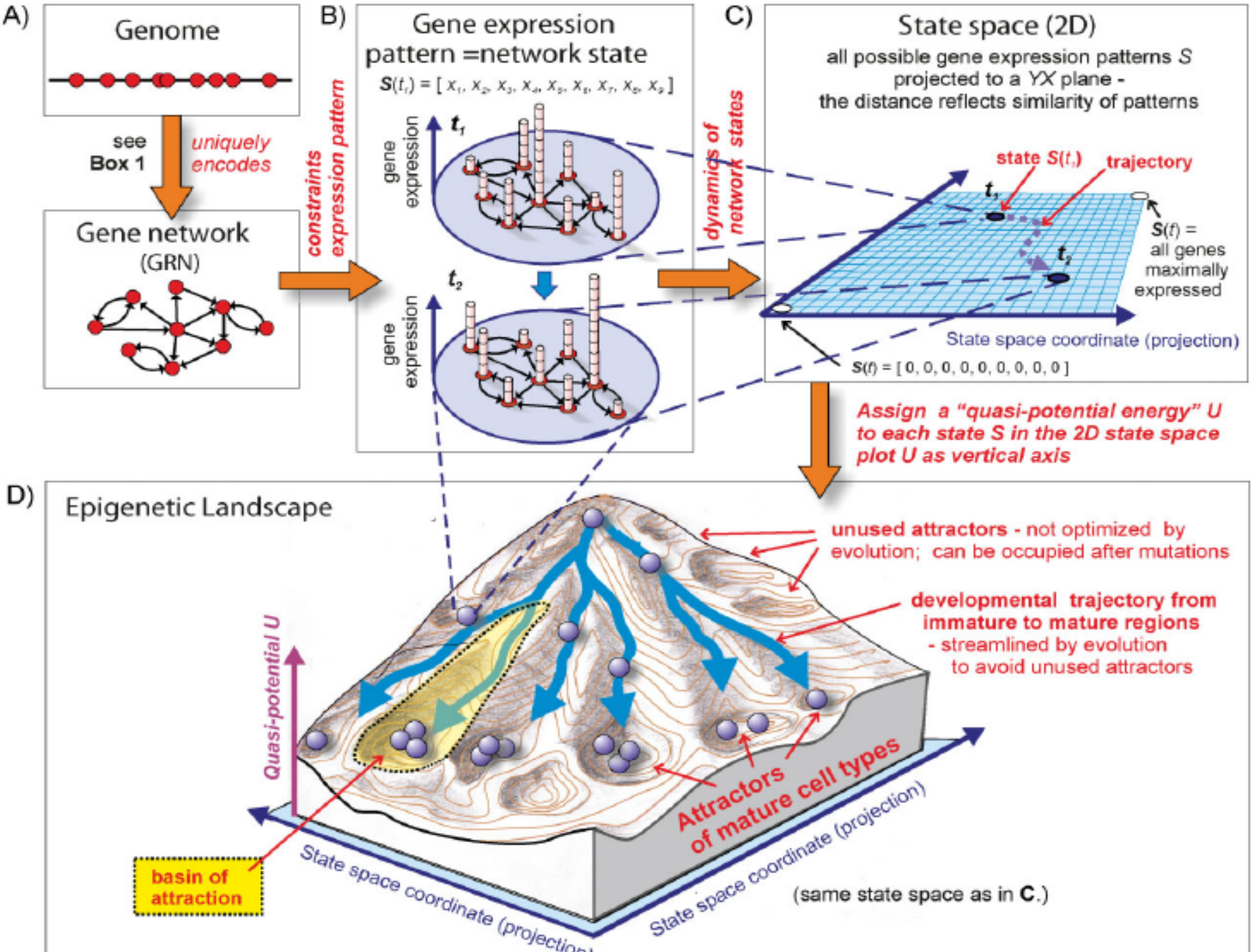
3. Searching for laws governing the non-equilibirum dynamical systems


Cross-Section of an Animal Cell
Cell Membrane
Centrosome
Cytoplasm
Lysosome
Rough ER
Nucleus
Nucleolus
Smooth ER
Nuclear Membrane
Ribosomes
Vacuole
Golgi Body
Mitochondrion
©EnchantedLearning.com

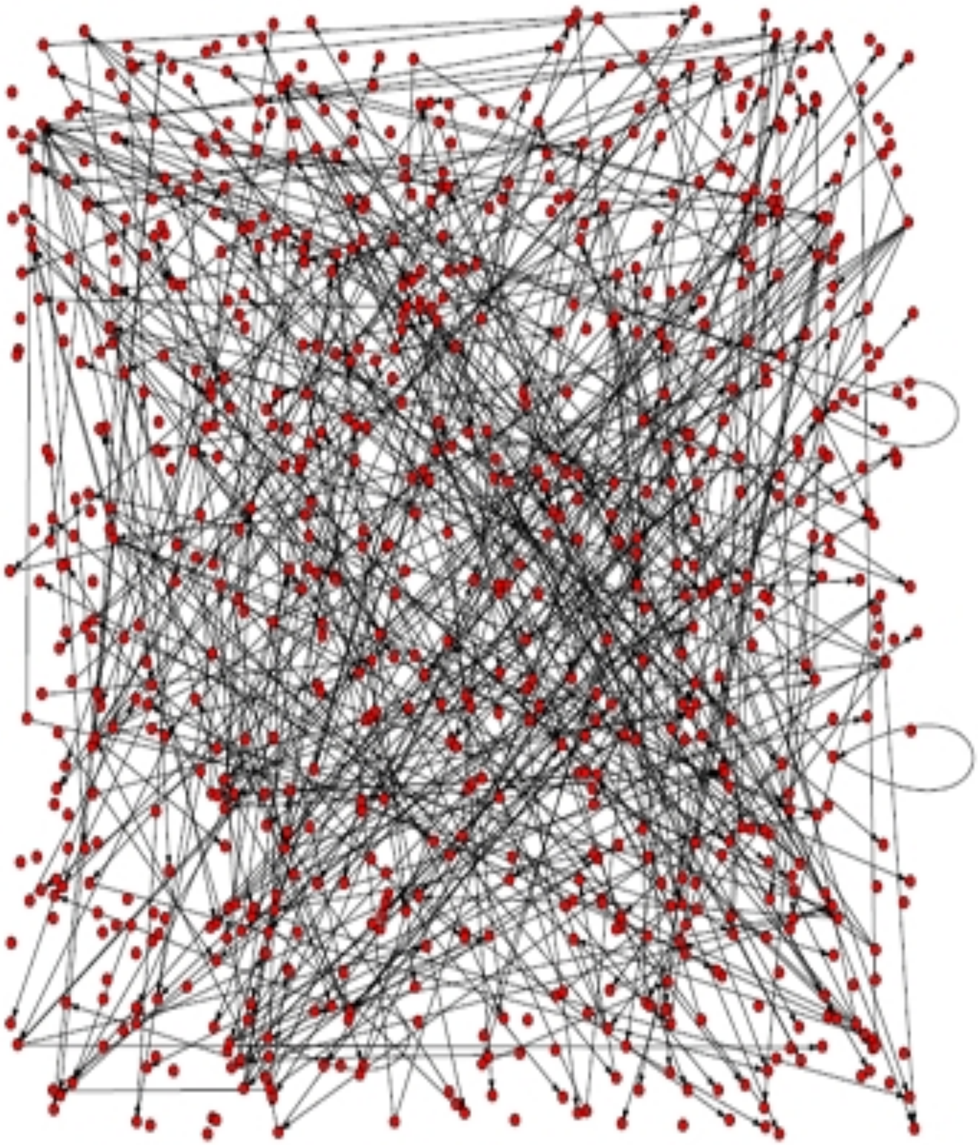

GENOMES to LIFE
A GENE REGULATORY NETWORK
INPUT signal A
INPUT signal B
receptor proteins
receptor proteins
inactive transcription factor A
inactive transcription factor B
inhibitory factor
cascade of interacting kinase proteins or other molecules
active transcription factor A
active transcription factor B
OUTPUT mRNA
cell functions
OUTPUT protein
DNA
target gene
RNA polymerase
cis-regulatory DNA sequence elements
feedbacks
YGG 01-0083

1. Gene Expression State Space





A)
Genome
see
Box 1
uniquely
encodes
Gene network
(GRN)
constraints
expression pattern
B)
Gene expression
pattern =network state
S(t1) = [x1, x2, x3, x4, x5, x6, x7, x8, x9]
gene
expression
t1
t2
dynamics of
network states
C)
State space (2D)
all possible gene expression patterns S
projected to a YX plane -
the distance reflects similarity of patterns
state S(t1)
trajectory
S(t) =
all genes
maximally
expressed
State space coordinate (projection)
S(t) = [0, 0, 0, 0, 0, 0, 0, 0, 0]
Assign a "quasi-potential energy" U
to each state S in the 2D state space
plot U as vertical axis
D)
Epigenetic Landscape
unused attractors - not optimized by
evolution; can be occupied after mutations
developmental trajectory from
immature to mature regions
- streamlined by evolution
to avoid unused attractors
Quasi-potential U
Attractors
of mature cell types
basin of
attraction
State space coordinate (projection)
State space coordinate (projection)
(same state space as in C.)



$$d[Ca^{2+}]_c / dt = [Ca^{2+}]_{out} \varphi_{(i)} - k_{+5}[Ca^{2+}]_c$$

$$d[ACh_v] / dt = -k_c[Ca^{2+}]_c[ACh_v]$$

$$d[ACh_f] / dt = k_c[Ca^{2+}]_c[ACh_v] - k_d[ACh_f] + k_{+6}[S]$$

$$d[ACh_c] / dt = k_d\,[ACh_f] - k_{+p}[ACh_c]$$

$$\begin{aligned} d[ACh_p] / dt = {} & k_{+p}[ACh_c] - [ACh_p](k_{+1}[R^0] + k_{+2}[E^0]) \\ & + [ACh_p](k_{+1}[ACh\text{-}R] + k_{+2}[AChE]) \\ & + k_{-1}[ACh\text{-}R] + k_{-2}[AChE] \end{aligned}$$

$$d[ACh\text{-}R] / dt = k_{+1}[ACh_p][R^0] - [ACh\text{-}R](k_{-1} + k_{+4} + k_{+1}[ACh_p])$$

$$d[AChE] / dt = k_{+2}[E^0][ACh_p] - [AChE](k_{-2} + k_{+3} + k_{+2}[ACh_p])$$

$$d[S] / dt = k_{+4}[ACh\text{-}R] - k_{+6}[S] + k_{+3}[AChE]$$

$$[R] = [R^0] - [ACh\text{-}R]$$

$$[E] = [E^0] - [AChE],$$

Local and Global Nature of the Dynamic System

$$\dot{\vec{x}} = \vec{F}(\vec{x})$$

- Linear analysis around fixed points only gives local stability information.

- Global stability information is missing from local stability analysis and is required to characterize the whole system.

Second Law of Equilibrium Dynamical Systems

$$\dot{\vec{x}} = \vec{F}(\vec{x}) \qquad \vec{F} = -\vec{\nabla} U$$

1. Probability is controlled by landscape
P~exp[-U]: Distributions of barriers and basins determine global emergence, stability & function

2. Dynamics is determined by landscape
for gradient systems, F=-∇U

1. Introduction

- ***Global Approach Requires A Potential Landscape:***

- Liquid, gas and associated phase transitions of physical systems
- Evolution (Wright, 1930s)
- *Differentiation and Development (Waddington, 1950s)*
- Protein Dynamics (Frauenfelder, Wolynes, 1970-1980s)
- Associate Memory Neural Networks (Hopfield, 1980s)
- Protein Folding and Binding (Wolynes, Onuchic, Dill, Thirumalai, 1980-1990's)
- Potential Known $\vec{F} = -\vec{\nabla} U$

- General Dynamics of Nonequilibrium Systems: $\dot{\vec{x}} = \vec{F}(\vec{x})$
- No Potential:

$$\vec{F} \neq -\vec{\nabla} U$$

Our Way of Force Decomposition:
A General Framework for Non-Equilibrium Systems:
Detailed Balance: Equilibrium Probability; Force = Gradient
No Detailed Balance: Steady State Probability; Force=Gradient + Flux

Jin Wang, Li Xu, E.K. Wang, PNAS 2008

$$\dot{\vec{x}} = \vec{F}(\vec{x})$$

$$\dot{\vec{x}} = \vec{F}(\vec{x}) + \vec{\xi}(t); < \xi_i(t)\xi_j(t') >= 2DD_{ij}\delta(t-t')$$

$$\frac{\partial P}{\partial t} = -\vec{\nabla} \cdot \vec{J}, \qquad \vec{J} = \vec{F}P - \vec{\vec{D}} \cdot \vec{\nabla} P$$

$$Steady \quad State: \quad \frac{\partial P_{ss}}{\partial t} = 0 \rightarrow \vec{\nabla} \cdot \vec{J}_{ss} = 0$$

1. $\vec{J}_{ss} = 0 \rightarrow \vec{F} = \vec{\vec{D}} \cdot \vec{\nabla} \ln P_{ss} = -\vec{\vec{D}} \cdot \vec{\nabla} U$

$\Rightarrow \vec{F} = -\vec{\vec{D}} \cdot \vec{\nabla} U \quad ; U = -\ln P_{ss}$

Global Quantification via Equilibrium Probability

$-> Detailed \quad Balance \quad (J_{ss} = 0): \quad Force \quad Decomposed \quad to: \quad Gradient$

2. $\vec{J}_{ss} \neq 0 \rightarrow \vec{F} = \vec{\vec{D}} \cdot \vec{\nabla} \ln P_{ss} + \vec{J}_{ss} / P_{ss}$

Global Quantification via Steady State Probability

$\Rightarrow \vec{F} = \vec{F}_{gradient} + \vec{F}_{curl} = -\vec{\vec{D}} \cdot \vec{\nabla} U + \vec{J}_{ss} / P_{ss}; \quad U = -\ln P_{ss}; \vec{F}_{gradient} = -\vec{\vec{D}} \cdot \vec{\nabla} U; \vec{F}_{curl} = \vec{J}_{ss} / P_{ss}$

$-> Non-Detailed \quad Balance \quad (\vec{J}_{ss} \neq 0): \quad Force \quad Decomposed \quad to: \quad Gradient \quad + \quad Curl \quad Flux$

Dynamics on Landscapes: Gradient Dynamics vs. Spiral Dynamics

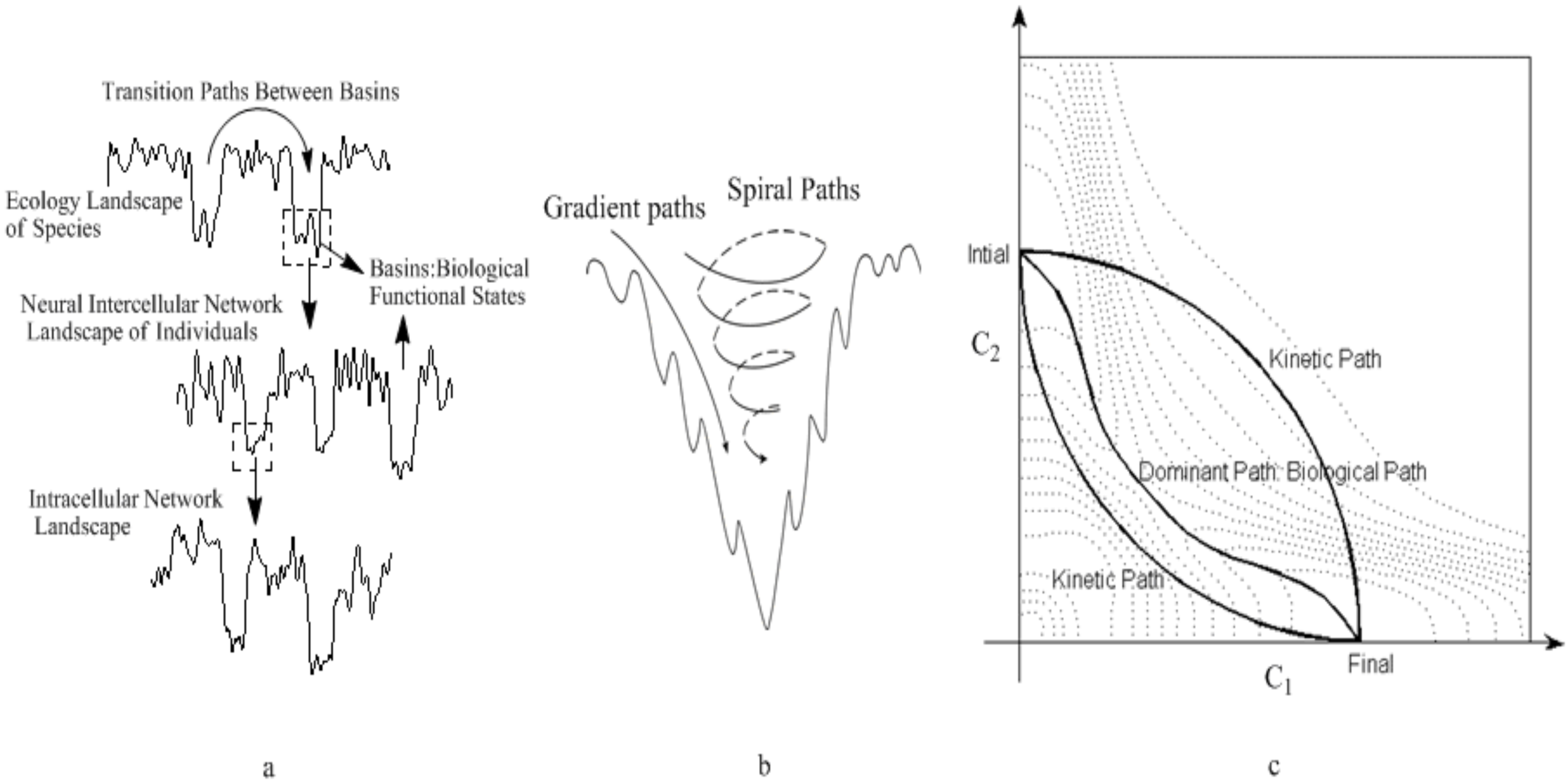


Fig2

Equilibrium and Non-Equilibrium Dynamics

Equilibrium systems:

1. Equilibrium probability landscapes as global characterization of the systems
2. Follow gradient dynamics of the landscape

Analogy: Charge particle moving in electric field, down hill trajectory to the gradient

Non-equilibrium active systems:

1. Steady state probability landscapes as global characterization of the systems
2. Follow landscape gradient and curl flux dynamics

Analogy: Charge particle moving in electric and magnetic field, spiral downhill trajectory to the gradient

Potential as Lyapunov Function and Global Stability

Graham, Hu (1988); Zhang, Xu, Zhang, Wang, Wang (2012), Wu, Wang(2013)

$$P_{ss}(\vec{x}) = \exp[-\tfrac{\phi_0}{D} + \phi_1 + D\phi_2 + \ldots]$$

$$\phi_0(\vec{x}) = -\lim_{D\to 0} D \ln P_{ss}(\vec{x})$$

$$(\vec{\nabla}\phi_0(\vec{x}))^2 + \vec{F}(x) \bullet \vec{\nabla}\phi_0(x) = 0$$

Hamilton-Jacobi Equation

$$\overset{\bullet}{\vec{x}} = \vec{F}(x)$$

$$\frac{d\phi_0(\vec{x})}{dt} = \vec{\nabla}\phi_0(\vec{x}) \bullet \frac{d\vec{x}}{dt} = \vec{\nabla}\phi_0(\vec{x}) \bullet \vec{F}(\vec{x}) = -(\vec{\nabla}\phi_0(\vec{x}))^2 \le 0$$

$$\vec{J}_{ss} \bullet \vec{\nabla}\phi_0(\vec{x}) = 0$$

Path Integral and Dominant Kinetic Paths (One Gun with Path Integral Kills Four Birds: Landscape, Kinetics, and Paths, and Computation Efficiency

Wang, Zhang, Wang, JCP 2010

$$\frac{d\vec{x}}{dt} = \vec{F}(\vec{x}) + \vec{\eta}$$

$$P(\vec{x}_{fianl}, t, \vec{x}_{initial}, 0) = \int D\vec{x} Exp[-\int dt(\frac{1}{2}\vec{\nabla} \bullet \vec{F}(\vec{x}) + \frac{1}{4}(d\vec{x}/dt - \vec{F}(\vec{x})) \bullet \frac{1}{\overleftrightarrow{D}} \bullet (d\vec{x}/dt - \vec{F}(\vec{x})))]$$

$$= \int D\vec{x} Exp[-S(\vec{x})] = \int d\vec{x} Exp[-\int L(\vec{x}(t))dt]$$

$$\ddot{\vec{x}} = \vec{E} + \dot{\vec{x}} \times \vec{B}$$

$$\frac{d}{dt}\frac{\partial L}{\partial \dot{x}_i} - \frac{\partial L}{\partial x_i} = 0$$

$$\vec{B} = \vec{\nabla} \times (-\vec{F})$$

$$\vec{\nabla} \bullet \vec{B} = 0$$

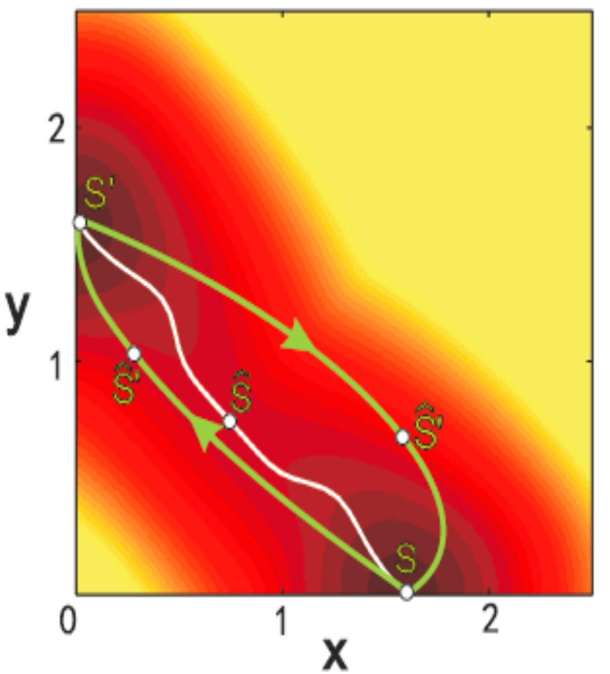
$$\ddot{\vec{x}} = \vec{E} - \nabla(\dot{\vec{x}} \bullet \nabla)\vec{F} + (\dot{\vec{x}} \bullet \nabla)F$$

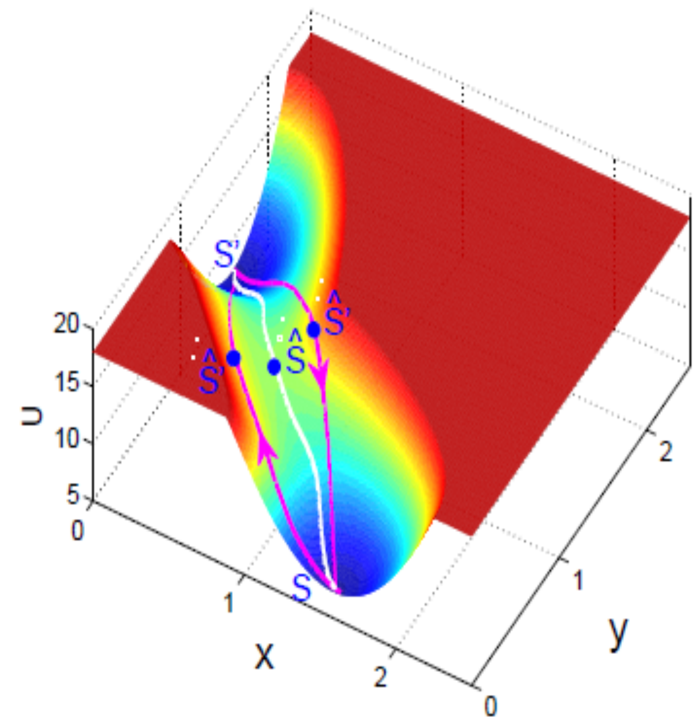
$$\vec{E} = 2\overleftrightarrow{D} \bullet \vec{\nabla} V(\vec{x}) \qquad V(\vec{x}) = \frac{1}{4}\vec{F} \bullet \frac{1}{\overleftrightarrow{D}} \bullet \vec{F} + \frac{1}{2}\vec{\nabla} \bullet \vec{F}$$

2.2. Equilibrium Systems: Steepest Descent Reversible Path and Kinetic Rates Determined by Transition State Theory

Nonequilibrium Systems: Irreversible Paths Deviate from Steepest Descent Paths and Do Not Go Through Transition State; Kinetic Rate Determined by Saddle on the Paths

K. Zhang, E.K. Wang, J. Wang, JCP (2010);
H. Feng, K. Zhang, J. Wang, Chemical Science (2014)





$$r_K^{noneq} = (E\tau)^{-1} = \frac{\lambda_u(\hat{S}')}{2\pi}\sqrt{\frac{detM(S)}{|detM(\hat{S}')|}}e^{-S_{HJ}^{DOM}}$$

1.4. Fluctuation-Dissipation Theorem for Non-equilibrium System:

Equlibrium: Relaxation(Response)=Equilibrium Fluctuations

Non-Equilibrium: Relaxation(Response)=Steady State Fluctuations + Flux Correlations

Seifert (2011); H. Feng, J. Wang (JCP, 2011)

$$R_{\Omega}(t_0,t) = \frac{\delta(\langle\Omega\rangle(t) - \langle\Omega\rangle^0)}{\delta h(t_0)}\Big|_{h=0}$$

$$F_i(\mathbf{x}) \to F_i'(\mathbf{x}) = F_i(\mathbf{x}) + h_i(t)\delta F_i(\mathbf{x})$$

$$\begin{aligned}
&R_{\Omega,j}(t-t') \\
&= \int d\mathbf{x}\Omega e^{\hat{L}(t-t')}\{\sum_k \delta F_j[-\tilde{F}_k - \frac{j_k^{SS}}{P^{SS}}]2D_{jk}^{-1} - \frac{\partial\delta F_j}{\partial x_j}\}P^{SS} \\
&= -\langle\Omega(t)\frac{\partial\delta F_j}{\partial x_j}\rangle - \sum_k \Big[2\langle\Omega(t)\delta F_j(t')\tilde{F}_k(t')D_{jk}^{-1}(t')\rangle \\
&\qquad +2\langle\Omega(t)\delta F_j(t')\frac{j_k^{SS}}{P^{SS}}(t')D_{jk}^{-1}(t')\rangle\Big]
\end{aligned}$$

Equilibrium System

$$R_{\Omega,j}(t-t') = -D_{jk}^{-1}\left[\frac{d}{dt}\langle x_j(t)\Omega(t')\rangle\right]$$

Non-Equilibrium System

$$R_{\Omega,j}(t-t') = -2\sum_k \Big[\langle\Omega(t)\tilde{F}_k(t')D_{jk}^{-1}(t')\rangle + \langle\Omega(t)\frac{j_k^{SS}}{P^{SS}}(t')D_{jk}^{-1}(t')\rangle\Big]$$

1.5. Non-equilibrium Thermodynamics (Flux Decomposition) From Equal Time Fluctuation-Dissipation Theorem

Equlibrium: Entropy Production= Free Energy Relaxation

Non-Equilibrium: Entropy Production=Free Energy Relaxation + House Keeping

Ge, Qian (2010); Feng, Wang (2011)

$$\Omega = v_i(x) - v_i^{ss}(x) = \frac{J_i - J_i^{ss}}{P_{ss}}$$

$$t = t'$$

$$\frac{d\tilde{F}}{dt} = Q_{hk} - epr; \qquad epr = Q_{hk} - \frac{d\tilde{F}}{dt}$$

$$\frac{d\tilde{F}}{dt} =< v_i \partial_i \ln[P^{ss}(x) / P(x,t)] >$$

$$Q_{hk} =< v_i^{ss} D_{ij}^{-1} v_j^{ss} >$$

$$epr =< v_i D_{ij}^{-1} v_j >$$

1.6. Gauge Field Connections and Berry Phase

Stochastic Diffusion Dynamics in Gauge Field (Electric and Magnetic field)

Feng, Wang, JCP (2011)

Non-Equilibriumness (non-zero flux) = Gauge field curvature

Steady state entropy production: Gauge invariance

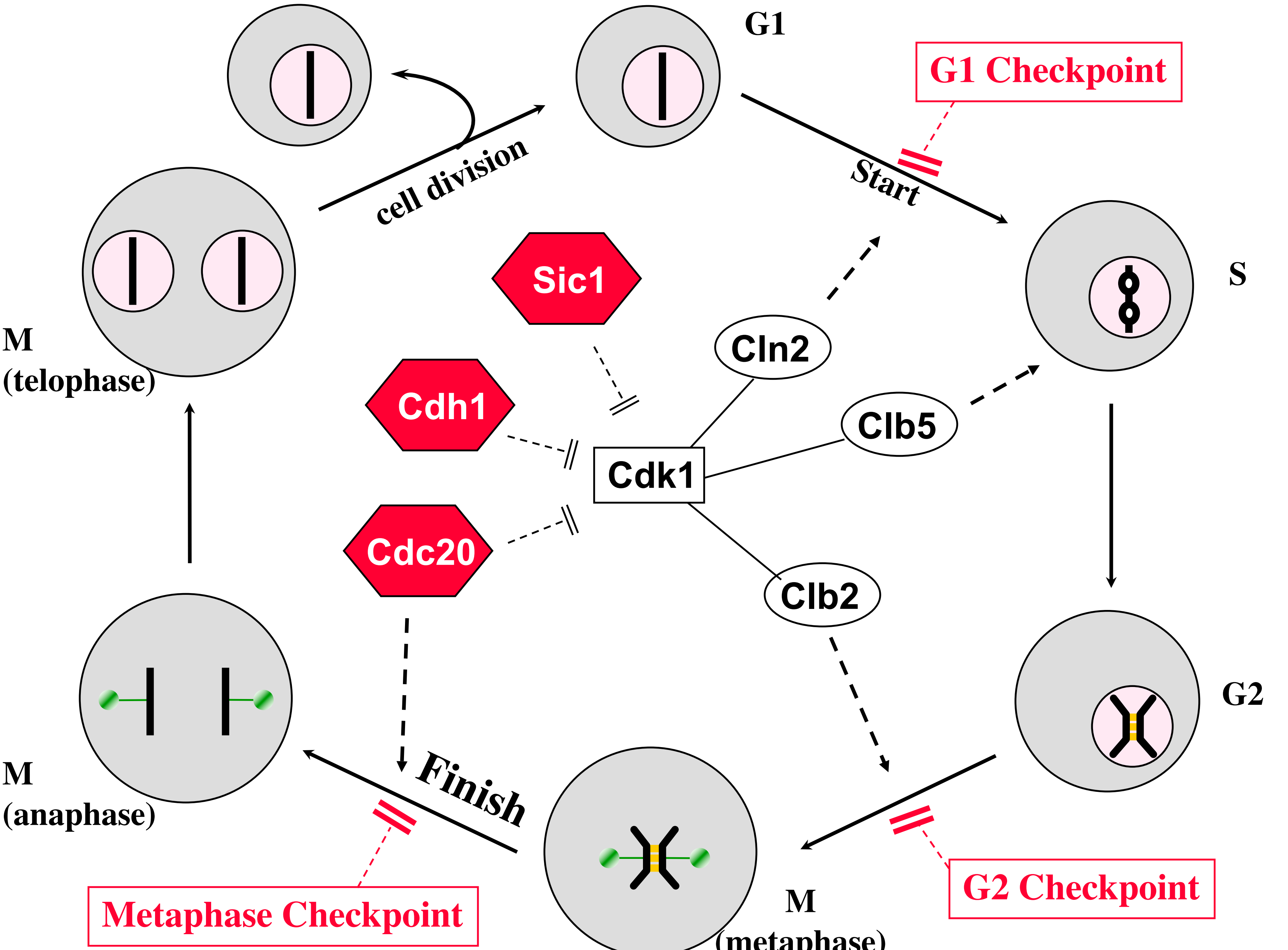
$$\nabla_i = \partial_i - D_{ij}^{-1}\tilde{F}_j = \partial_i + A_i$$

$$R_{ij} = \partial_i A_j - \partial_j A_i = [\nabla_i, \nabla_j]$$

$$J_{ss} = 0 \Rightarrow R_{ij} = 0$$

$$\partial_i (D_{jk}^{-1} v_k) - \partial_j (D_{ik}^{-1} v_k) = R_{ij}$$

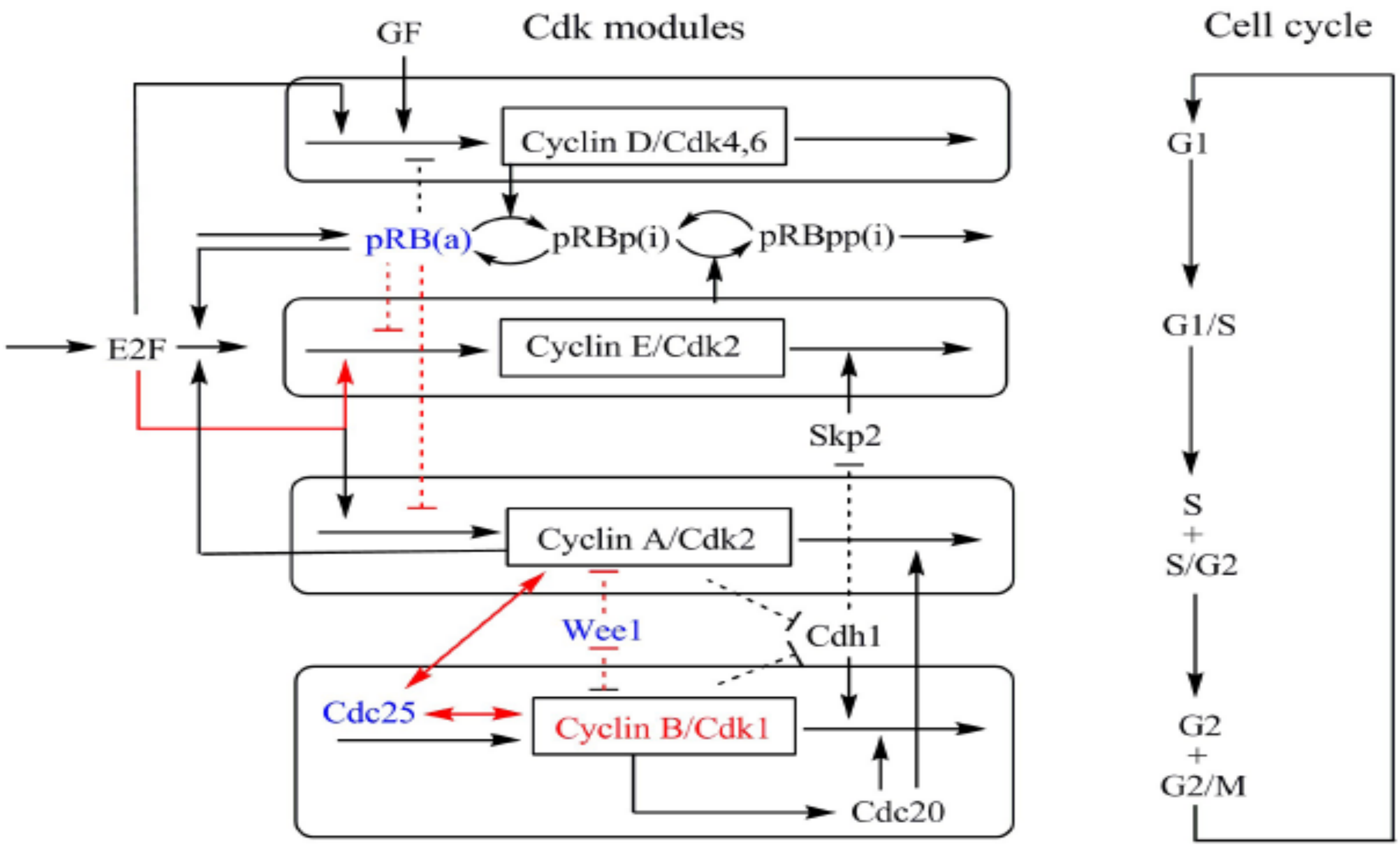
$$T\Delta s_m = -\int A_i dx_i = -\int D_{ij}^{-1} v_j^{ss} dx_i = -\int_{\Sigma} d\sigma_{ij} R_{ij}$$


