追寻*生命的物理*

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凝聚态物理-北京大学论坛　　2010年10月21日

什么是物理？

Physics (Ancient Greek: φύσις *physis* "nature") is a natural science that involves the study of matter and its motion through spacetime, as well as all applicable concepts, including energy and force. More broadly, it is the general analysis of nature, conducted in order to understand how the universe behaves. -Wikipedia

物理是研究物质结构、物质相互作用和运动规律的自然科学。是一门以实验为基础的自然科学,物理学的一个永恒主题是寻找各种序（orders）、对称性（symmetry）和对称破缺（symmetry-breaking）、守恒律（conservation laws）或不变性（invariance）. –百度百科

物理學是研究大自然現象及規律的學問。—维基百科

物理是几百年来物理学家在探索自然中形成的思维方式和思想方法，是一种追求、一种文化，也是一种科学信仰。它用理性和实证的方法去寻找万物万象背后的规律和道理，并用数学语言将其归纳成普适性原理。

经典物理的起源

观测　　数据积累

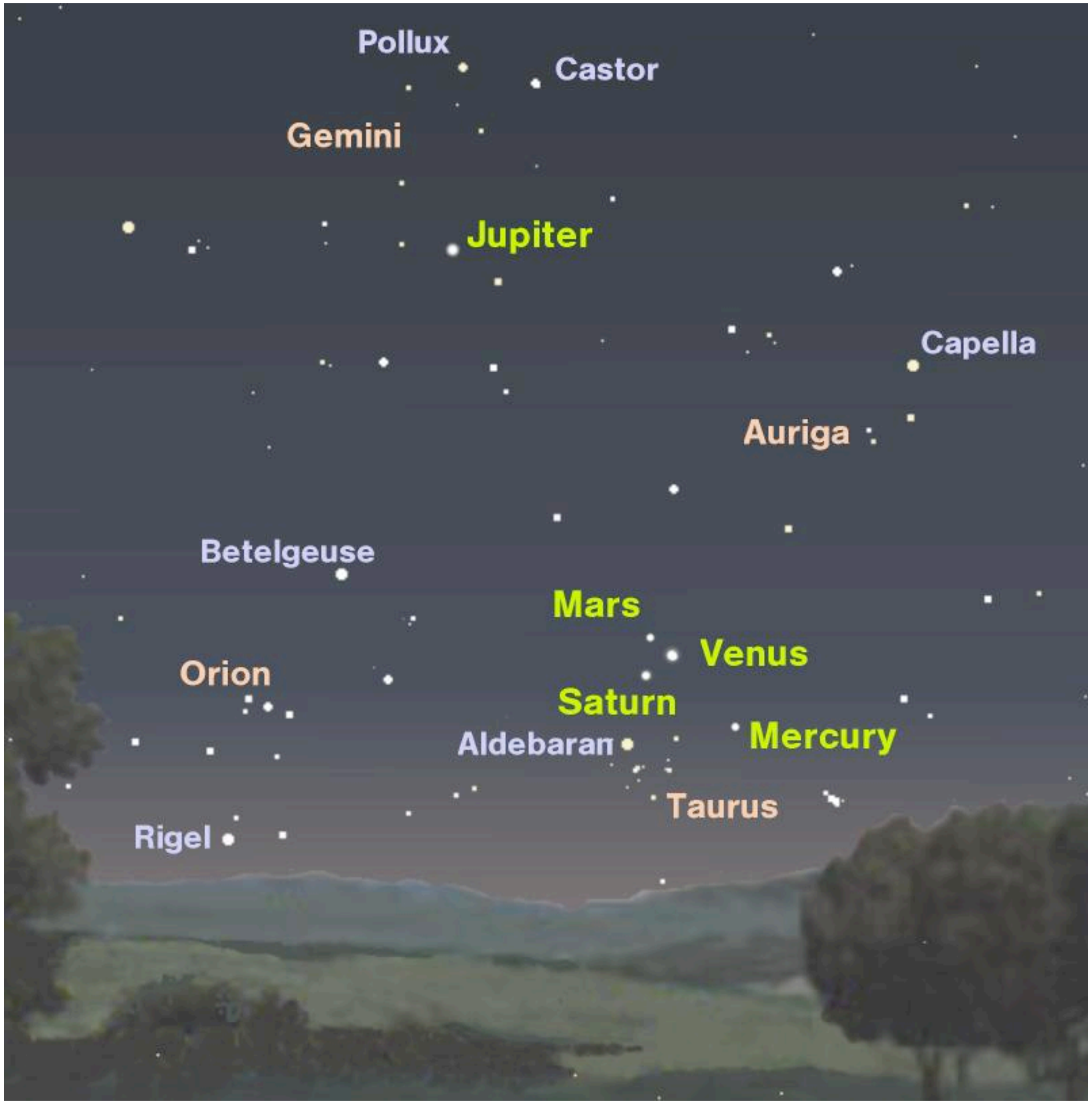
初步、表面、唯象的数学模型

技术进步　　大量更精确的数据

定量规律

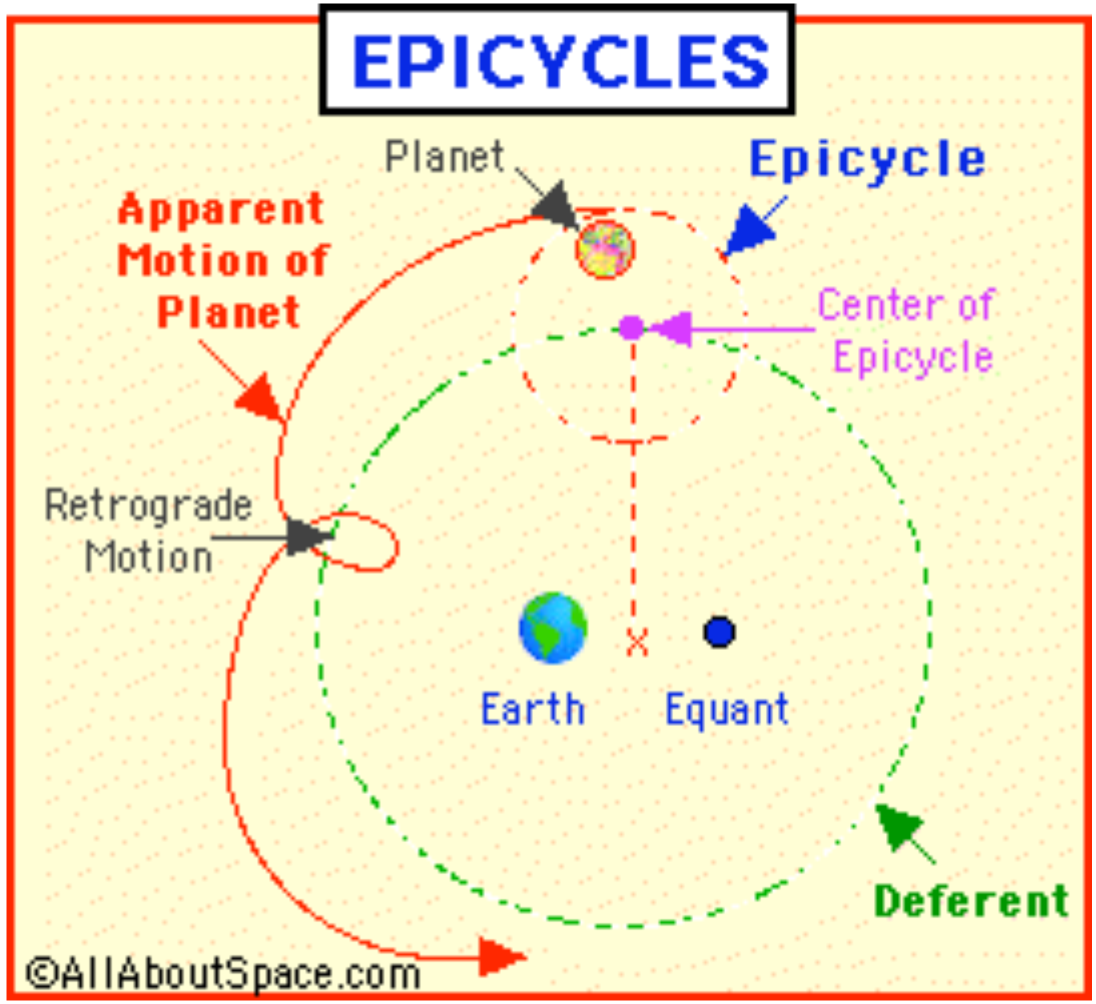
普适原理　　数学语言的发展

Stars in the sky

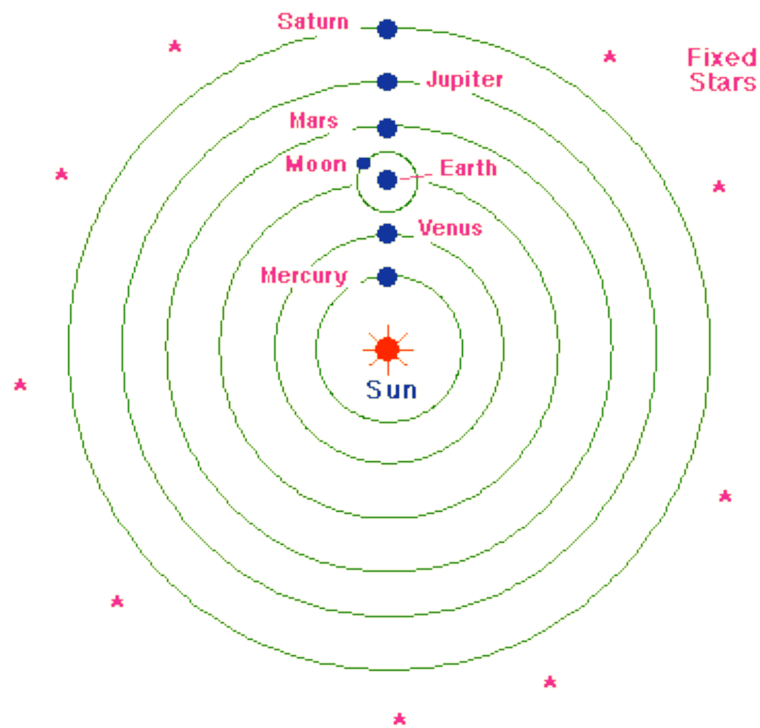


A plausible theory

Ptolemy 托勒密, 90-168



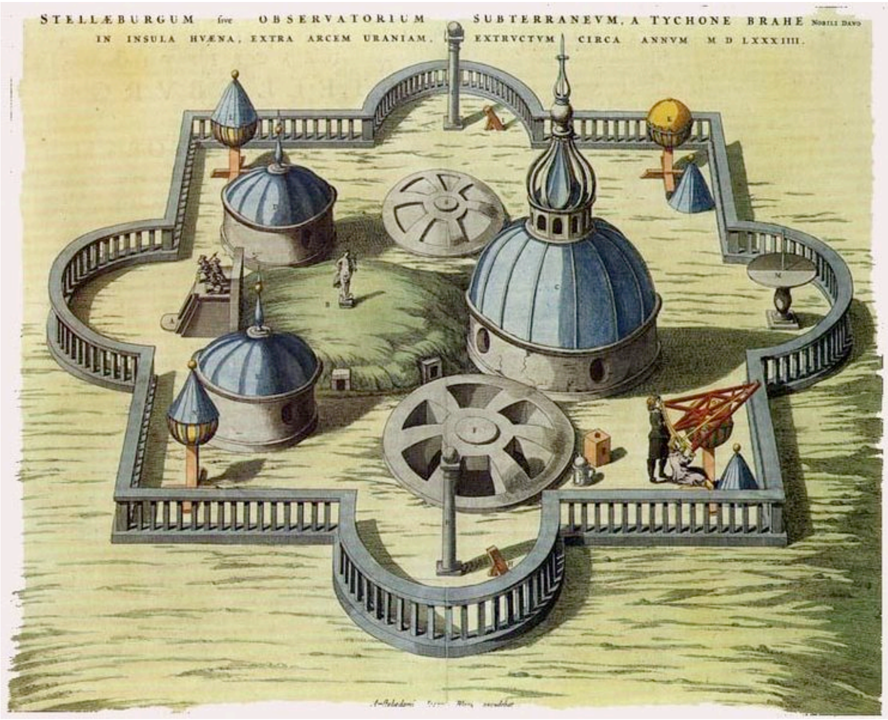
A revolutionary new view



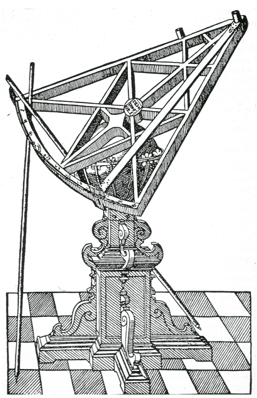
Copernicus 哥白尼, 1473-1543

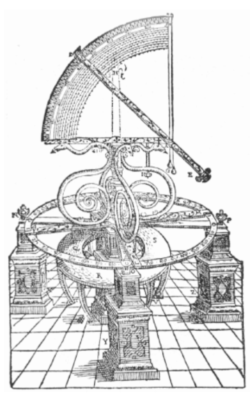
- A model that still needs epicycles
- Explains no more observations than the geocentric model

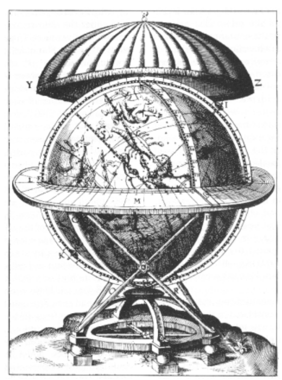
More quantitative instruments lead to more accurate measurement



Tycho Brahe (1546-1601)