G1
G1 Checkpoint
cell division
Start
S
M
(telophase)
Sic1
Cln2
Cdh1
Clb5
Cdk1
Cdc20
Clb2
G2
M
(anaphase)
Finish
M
(metaphase)
G2 Checkpoint
Metaphase Checkpoint

2. Applications of Landscape and Flux Theory

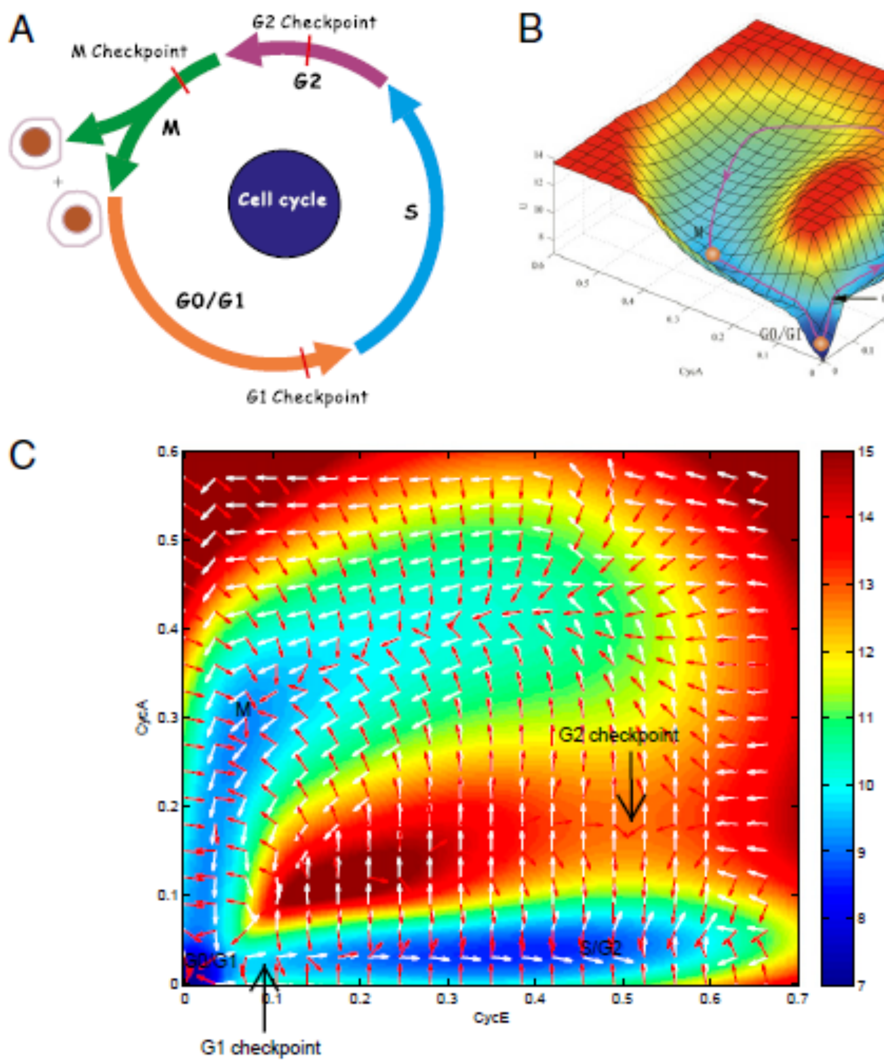
2.1. A Mammalian Cell Cycle Network

Gérard & Goldbeter, PNAS (2009)



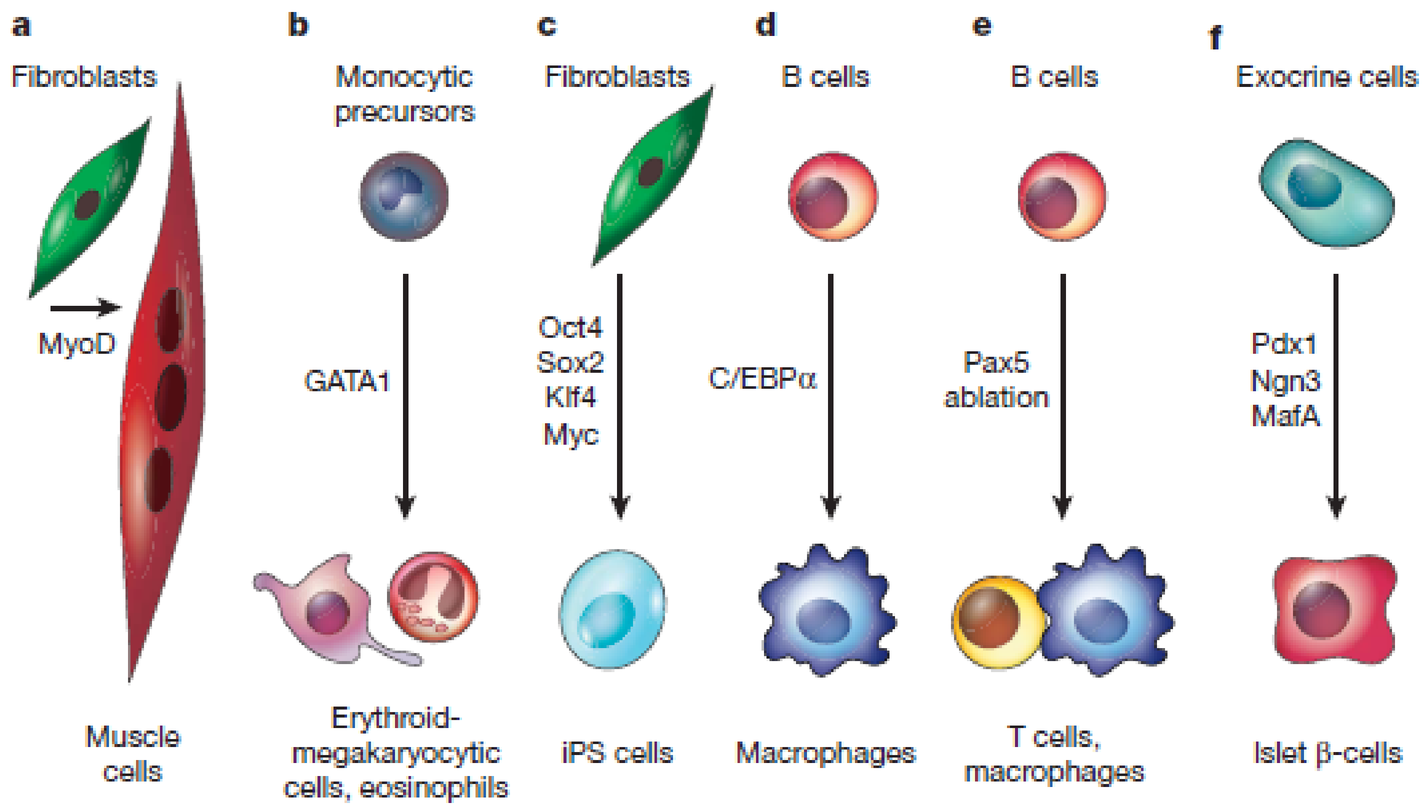
2.1. Quantified landscape & flux of mammalian cell cycle

C. Li, J. Wang, 2014, PNAS



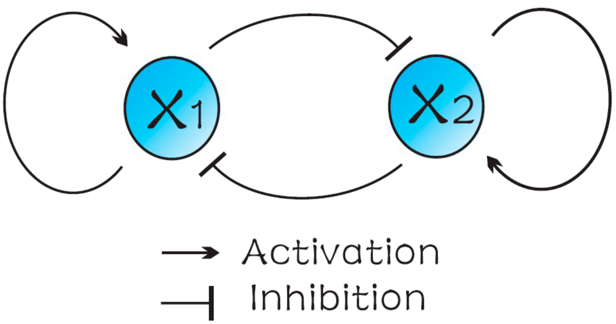
- (A) The four phases of cell cycle with the three checkpoints: G1, S, G2, and M phase.
- (B) The three phases (G1, S/G2, and M phase) and the two checkpoints (G1 checkpoint and S/G2 checkpoint) in our landscape view (in terms of gene CycE and CycA).
- (C) The 2D landscape, in which white arrows represent probabilistic flux, and red arrows represent the negative gradient of potential.
- (D) Speed of cell cycle and cancer
- (E) Origin of single cell life

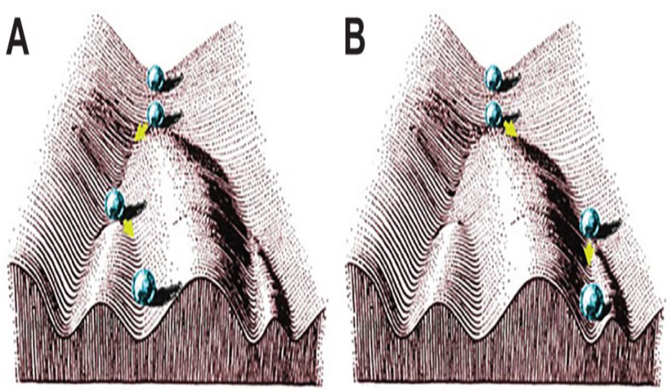
2.2. Differentiation & Tissue Engineering