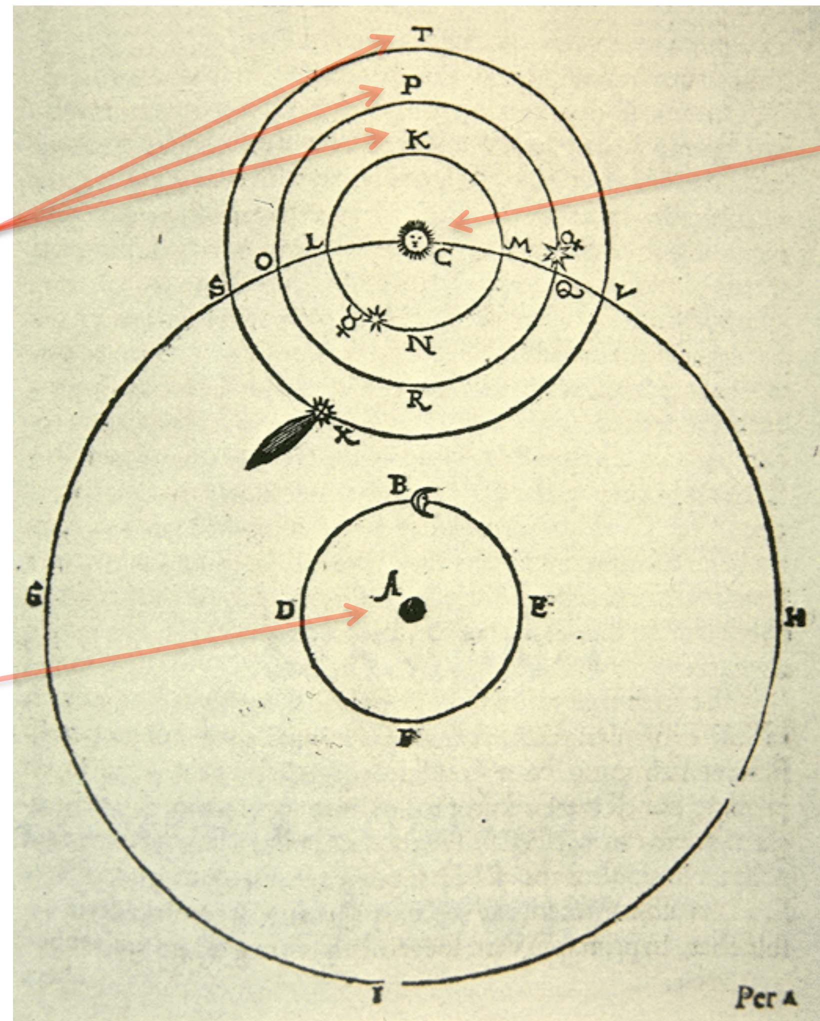
But not necessarily a better theory

Tycho's new theory

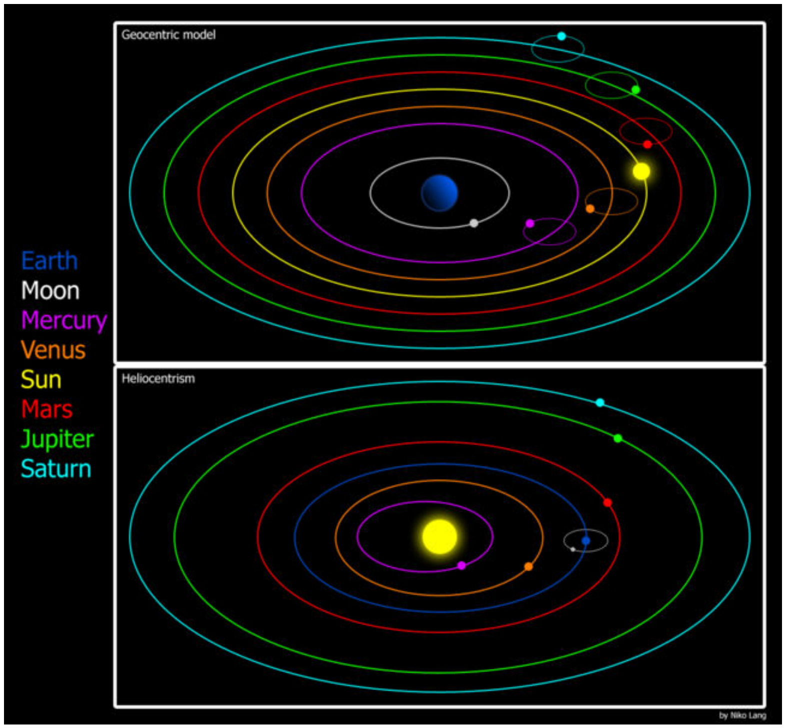
Other planets

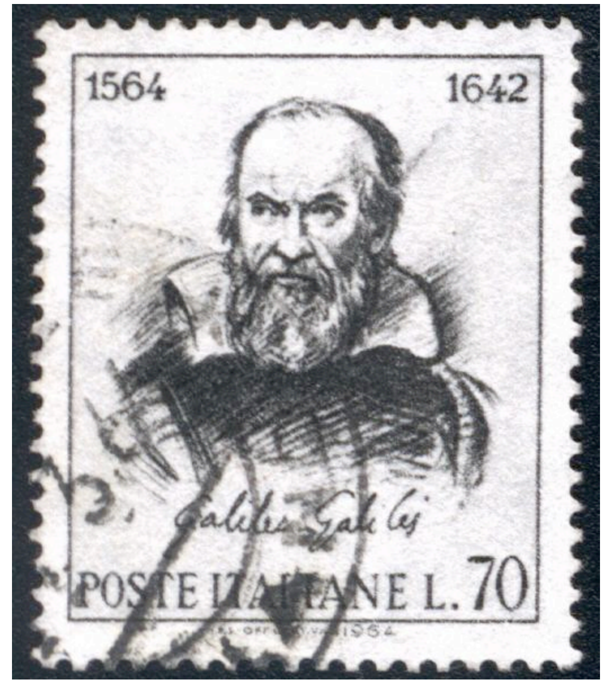
Sun

Earth



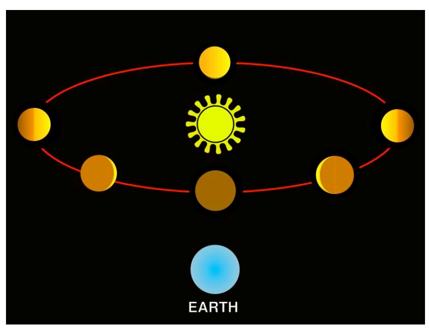
New instrument lead to new observation





Galileo Galilei 伽利略, 1564-1642

Jupiter's moons

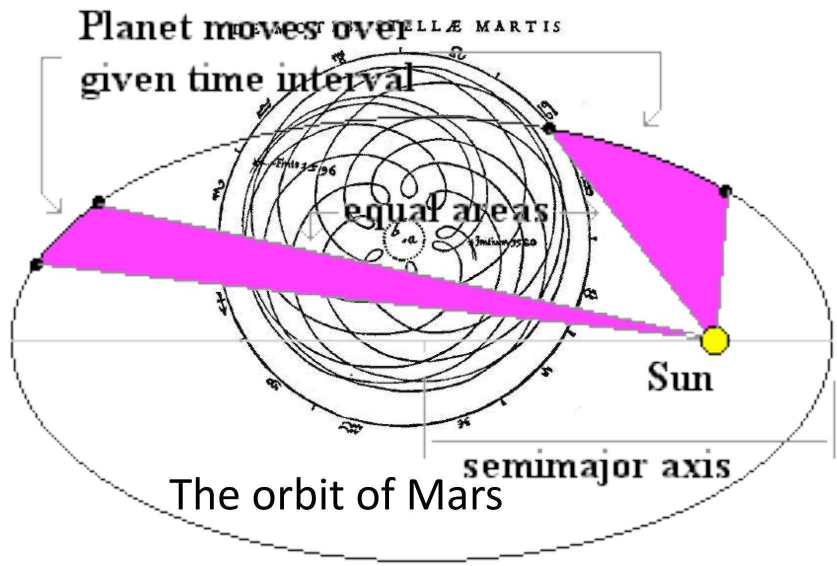


The phase of Venus

- Support Heliocentric model
- Qualitative observation

Accurate data lead to quantitative laws

Johannes Kepler (1571-1630)



The orbit of Mars

The three laws of planetary motion

- The orbits of the planets are ellipses, with the Sun at one focus of the ellipse.
- The line joining the planet to the Sun sweeps out equal areas in equal times.