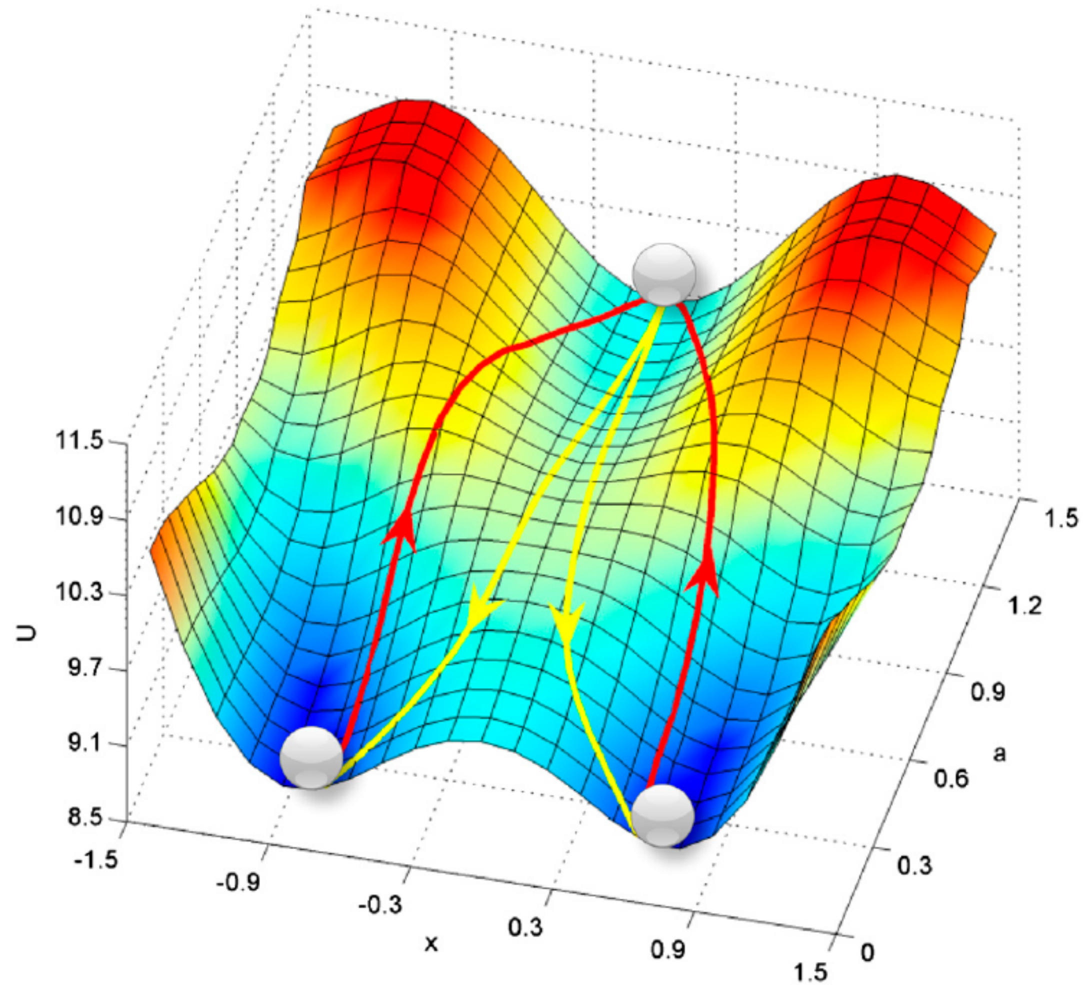


2.2. Quantifying Waddington Landscape & Paths of Differentiation

Wang, Zhang, Xu, Wang PNAS 2011, Xu, Zhang, Wang, Plos One 2014

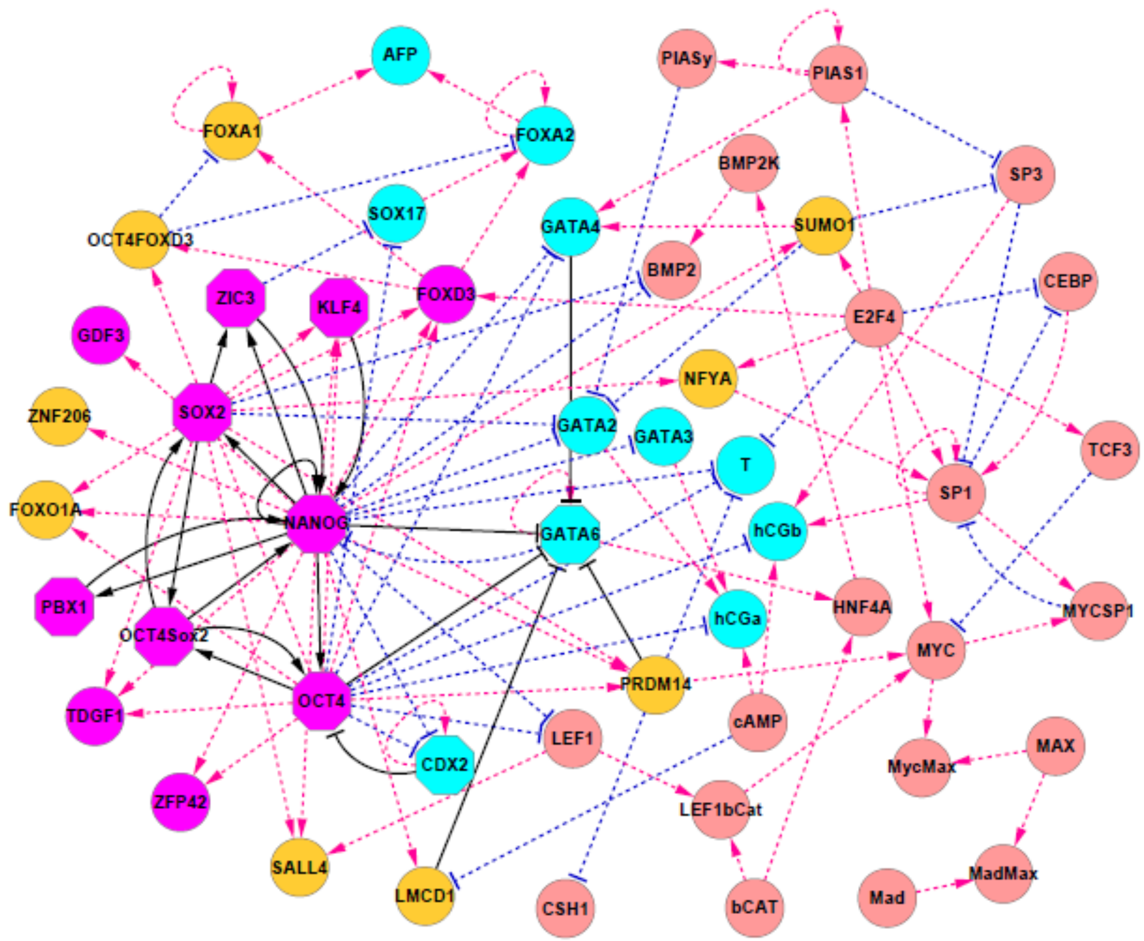






IV. Wiring Diagram of human embryonic stem cell differentiation and reprograming: Key Genes and Key Regulations

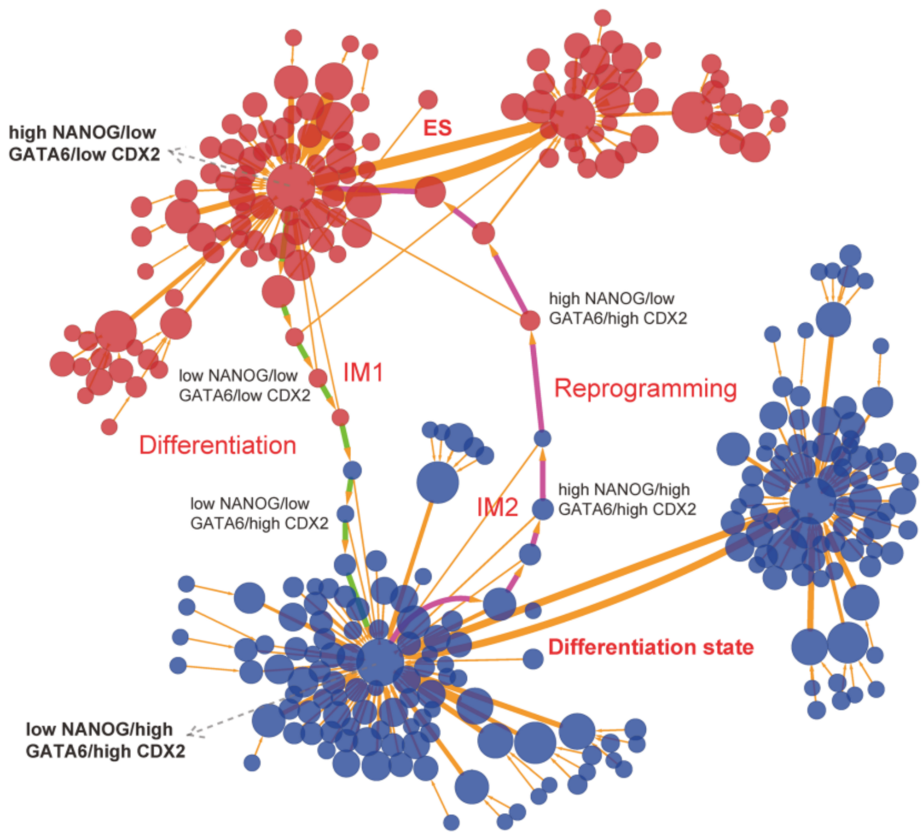
C. Li, J. Wang, Plos. Comp. Biol. 2013



The diagram for the stem cell developmental network including 52 gene nodes and their interactions. Arrows represent activation and perpendicular bars represent repression. The magenta node represent 11 marker genes for the pluripotent stem cell state, cyan nodes represent 11 marker genes for the differentiation state, and the yellow nodes represent genes activated by the stem cell marker genes. The solid black links represent the key links found by the global sensitivity analysis, and the octagon shape nodes represent key stem cell and differentiation markers found by global sensitivity analysis.

Differentiation and reprogramming process represented by 313 nodes (every node denotes a cell state, characterized by expression patterns of the 22 marker genes) and 329 edges (paths)

C. Li, J. Wang, Plos. Comp. Biol. 2013



- Red nodes represent states closer to stem cell states in terms of gene expression pattern, and blue nodes represent states closer to differentiation states. The green and magenta paths denote dominant kinetic paths from path integral separately for differentiation and reprogramming. The largest red node (high NANOG/low GATA6/low CDX2) represents most major ES state (stem cell state), and the largest blue node (low NANOG/high GATA6/high CDX2) represents most major differentiation state. IM1 represents a intermediate state (low NANOG/low GATA6/low CDX2), and IM2 represents another intermediate state (high NANOG/high GATA6/high CDX2).

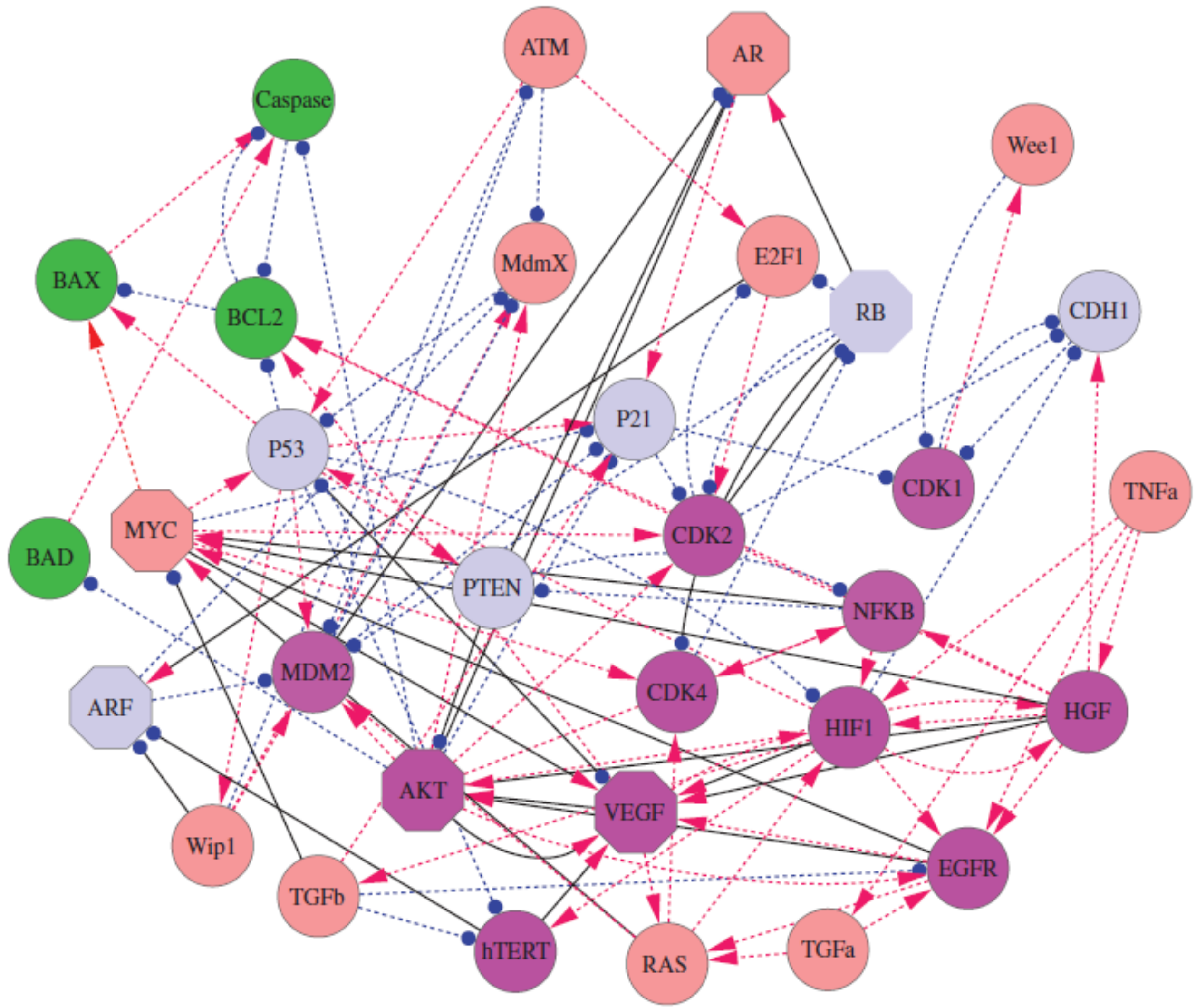
2.3. Cancer: Motivations

- Cancer conventionally thought as caused by **mutations**.
- More and more observations that contradict the paradigm of mutation-driven tumor-genesis. (Kauffman, Gatenby, et, al.)
- Cancer would be viewed as an **intrinsic state** determined by **selection** and a hidden default program, only released by a series of mutations.

- How to quantify the cancer and normal cell **states**?
- What is the mechanism of **switching** from normal to cancer states and from cancer back to normal states?
- How to come up with the potential recipes for cancer prevention and treatment from the network perspective?

Gene Regulatory Networks of Cancer

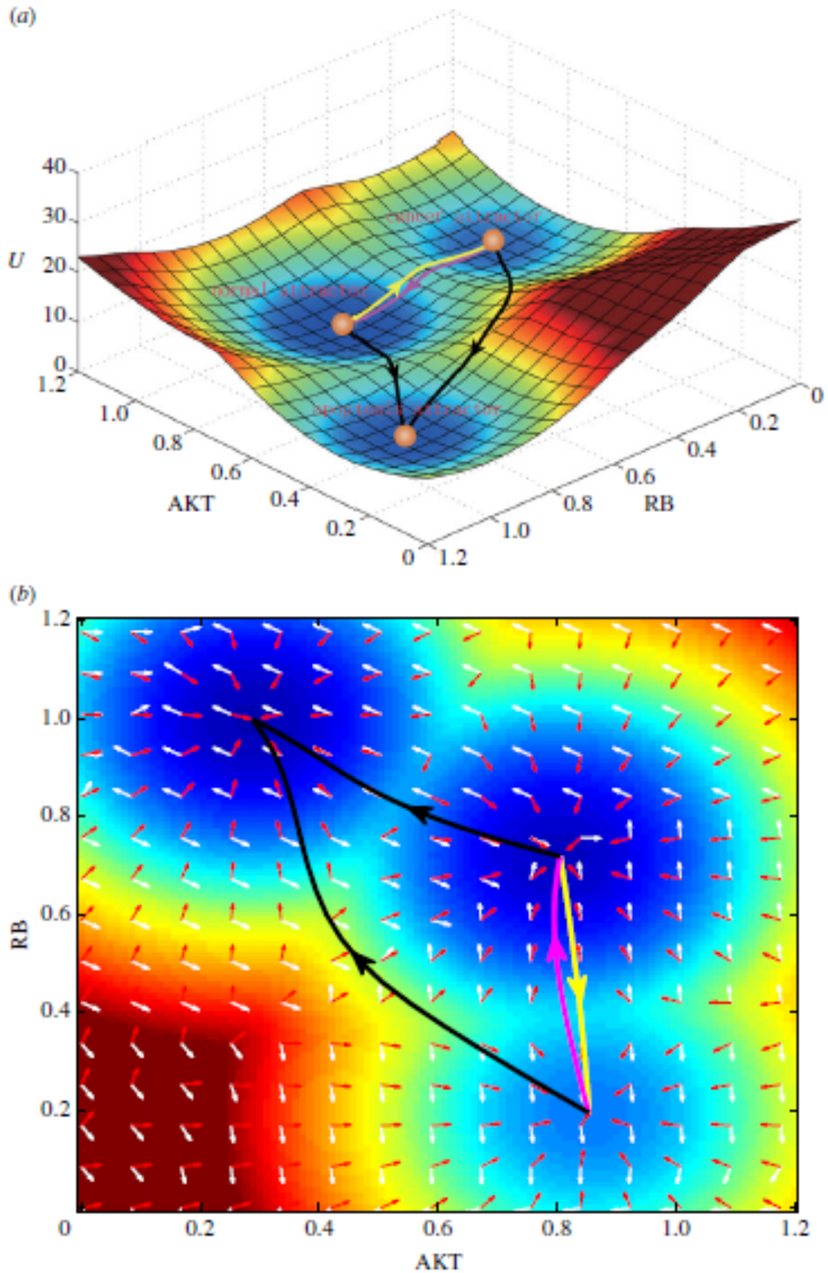
Li and Wang, J.Royal. Soc. Inter. 2014.



The diagram for the cancer network including 32 nodes (genes) and 111 edges (66 activation interactions and 45 repression interactions). Red arrows represent activation and blue filled circles represent repression. The network includes mainly three kinds of marker genes: apoptosis (green nodes), cancer marker genes (magenta nodes) and tumour repressor genes (light blue nodes). The cancer marker genes include EGFR for proliferative signal, VEGF for angiogenesis, HGF for metastasis, hTERT for unlimited replication, HIF1 for glycolysis, CDK2 and CDk4 for evading growth suppressors.

Quantified Cancer Landscape

Li and Wang, J.Royal. Soc. Inter. 2014.

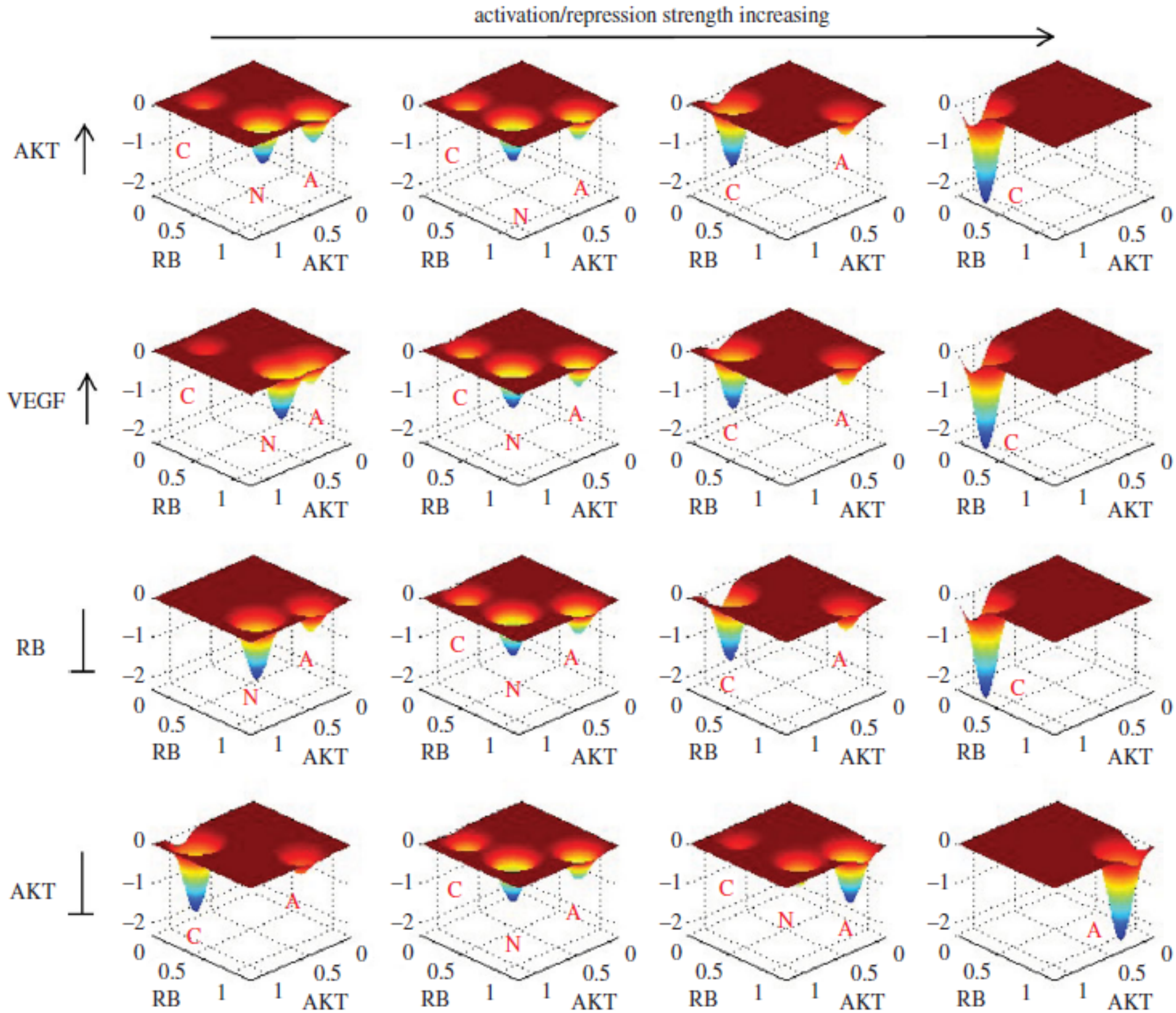


- (a) The three-dimensional landscape and dominant kinetic paths. The yellow path represents the path from normal state attractor to cancer state attractor, and the magenta path represents the path from cancer state attractor to normal state attractor. Black paths represent the apoptosis paths for normal and cancer states.

- (b) The corresponding two-dimensional landscape of cancer network. Red arrows represent the negative gradient of potential energy and white arrows represent the probabilistic flux.

Landscape changes when some key regulation strengths change

Li and Wang, J.Royal. Soc. Inter. 2014.



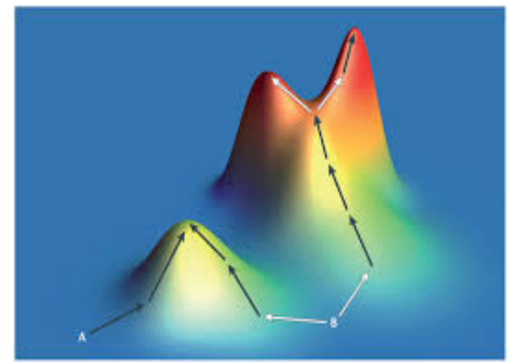
The four rows separately correspond to the change of four parameters. As labelled, the first row represents activation strength from VEGF to AKT, the second row represents the activation strength from AKT to VEGF, the third row represents the repression strength from CDK2 to RB and the fourth row represents the repression strength from PTEN to AKT. The labels C, N and A represent cancer attractor, normal attractor and apoptosis attractor, respectively.

General Evolution Dynamics

Zhang, Xu, Zhang, Wang, Wang, JCP(2012)

- Wright's adaptive evolution dynamics is determined by

Potential Landscape Gradient



Nature Reviews | Genetics

- General Evolution Dynamics is determined by

Potential Landscape Gradient + Curl Flux

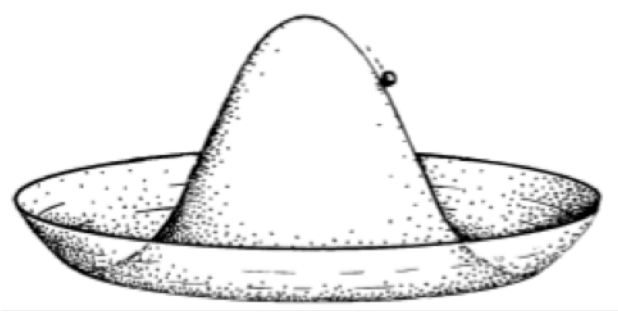
Red Queen Hypothesis Explained

Zhang, Xu, Zhang, Wang, Wang, JCP(2012)

- Red Queen hypothesis is the biological expression of the intrinsic flux:

  the system lies in the optimum where the gradient of potential is zero, but the intrinsic flux drives the endless evolution.

- As Van Valen himself remarked, this cannot be explained by traditional evolutionary theory, since the flux is the missing part of the traditional evolutionary theory.

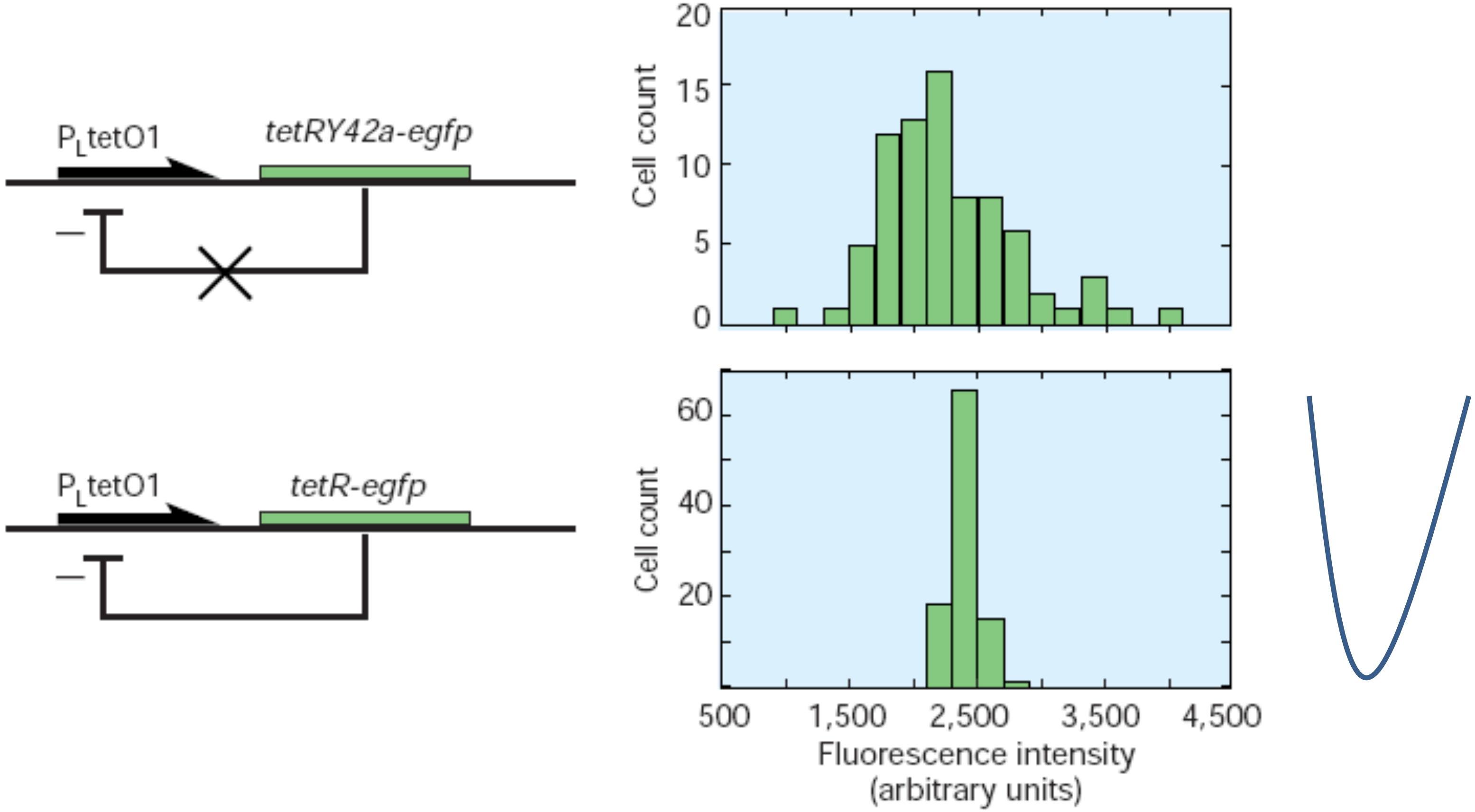


Landscape and Flux Framework for Nonequilibrium Systems

J. Wang, Adv. Phys. (2015), Fang, Kruse, Lu, Wang, to appear Rev. Mod. Phys. (2019)

- Biochemical Oscillations (J. Wang, L. Xu, E. K. Wang, PNAS 2008)
- Cell Cycle (C. Li, J. Wang, PNAS, 2014)
- Signaling (S. Lapidus, J. Wang, PNAS, 2008)
- Stem Cell Differentiation & Reprograming (K. Zhang, L. Xu, J. Wang, PNAS, 2011)
- Metabolic Networks (W.B. Li, J. Wang, 2019)
- Immune Networks (W.B. Li, J. Wang, J. Royal Soc. Interf. 2017)
- Cancer Networks (C. Li, J. Wang, J. Royal Soc. Interf, 2014)
- Ageing (L. Zhao, J. Wang, J. Royal Soc. Interf, 2016)
- Neural Networks (H. Yan, L. Zhao, W. Han, L. Hu, J. Wang, PNAS 2013)
- Evolution (F. Zhang, L. Xu, K. Zhang, J. Wang, JCP , 2012)
- Ecology (L. Xu, F. Zhang, K. Zhang, J. Wang, Plos One 2014).
- Game Theory (L. Xu, J. Wang, J. Theor. Biol. 2018)
- Sociology (C.L. Miao, J. Wang, 2019)
- Economy (K. Zhang, J. Wang, Physica 2018)
- Chaos (C. Li, J. Wang, JCP 2012)
- Turbulence (W. Wu, F. Zhang, J. Wang, Ann. Phys. 2018)
- Quantum Systems (Z. Zhang, J. Wang, JCP, 2014, Z. Wang, Wei Wu, J. Wang, PRA, 2018)
- Cosmology (H. Wang, J. Wang, 2019)

3. 1. Experimental Quantifications of the Landscape: Self Repressor

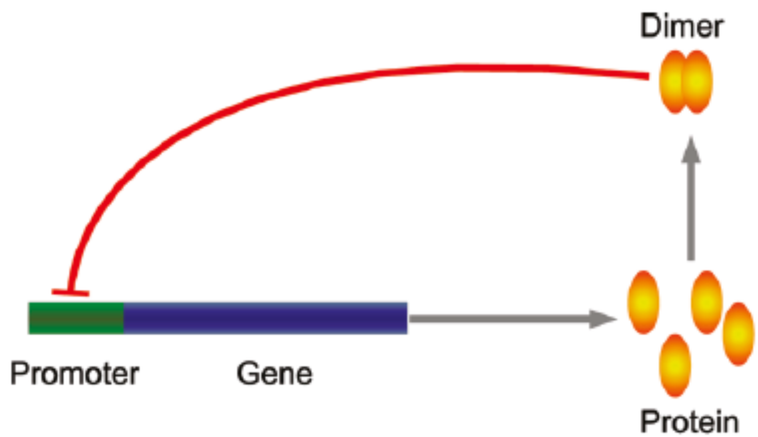


Becskei, A. & Serrano, L. **Engineering stability in gene networks by autoregulation**. *Nature* 405,590–593 (2000)

Emergence of two cell fates & their switching for self repressor

Hornos, Schultz, Innocentini, Wang, Walczak, Onuchic, Wolynes, PRE(2005);

Feng, Han, Wang, JPCB (2010)



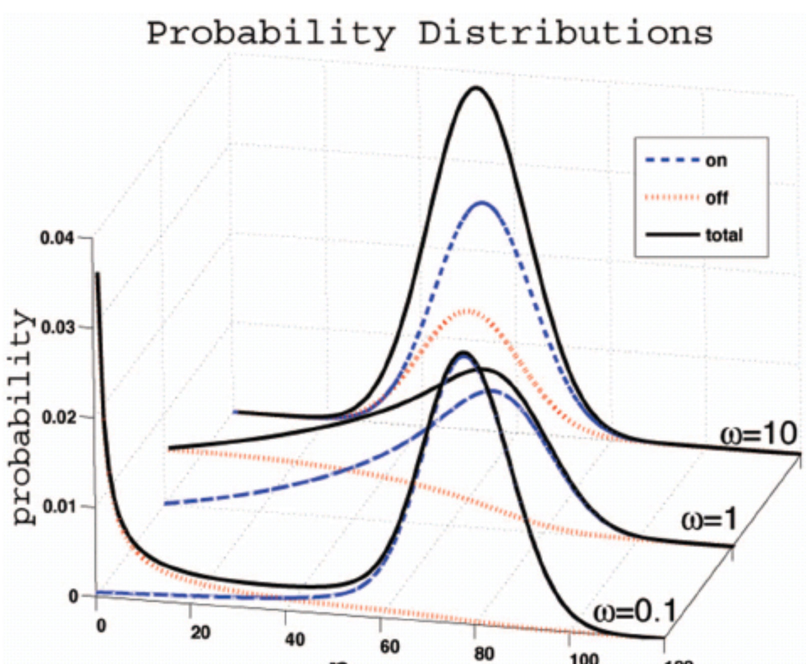
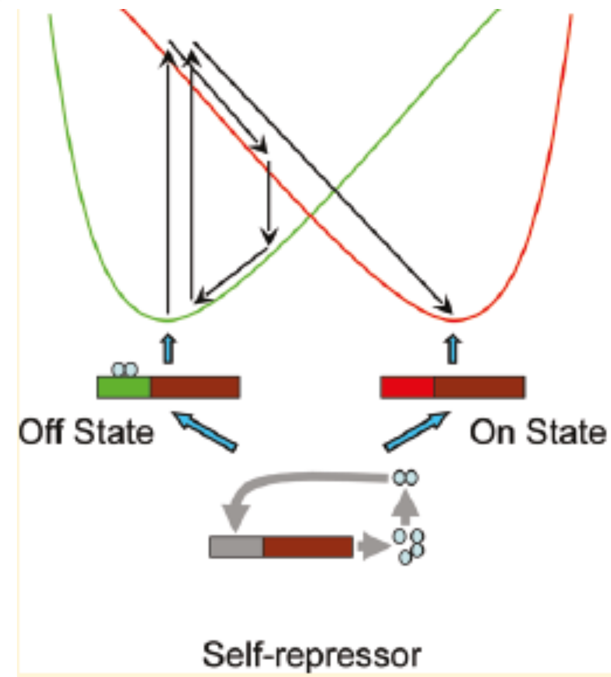
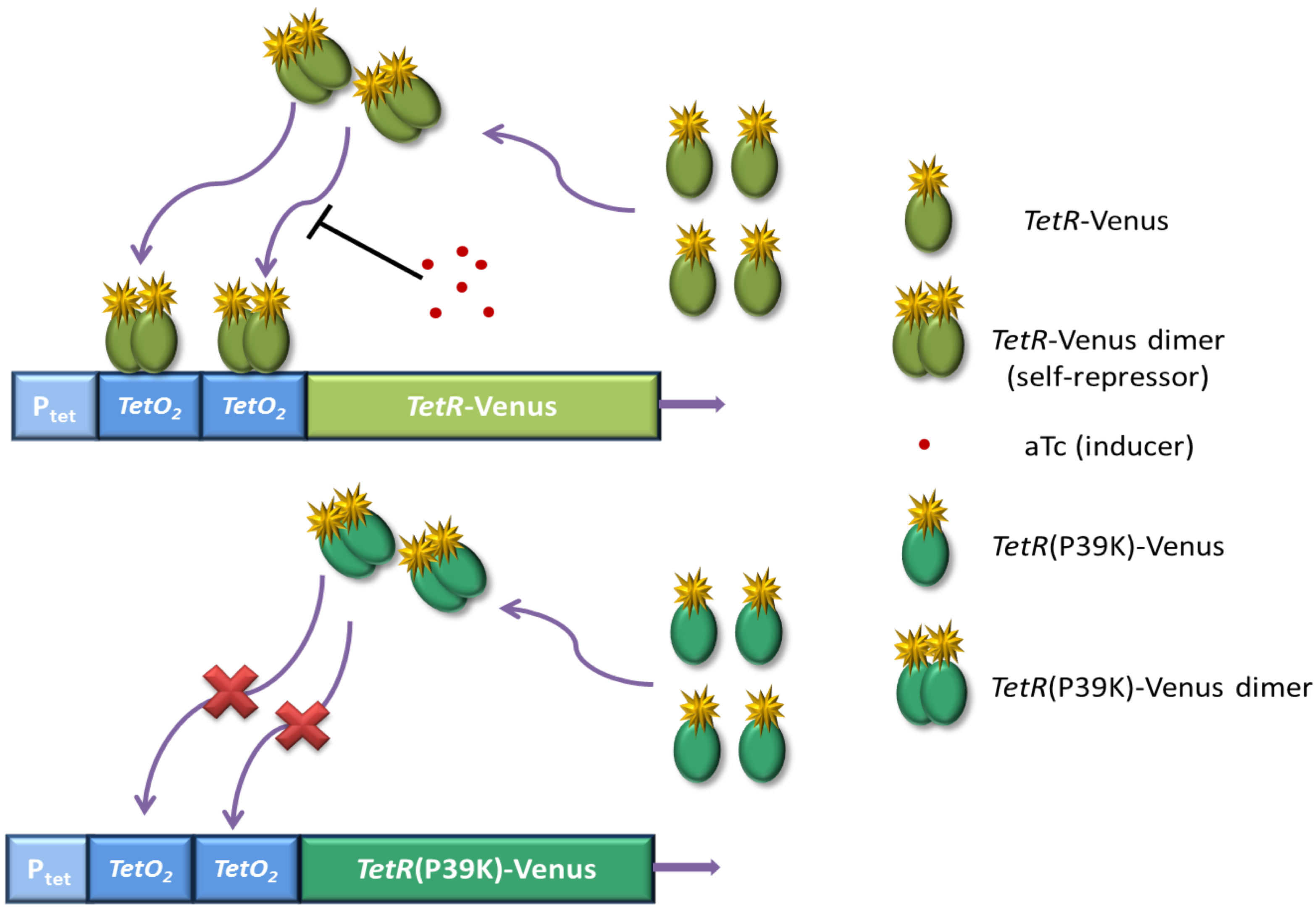


FIG. 1. (Color) The probabilities of the gene expression as a function of the number of proteins, n, for the on state, the off state, and the total. There are two peaks for small ω, but they converge to a single peak in the adiabatic regime of large ω. $X^{eq}=100$ and $X^{ad}=40$.