- $T_a^2 / T_b^2 = R_a^3 / R_b^3$

Universal laws

Also developed calculus

$\mathbf{F} = m\mathbf{a}$; $G = \text{constant} \times m_1 m_2 / R_{12}$

物理学的前沿在哪里？

Theories:

Classical mechanics; Thermodynamics & Statistical physics; Electrodynamics; Quantum mechanics; Relativity; …

Fields:

Condensed matter physics; Atomic, molecular, optical physics; High energy & particle physics; Astrophysics; Geophysics; Biophysics; …

Concepts:

Causality; symmetry; symmetry-breaking; conservation laws; invariance; …

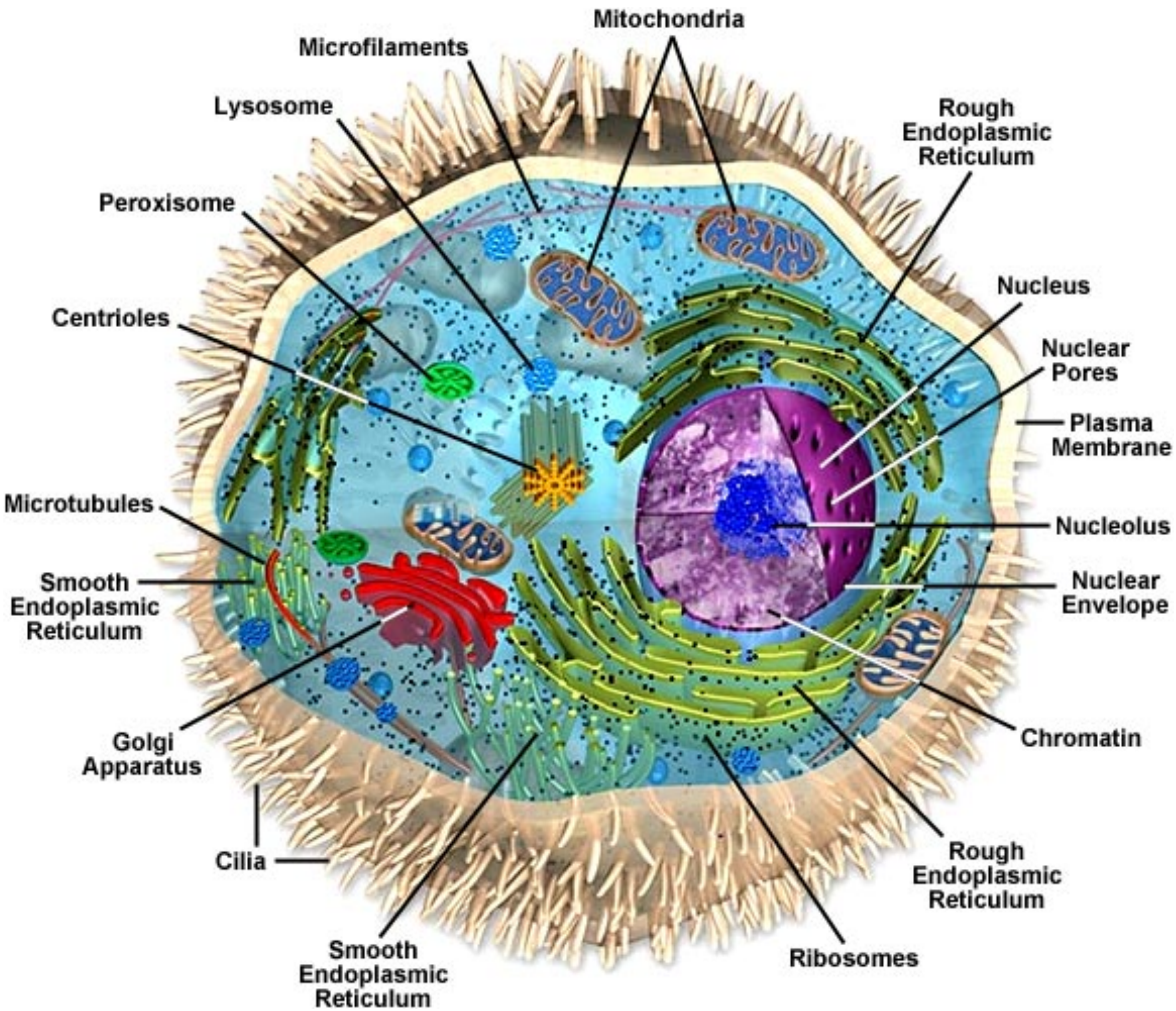
“死”的物质与态　“活”的物质与态

Six challenges in the next decade

"Condensed-Matter and Materials Physics: The Science of the World Around Us", Committee on CMMP 2010, National Research Council