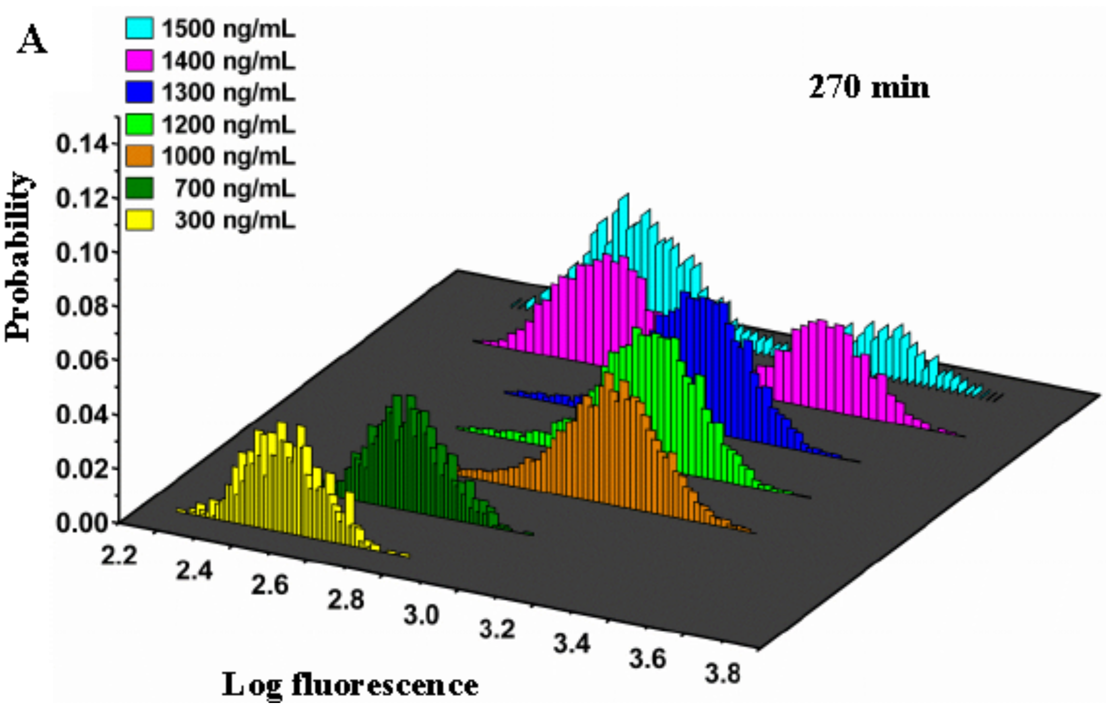
Schematic representation of self-repressing and non self-repressing gene circuit model

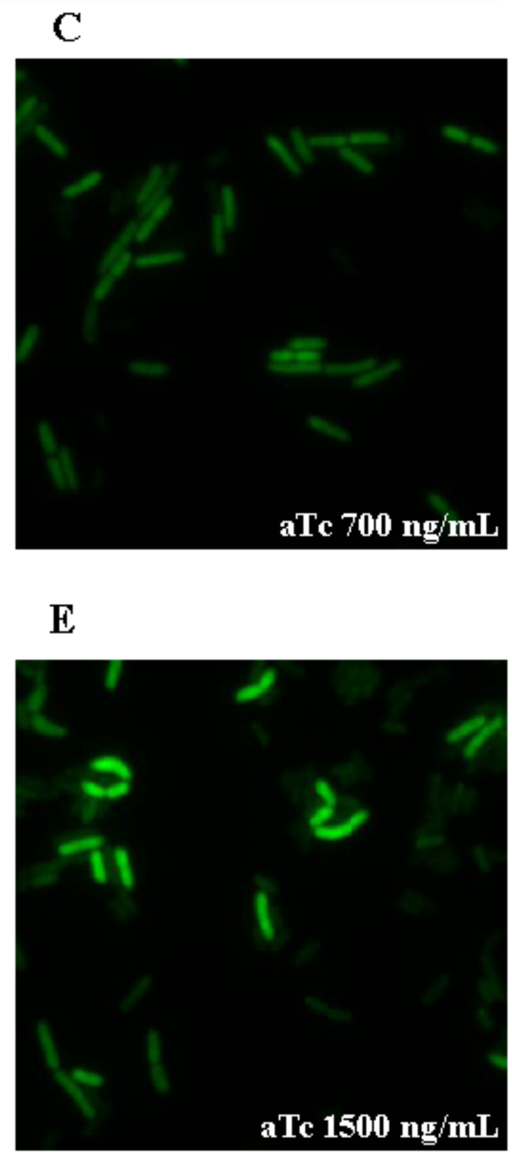
Jiang, Tian, Fang, Zhang, Liu, Dong, Wang, BMC Biology, 2019



The emergence of two cell fate expression distributions of the self-repressor gene circuit (MG::PR-8T**) at different aTc concentrations observed under a microscope**

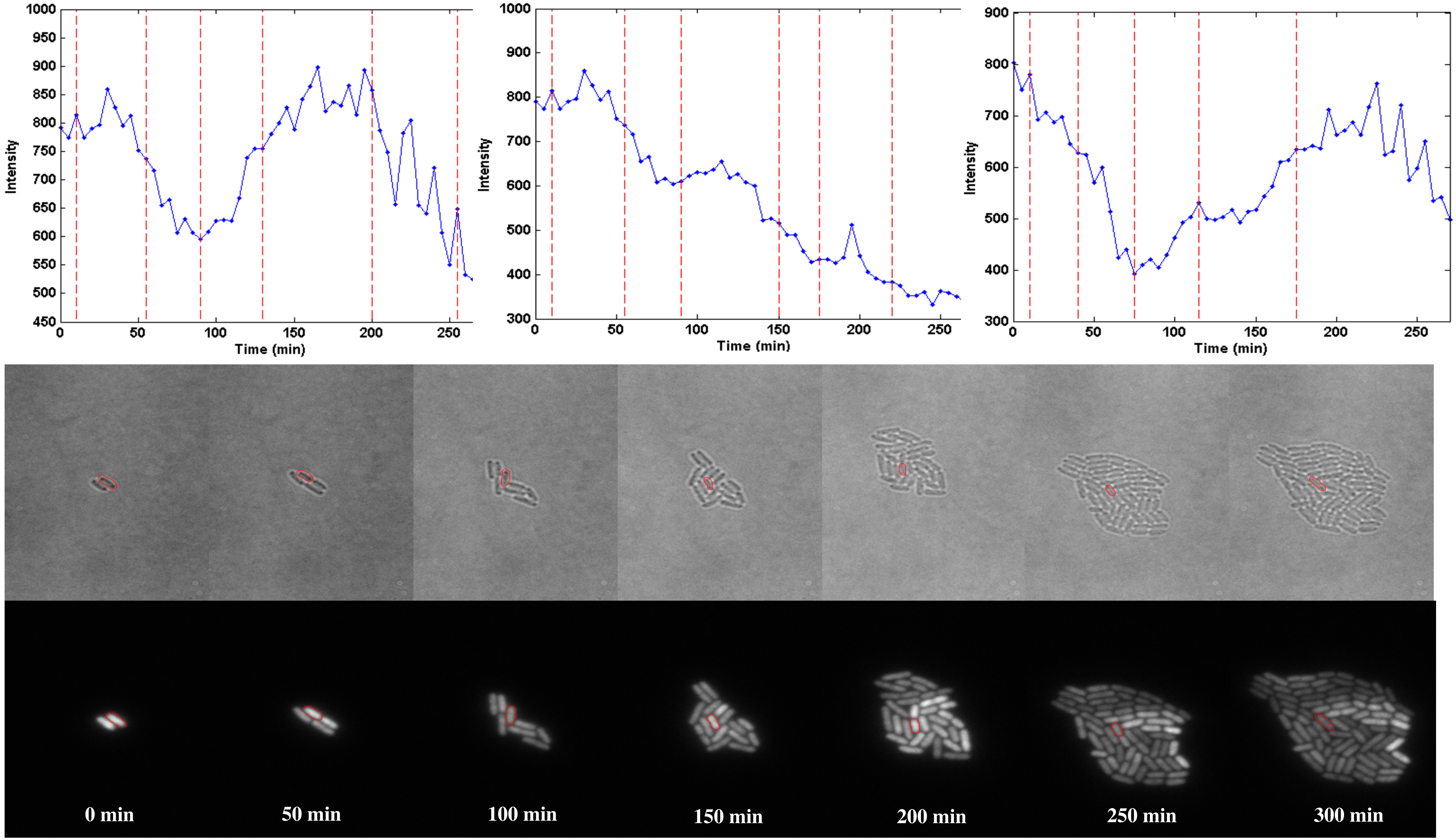
Jiang, Tian, Fang, Zhang, Liu, Dong, Wang, BMC Biology, 2019





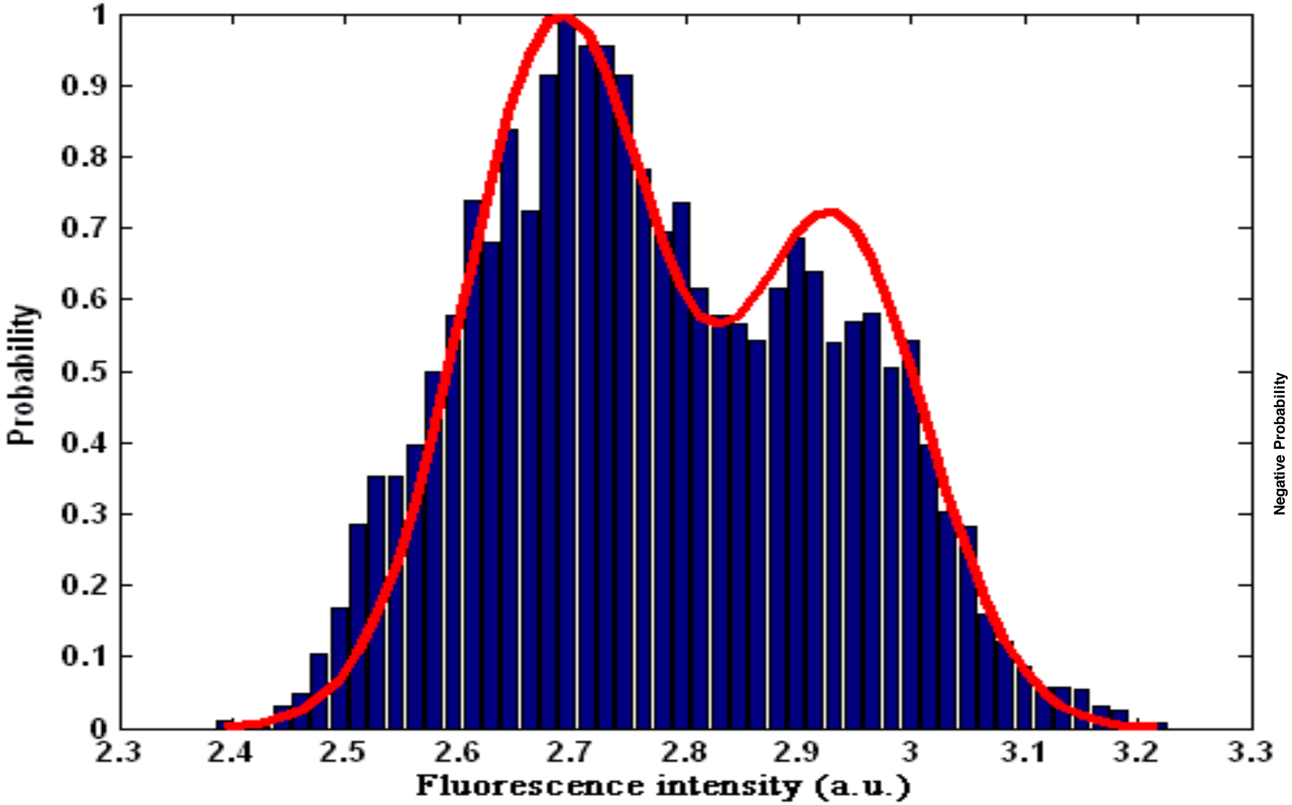
The representative trajectories collected at 1500 ng/mL of aTc

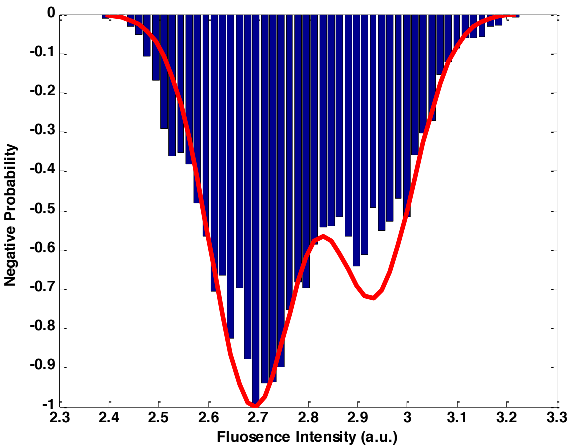
Jiang, Tian, Fang, Zhang, Liu, Dong, Wang, BMC Biology, 2019



The mean fluorescence intensity distribution of dynamics trajectories
High->low (High Expression State Residence Time): 92 min,
Low->high (Low Expression State Residence Time): 151 min

Jiang, Tian, Fang, Zhang, Liu, Dong, Wang, BMC Biology 2019





Conclusions and discussions

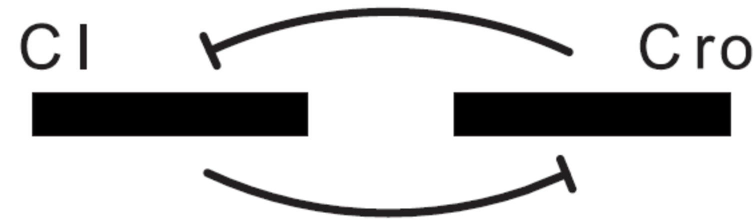
- We explore the stochastic dynamics of self-regulative genes
- Fast (slow) binding/unbinding relative to the synthesis/degradation of proteins, the self-regulators can exhibit one or two peak distributions, namely one or two cell fates.
- Even with the same architecture (topology of wiring), networks can have quite different phenotypes.
- Experimental verifications of the single peak to two peak transitions, namely cell fate switching/decision making. Epigenetics in a controllable way!
- Two sources of noise, molecular number and slow regulations.

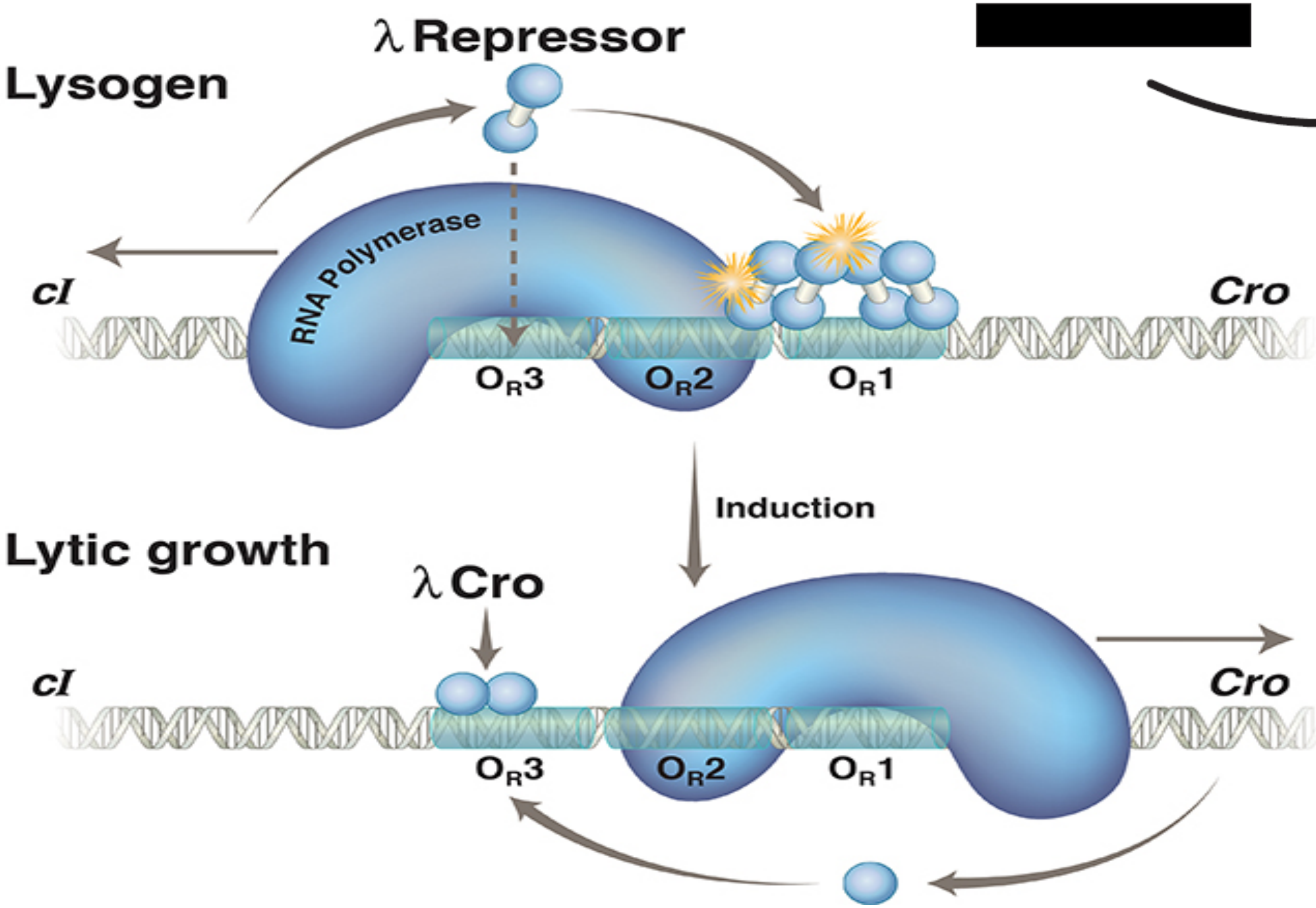
H. Feng, B. Han and J. Wang, J. Phys. Chem. B. 115, 1254 (2011), Jiang, Tian, Fang, Zhang, Liu, Dong, Wang, BMC Biology (2019)