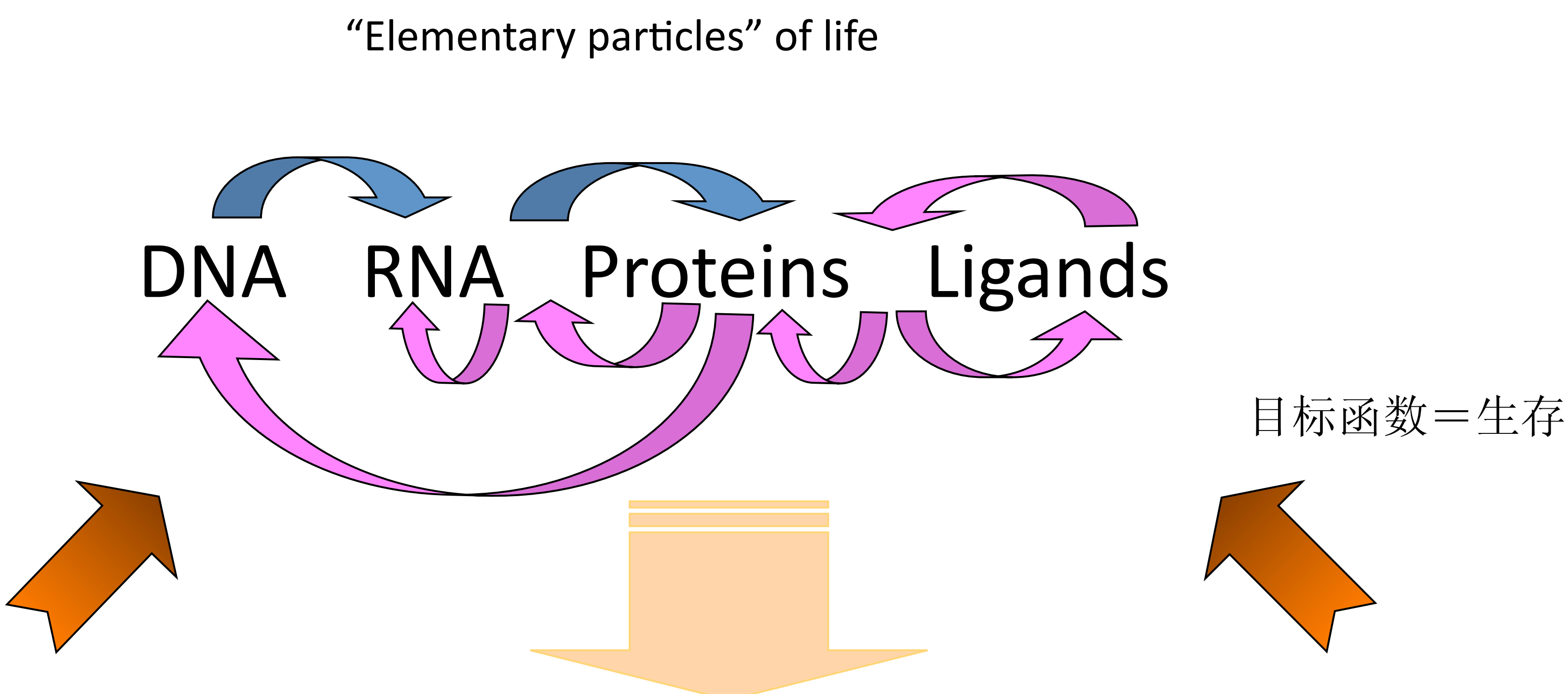
- How do complex phenomena emerge from simple ingredients?
- How will the energy demands of future generations be met?
- What is the physics of life?
- What happens far from equilibrium and why?
- What new discoveries await us in the nanoworld?
- How will the information technology revolution be extended?

Cell - a special condensed matter



DNA
RNA
Proteins
Ligands

A many body system state



Subcellular functions **Cells** **Organisms** **Ecosystems**

Many body systems

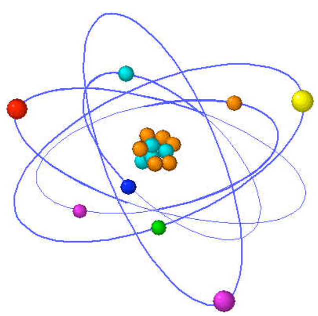
Physics versus Biology

Physical laws

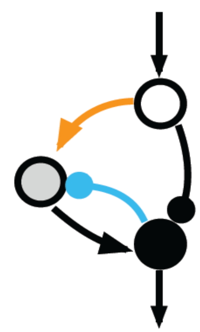
- Causality (Initial conditions + equations => future)
- Symmetry and simplicity
- Universal and time-invariant

Biological world

- Function centric ("purpose")
- History dependent, detailed, and "complex"
- Evolving



Order, structure, form



Physical interactions

Energy and matter

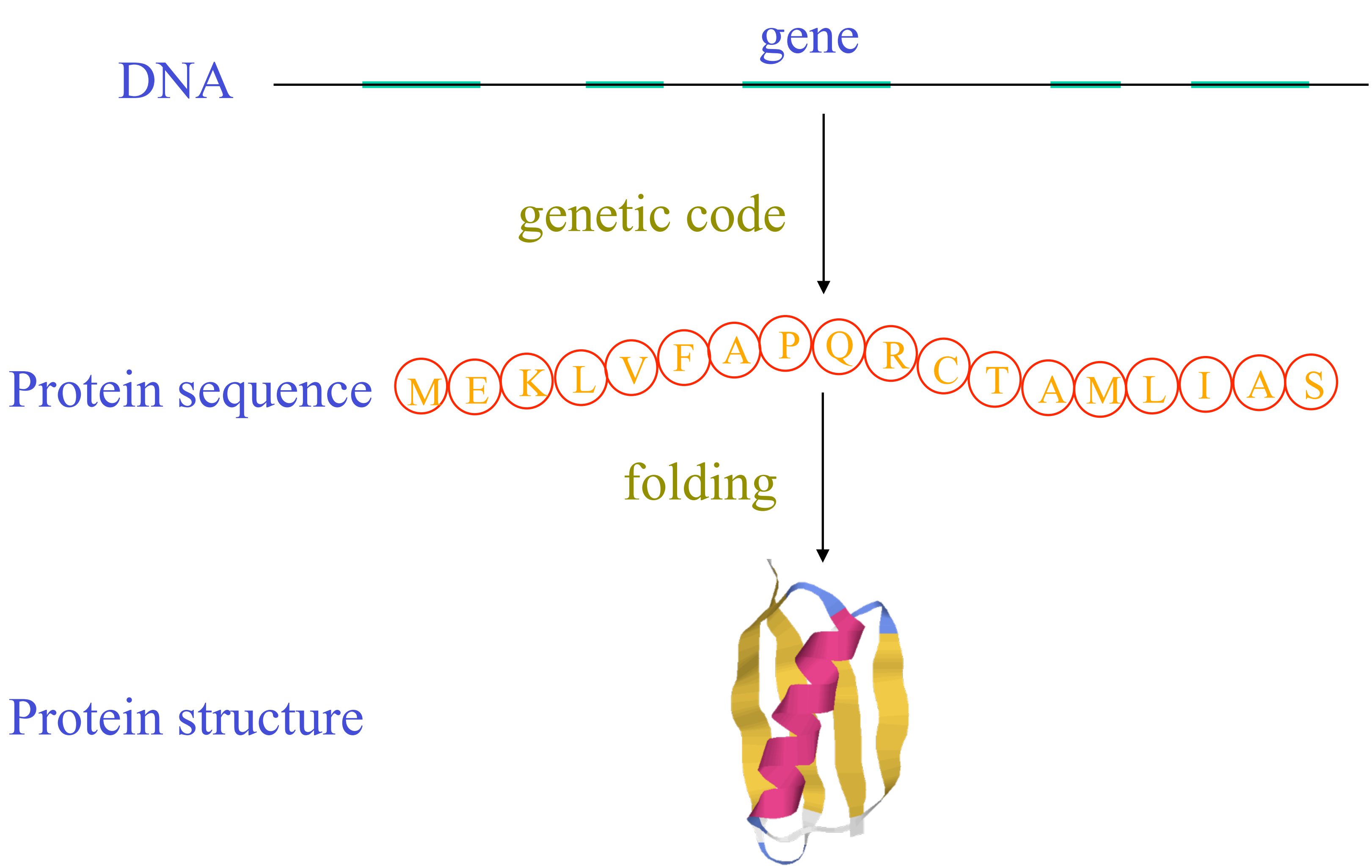
Evolutionary forces

Function

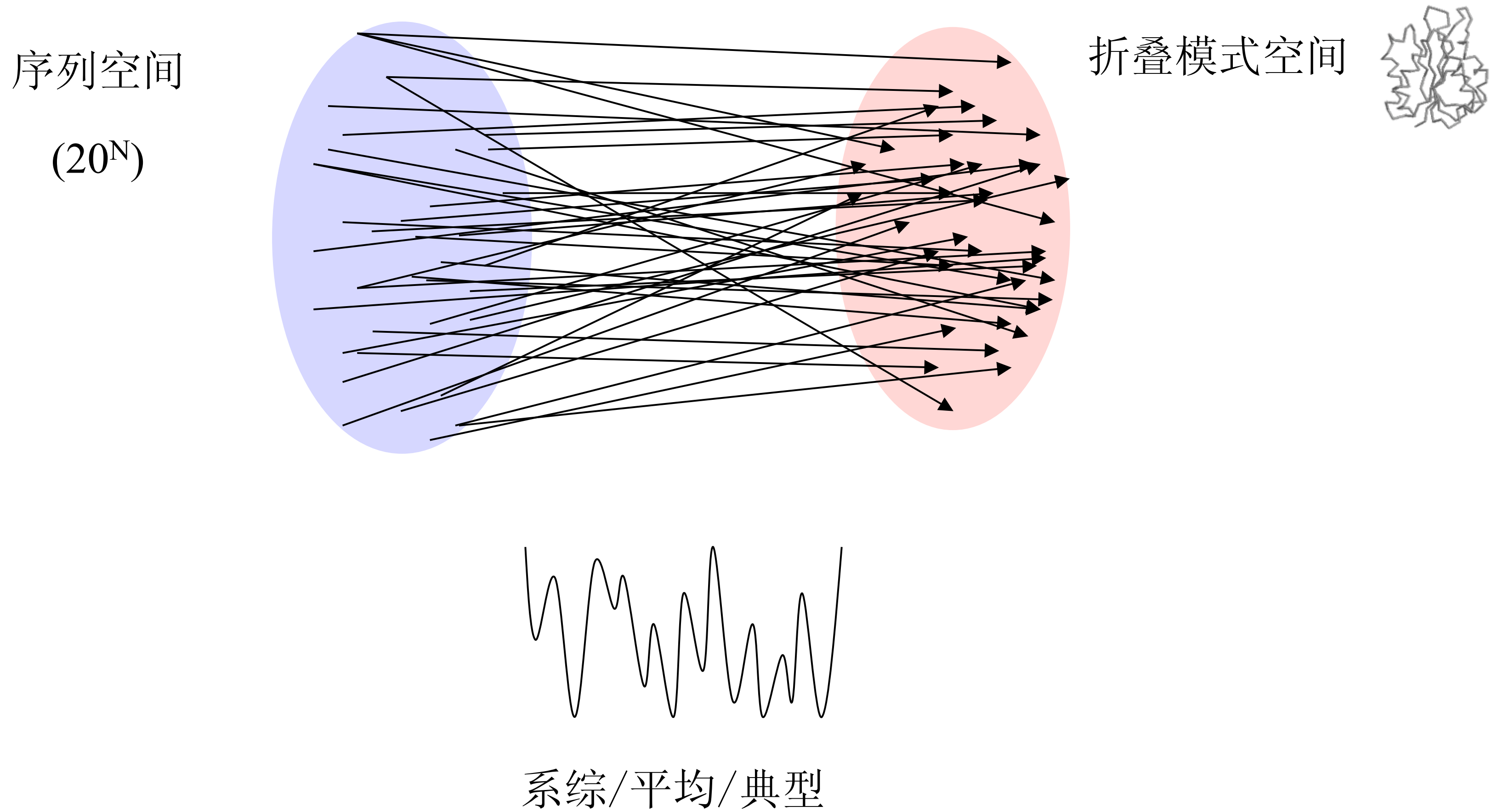
三个小故事
– a physicist’s random walk in the biological world