3.1. Bacteria Lambda Phage

Hydrogen Atom in Molecular Biology

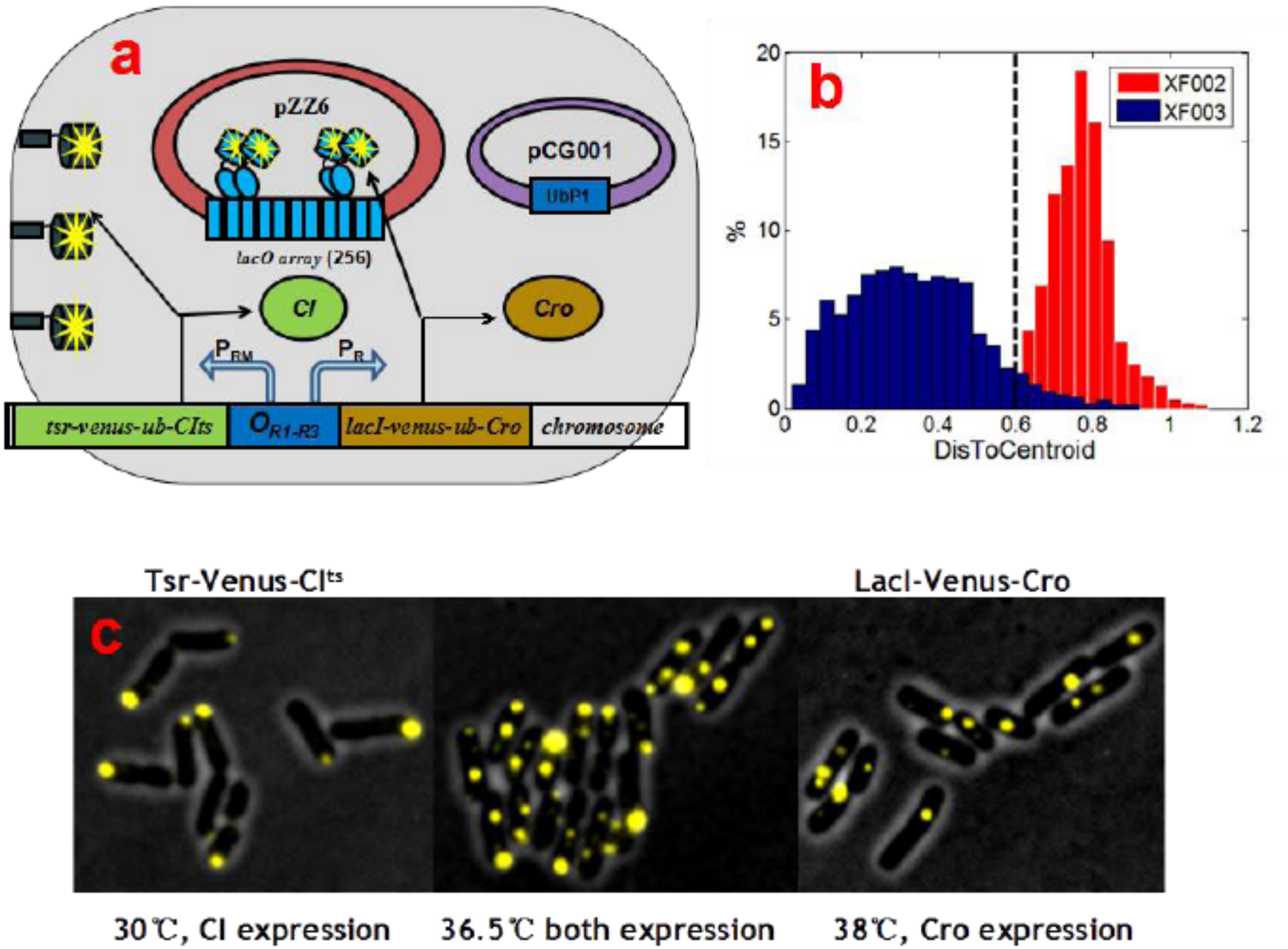
Ptashne (1986), Little (1984,2010), Zeng, Zong, Golding(2010,2010)





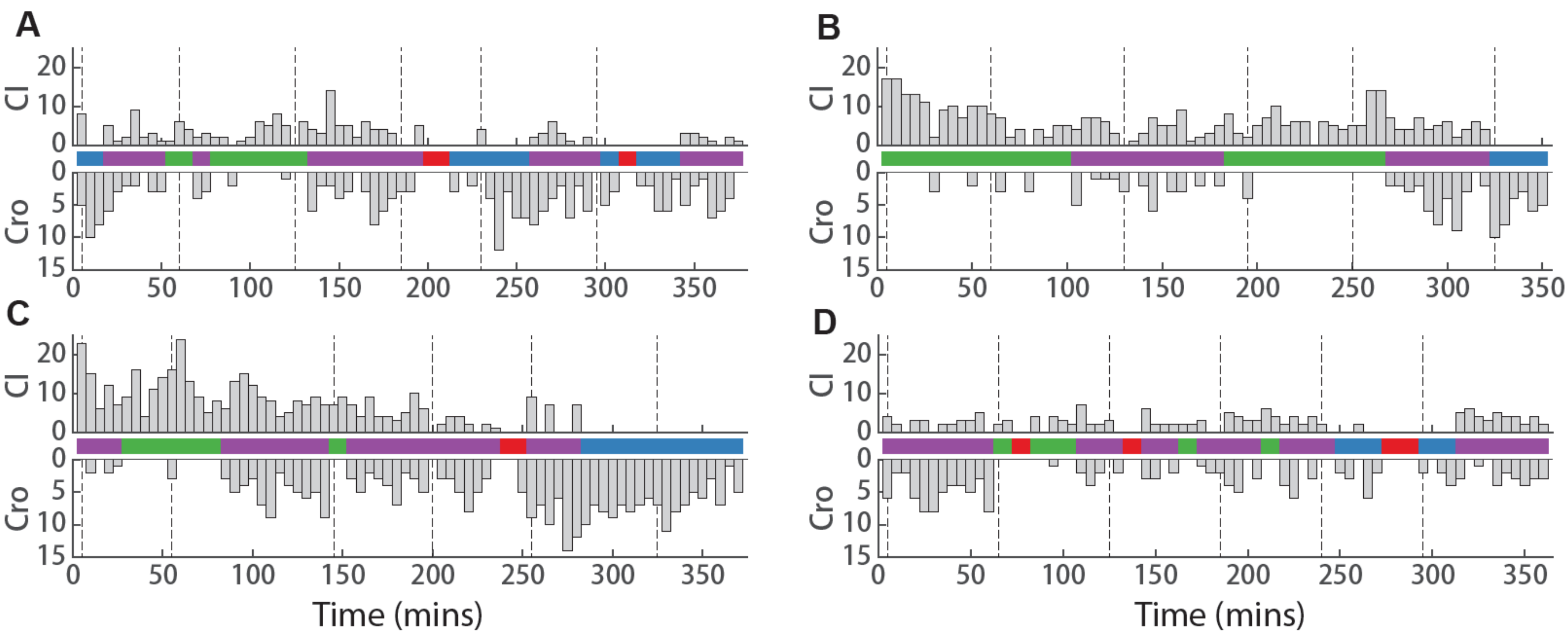
Localization Method

Fang, Liu, Hensel, Wang, Xiao Nature Communications (2018)



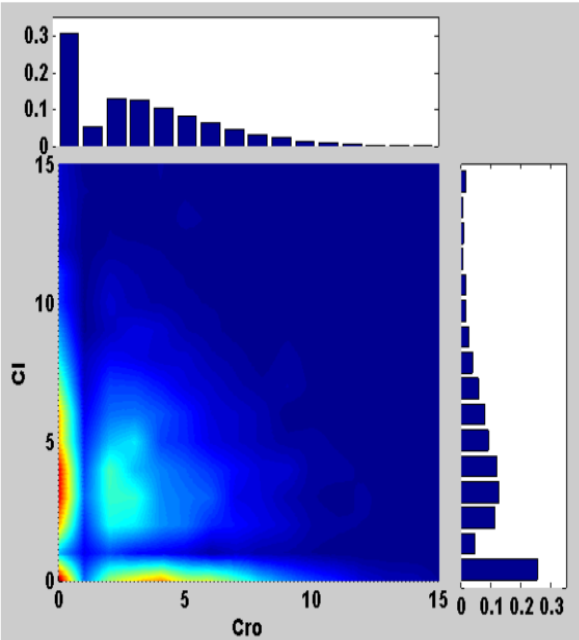
CI or Cro, CI and Cro and CI-Cro Switching at 36.5 °C

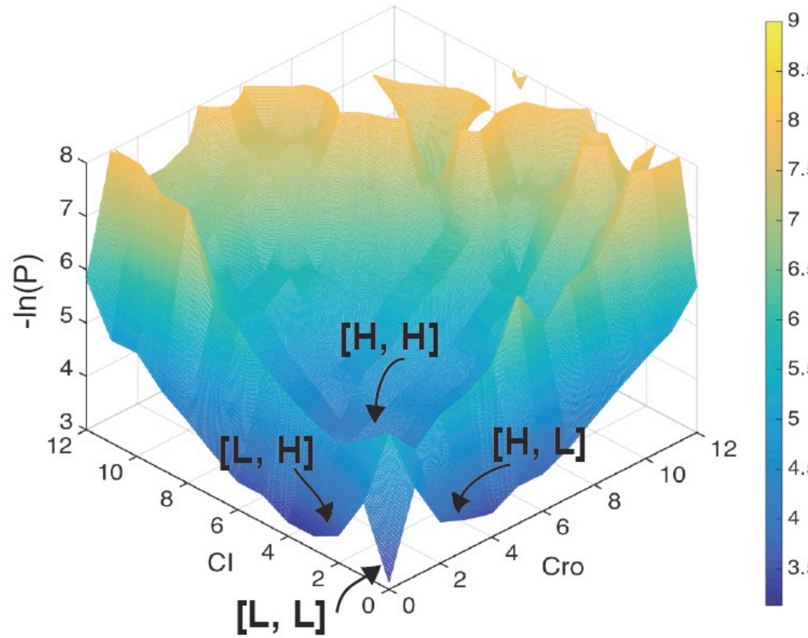
Fang, Liu, Hensel, Wang, Xiao Nature Communications (2018)

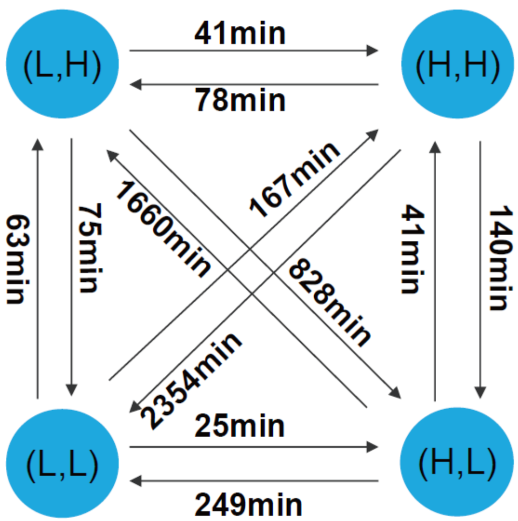


Landscape of CI and Cro & Switching Times among Cell Fates at 36.5 °C

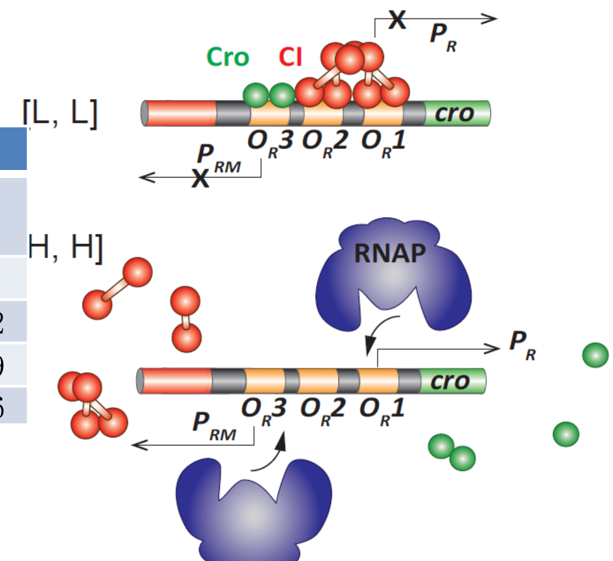
Fang, Liu, Hensel, Wang, Xiao Nature Communications (2018)







		dwell time		
state	[cro,cI]	min	se	n
1	[0, 0]	17	2	41
2	[1, 0]	36	3	162
3	[0, 1]	27	1	269
4	[1, 1]	47	3	396



Lambda Phage Cell Fate Summary

Fang, Liu, Hensel, Wang, Xiao Nature Communications (2018)

- Quantified Landscapes of Cell Fates: LH, HL, HH, LL.
- Quantified the Cell Fate Switching Kinetics among LH, HL, HH and LL
- Quantified the Residence Times of LH, HL, HH and LL and therefore the Associated Stabilities
- Direct switching between HL and LH is unlikely while their switching most likely through HH.
- Genetic & Epigenetic Control for Cell Fates

3.2. Enzyme Michalis-Menton Kinetics

Michaelis, Menten(1913); Lu and Xie (1998); Rigler et al. (1999, 2000); Xie, et al. (2006); Min,Gopich, Xie,Szabo et al. (2006) ; Xie (2013); Qian (2002); Qian(2008); Cao (2011)

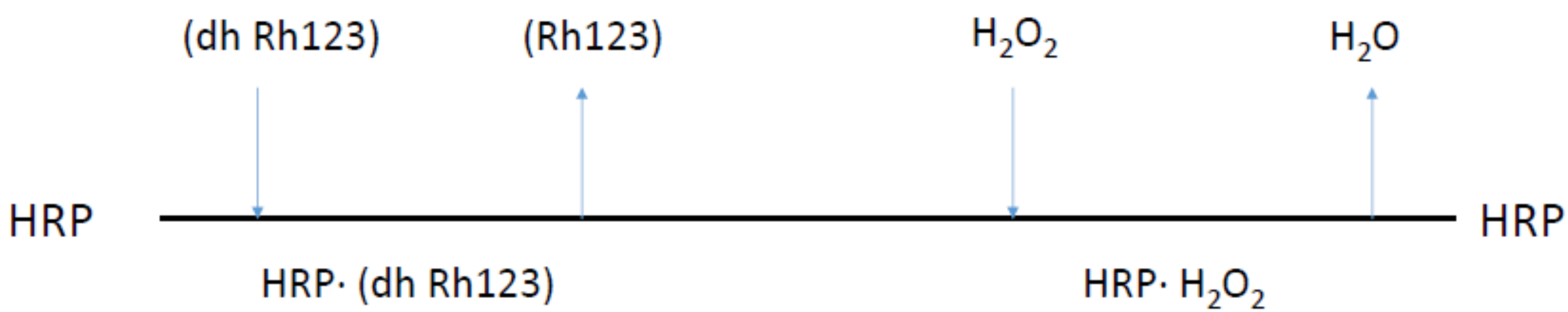
$$E + S \underset{k_r}{\overset{k_f}{\rightleftharpoons}} ES \xrightarrow{k_{cat}} E + P$$

$$\frac{1}{V} = \frac{1}{dP/dt} = \frac{1}{V_{Max}} + \frac{K_M}{V_{Max}} \frac{1}{[S]}$$

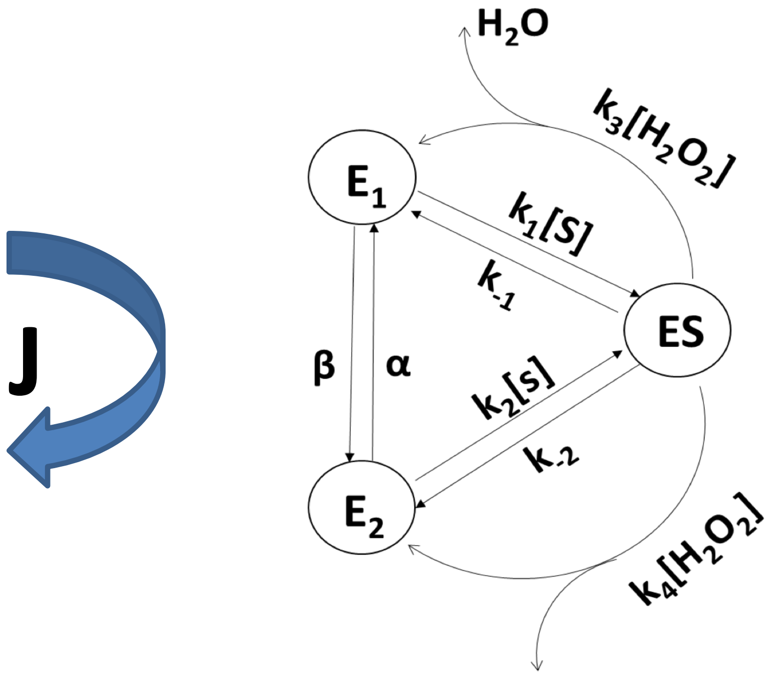
Enzyme Dynamics under Conformational Changes