- 蛋白质折叠问题
- 生物网络的稳定性问题
- 功能和形式的问题

Protein folding



蛋白与随机序列的区别 － 可设计性原理



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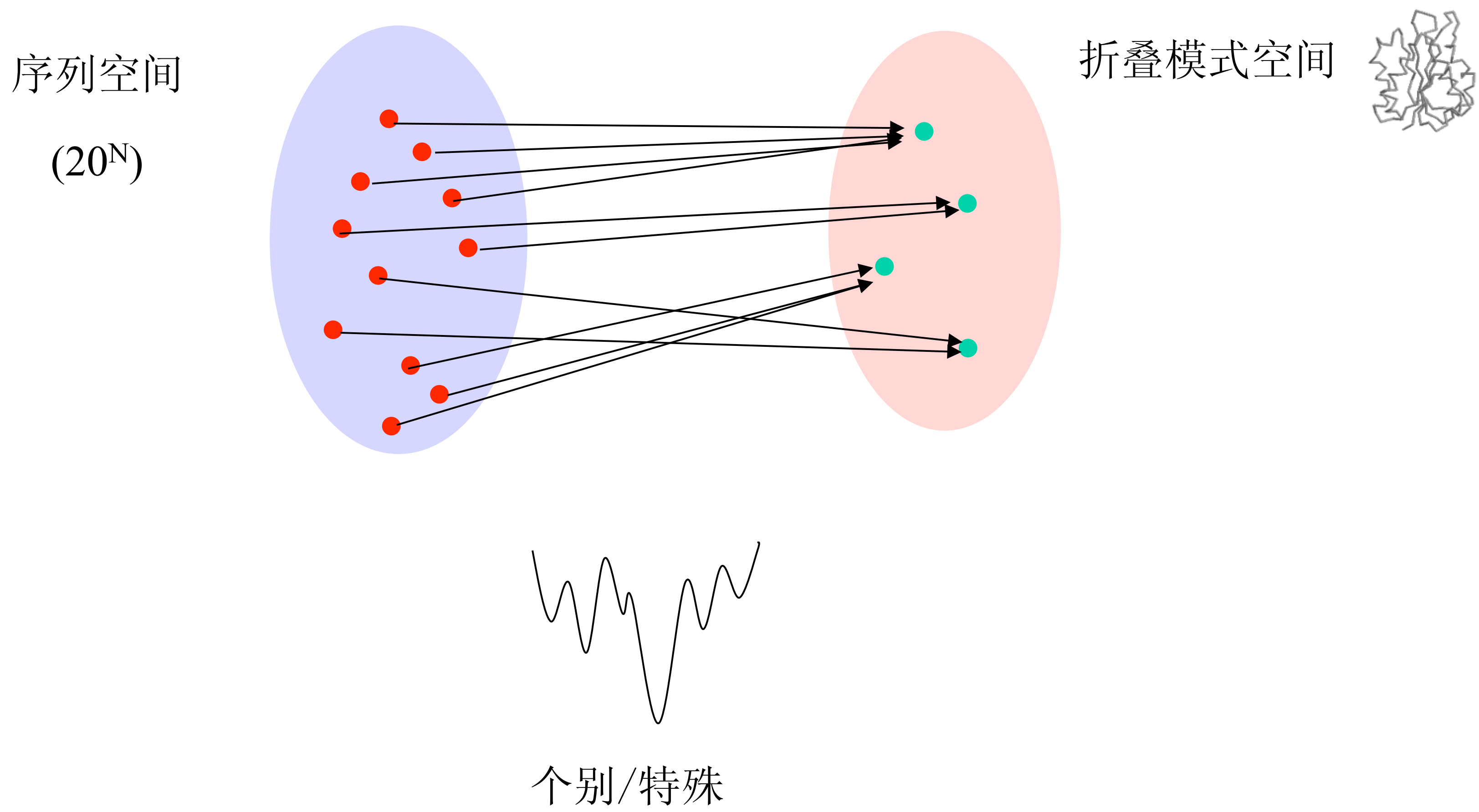
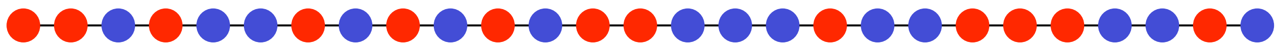


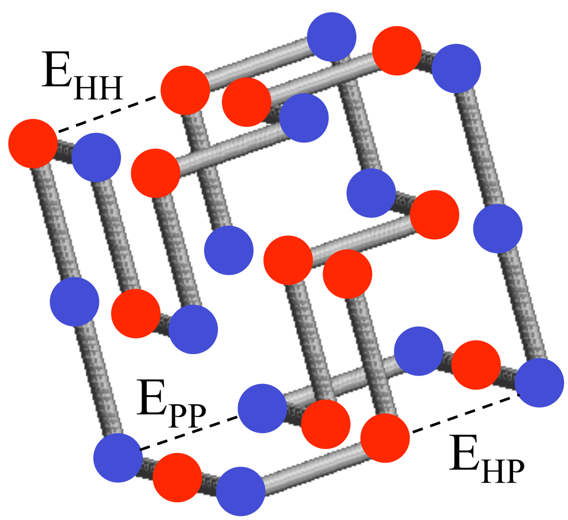
HP Lattice Model

H--Hydrophobic

P--Polar

(Dill, Onuchic, Shakhnovich, Wolynes, …)





$$H = \sum_{i,j} E_{\sigma_i \sigma_j} \Delta(r_i - r_j)$$

$E_{HH} < E_{HP} < E_{PP}$ Hydrophobicity

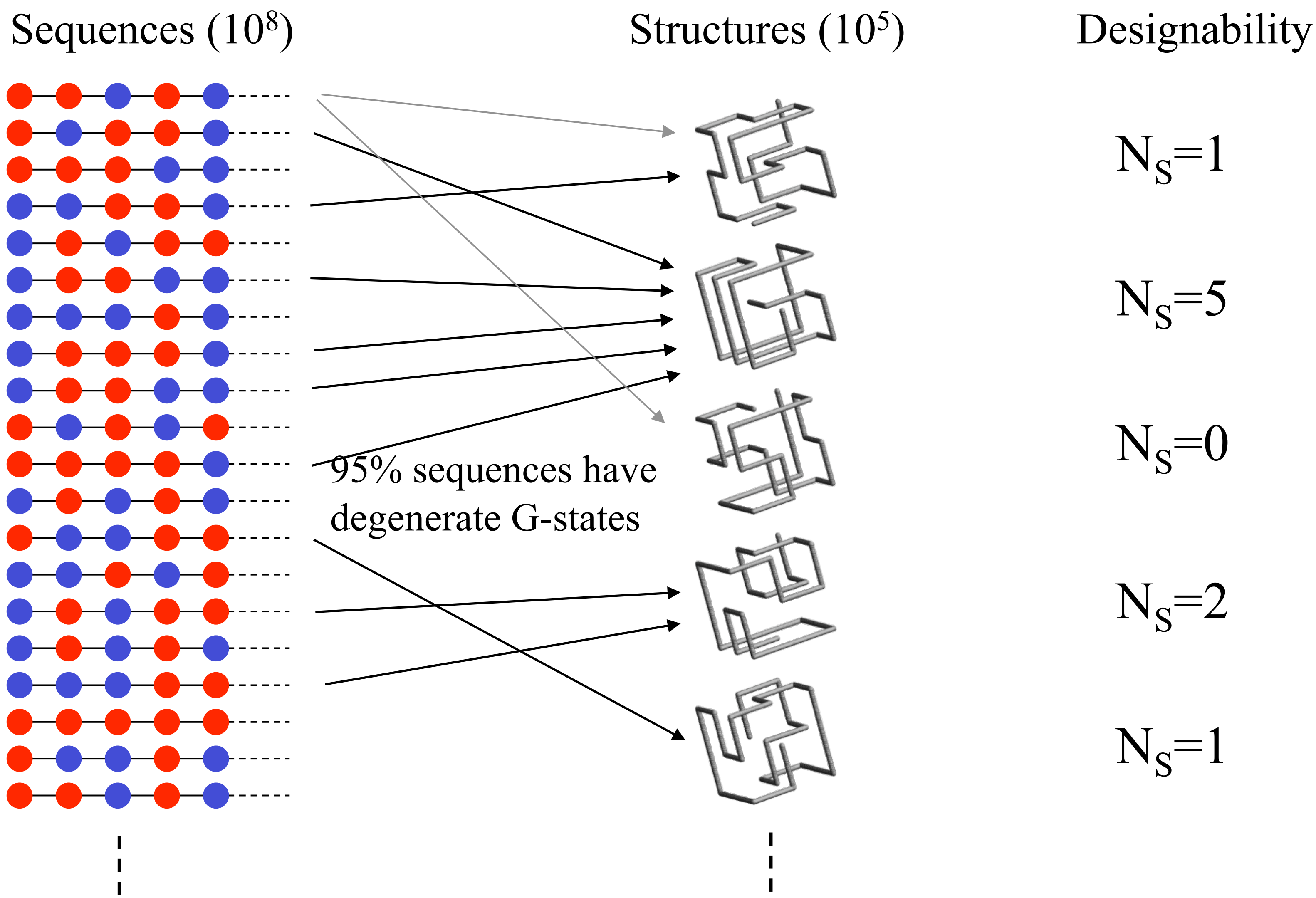
$E_{HH} + E_{PP} \le 2E_{HP}$ Segregation