Rigler et al. (1999, 2000), Q. Liu and J. Wang (2019) PNAS， accepted

$$\text{dihydrorhodamine 123(dh Rh123)} + H_2O_2 \xrightarrow{\text{HRP}} \text{rhodamine 123} + H_2O$$



Single Molecule Enzyme Kinetic Scheme under Different Conformations



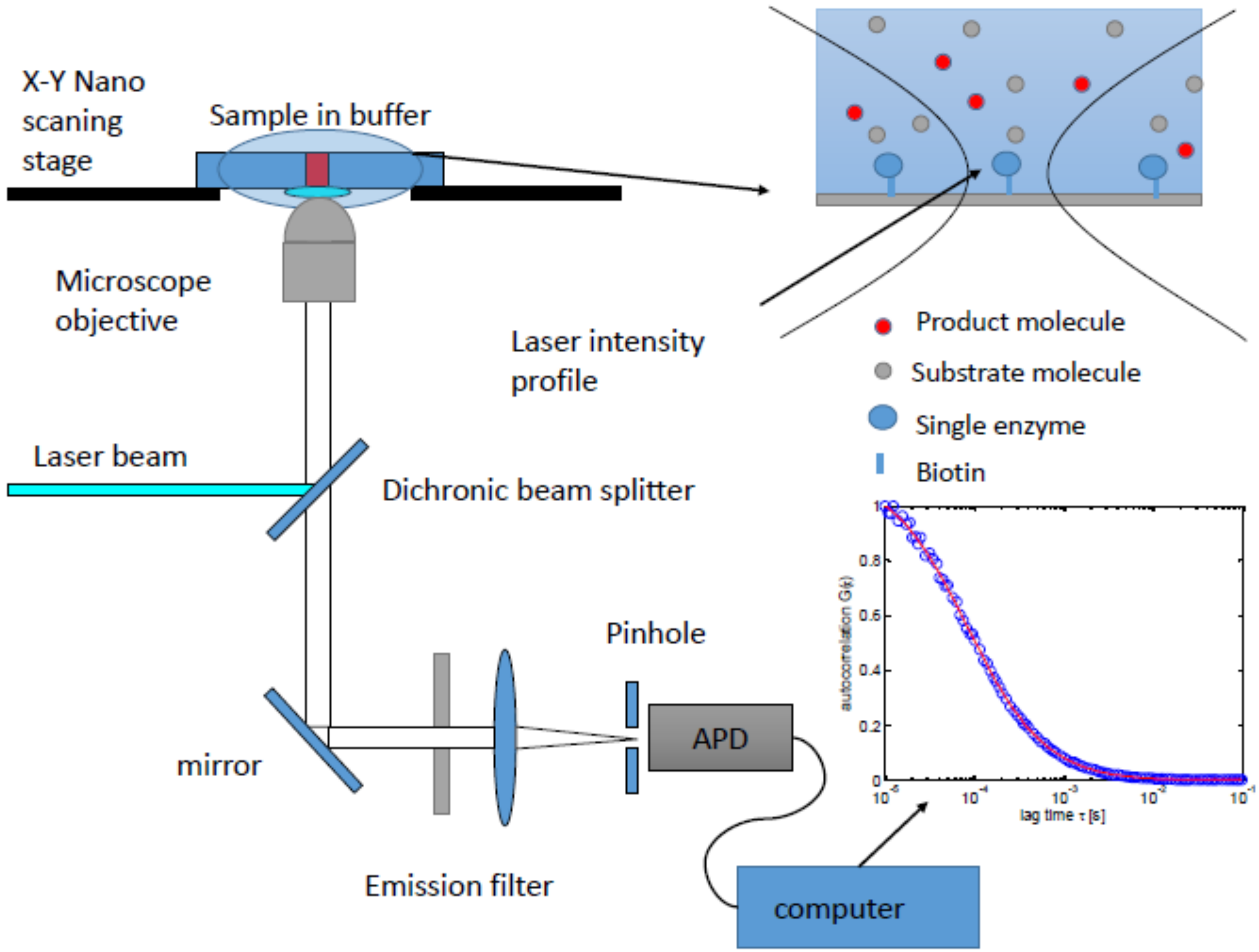
E_1--------HRP
E_2--------HRP
ES---------HRP· (dh Rh123)
S--------- dh Rh123

$$If \quad \frac{\alpha}{\beta}=\frac{k_{-1}k_2+k_2k_3[H_2O_2]}{k_{-2}k_1+k_1k_4[H_2O_2]}; \quad J=0; \quad Detailed \quad Balance \quad \frac{1}{V}=C_0+\frac{C_1}{[S]}$$

$$If \quad \frac{\alpha}{\beta}\neq\frac{k_{-1}k_2+k_2k_3[H_2O_2]}{k_{-2}k_1+k_1k_4[H_2O_2]}; \quad J\neq 0; \quad Detailed \quad Balance \quad Broken \quad \frac{1}{V}=C_0+\frac{C_1}{[S]}+\frac{C_2}{[S]+\lambda}$$

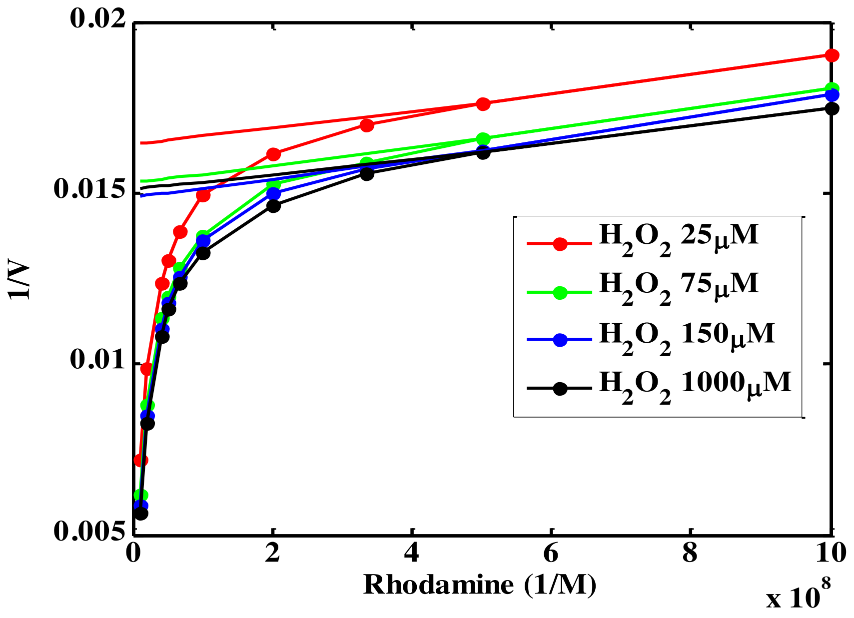
Single Molecule Measurement

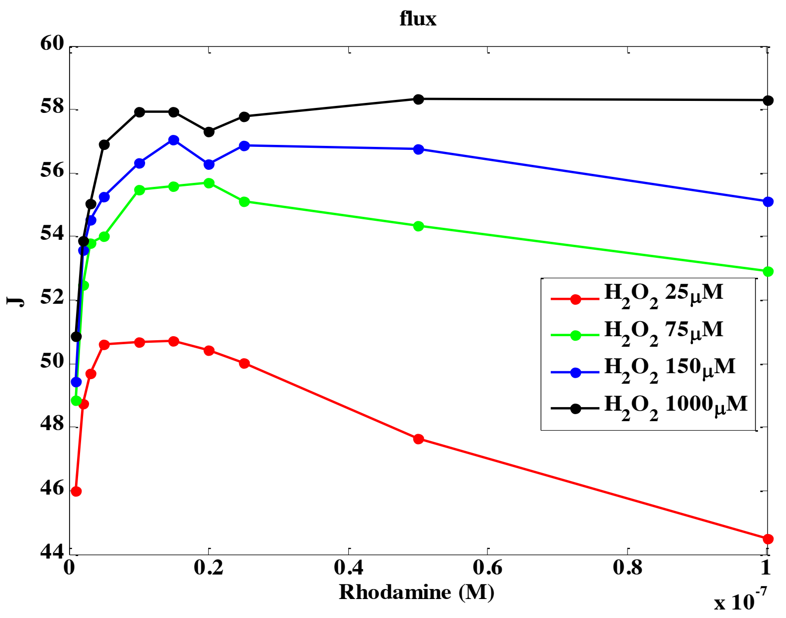
Q. Liu, J. Wang (2019) PNAS， accepted



Left: Non-Straight Line: Non Michalis-Menton Enzyme Kinetics
Right: The values of Flux versus substrate concentrations

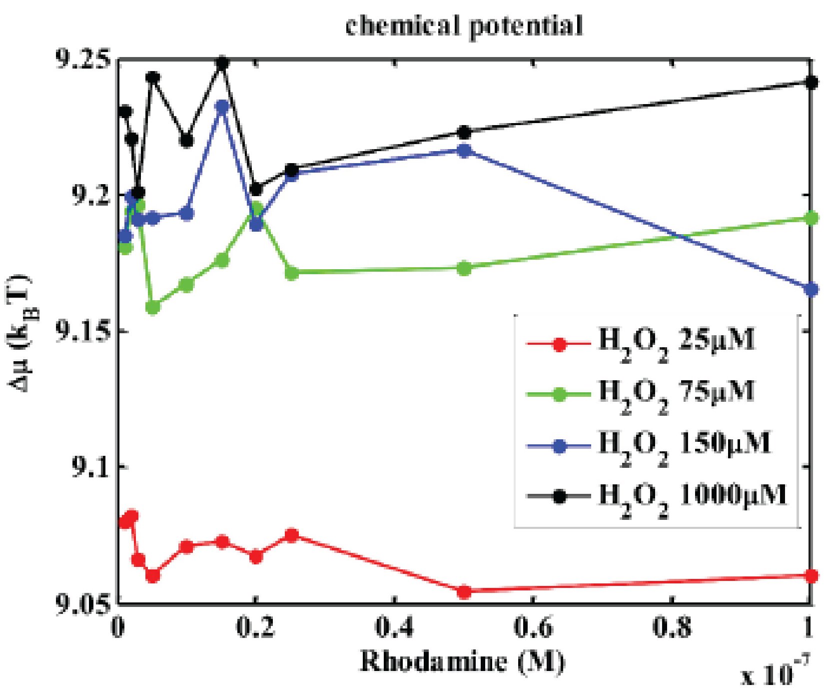
Q. Liu, J. Wang (2019) PNAS, Accepted

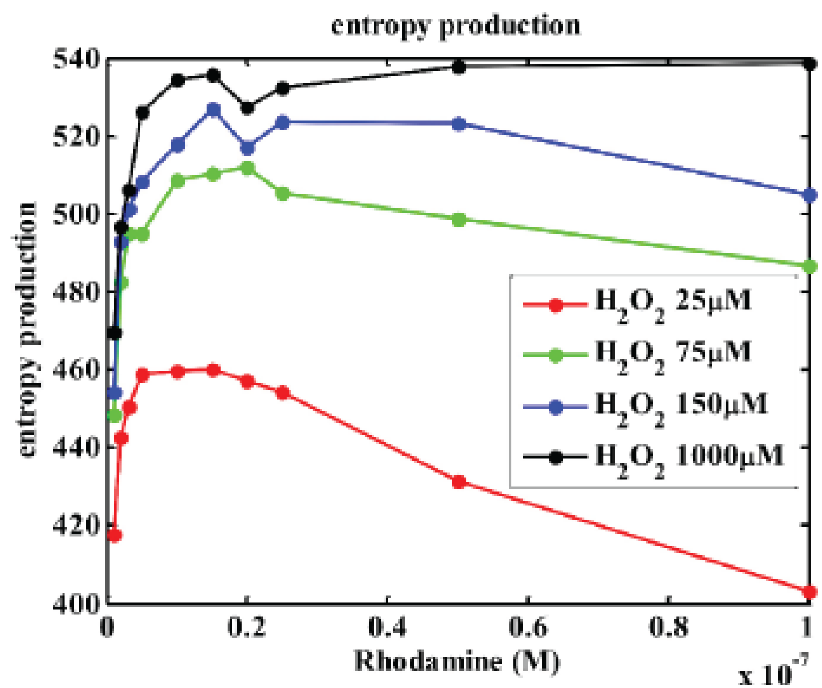




Left: Chemical Potential versus substrate concentrations
Right: Entropy Production versus substrate concentrations

Q. Liu, J. Wang (2019) PNAS， accepted





Summary of Experimental Flux Quantification

Q. Liu, J. Wang (2019) PNAS，accepted

- Quantifying the Non Michalis-Menton Enzyme Kinetics
- Identifying the Origin of Non Michalis-Menton Enzyme Kinetics as the Detailed Balance Breaking.
- Quantified the Flux as the Degree of Detailed Balance Breaking
- Quantified the Chemical Potential as the Chemical Driving Force
- Quantified the entropy production rate
- Quantified the relationship between time irreversibility and flux

Comparisons between Equilibrium and Our Non-Equilibrium Theory

Equilibrium Systems

- Equilibrium Probability by Energy
- Energy Landscape
- Detailed Balance: Zero Flux
- Dynamics: Gradient

  Diffusion Under E Field.
- Kinetics Rates: Kramer's TS Rates
- Paths: Reversible Gradient TS Paths
- FD: Response=Fluctuation around Equilibrium
- Thermodynamics: Energy and Free Energy Given. System Entropy Does not Maximize Itself.
- No Nutrition Supply. Cell Cycle Stops.
- Stem Cell: Problem with Irreversibility, Differentiation and Reprograming.
- Evolution: Equilibrium Landscape (Wright)+ Fisher's FTNS (Zero Flux)

Non-equilibrium Systems

- Emergent Steady State Probability/Process
- Potential Landscape & Lyapunov
- Broken Detailed Balance: Curl Flux
- Dynamics: Gradient + Flux Duality

  Diffusion Under Gauge Field (E & M)
- Rates by Highest Point on Paths
- Paths: Irreversible Not Through TS
- FD: Response=Fluctuation around Steady State + Flux Correlation
- Thermodynamics First Law: Emergent Energy and Free Energy. Free Energy Minimizes Itself.
- Yeast Cell Cycle: Gradient + Flux
- Stem Cell: Waddington Landscape for Differentiation, Development. Reprograming
- Non-Equilibrium Landscape, Generalizes Fisher's FTNS (Flux): Red Queen

Summary

- Dynamical laws of nonequilibirum systems uncovered
- Potential and Flux Landscape (Yin/Yang Duality & Emergence) for Non-Equilibrium Networks
- Potential Attracts the System to the Basin Ring & Flux Drives the Periodic Cycle Dynamics on the Ring
- Barrier Height Determines Stability of Cell Network and Can Be Used to Probe Underlying Wiring Structure by Global Sensitivity Analysis
- ->More Robust, More Stable, Less Dissipative, and More Coherent Network
- Kinetic Path is irreversible due to Curl Flux
- Equilibrium Transition State Theory Breaks Down and Non-Equilibrium Transition State is Different for Different Path and TS Barrier Depends on Path
- Non-equilibrium Fluctuation-Dissipation Theorem

Conclusions

- Law & Principle of Nonequilibrium Dynamical Systems:

Equilibrium Systems: Landscape (Emergence)

Non-Equilibrium Systems: **Landscape + Curl Flux (Duality & Emergence)**

- Physical Pictures and Global Mechanisms
- Applied to Biological and Physical Systems
- Key Element Finding: Design and Control

Thanks

Landscape and Flux Theory

Dr. Li Xu, Mr. Kun Zhang , Dr. Feng Zhang, Dr. Han Yan, Dr. Wei Wu, Dr. Qian Zeng, Dr. Wenbo Li, Ms. Chong Yu, Dr. Chunhe Li, Dr. Haidong Feng, Dr.Bo Han, Dr. Saul Lapidus, Dr. Cong Chen, Prof. Masaki Sasai, Prof. E.K. Wang

Self Repressor Gene Circuit Landscape

Dr. Z. L. Jiang, Dr. L. Tian, Dr. X.N. Fang, Mr. K. Zhang, Dr. Q. Liu

Lambda Phage of Four Cell Fate Emergence and Their Switching:

Dr. Xiaona Fang, Dr. Qiong Liu, Dr. Zach Hensel, Dr. Jie Xiao

Single Molecule Non Michalis-Menton Kinetics and Quantification of Flux:

Dr. Qiong Liu

NSF, NIH