$E_{HH} = -2.3$

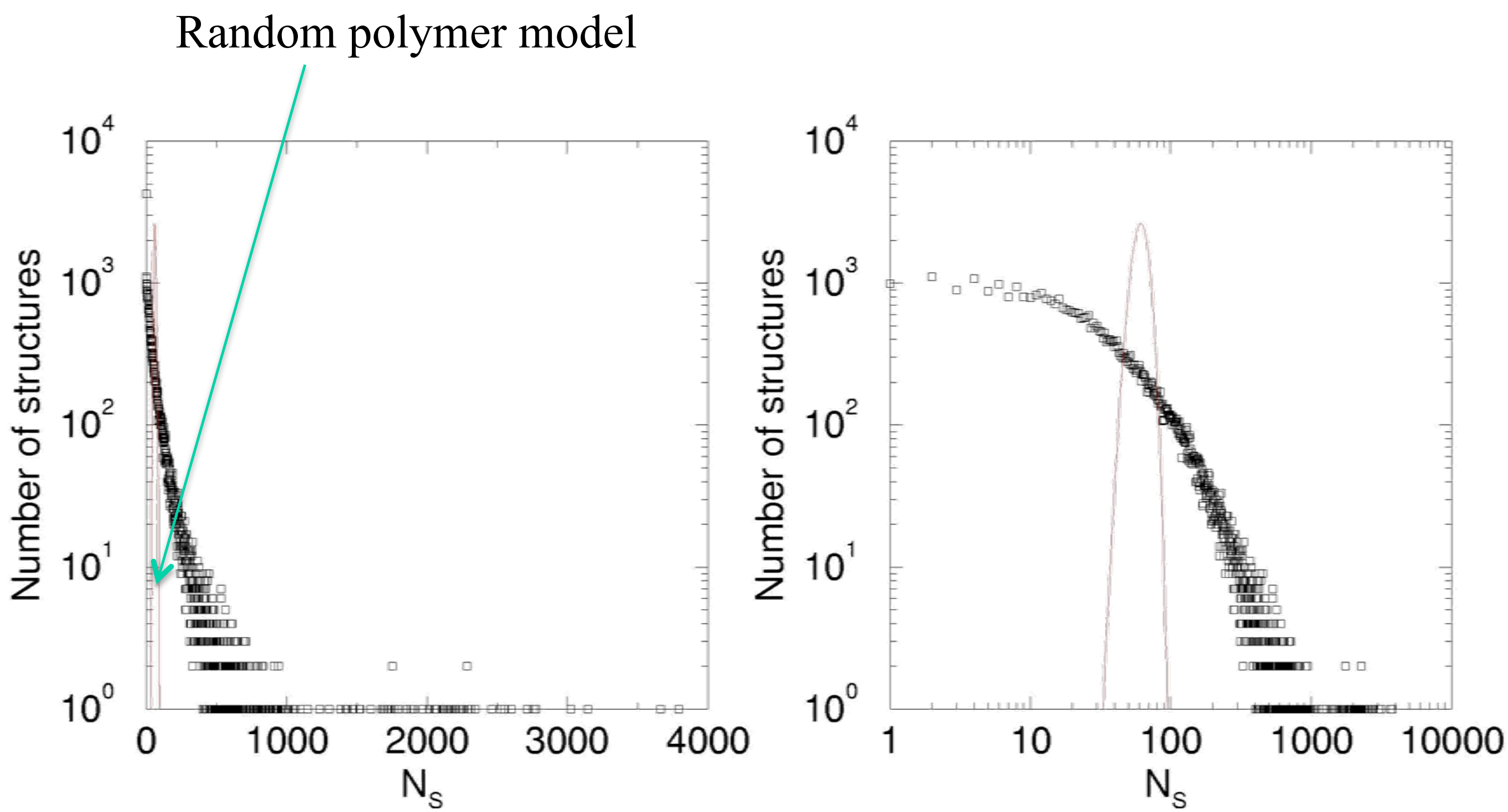
$E_{HP} = -1$

$E_{PP} = 0$

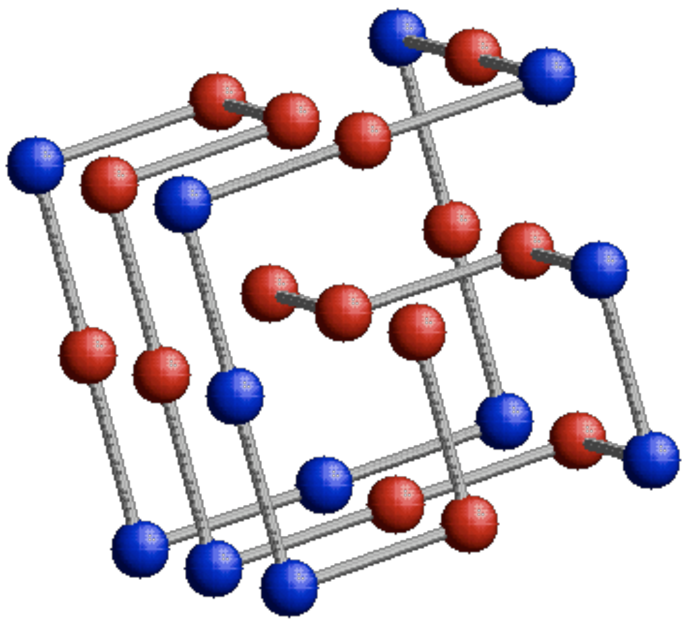
Enumeration

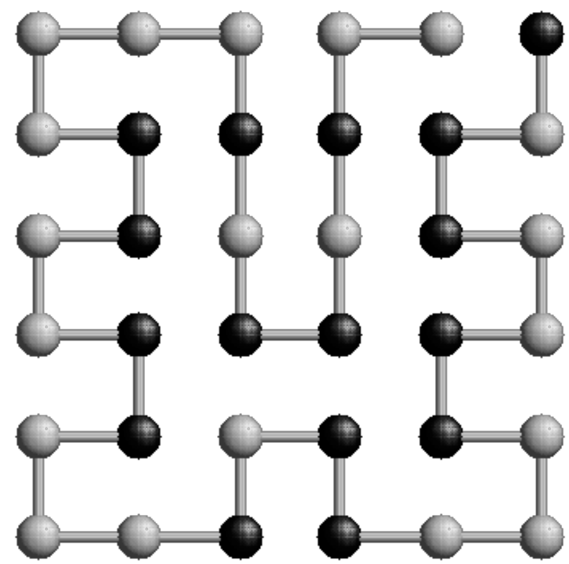


Histogram of Designability (3×3×3)



Top Lattice Structures



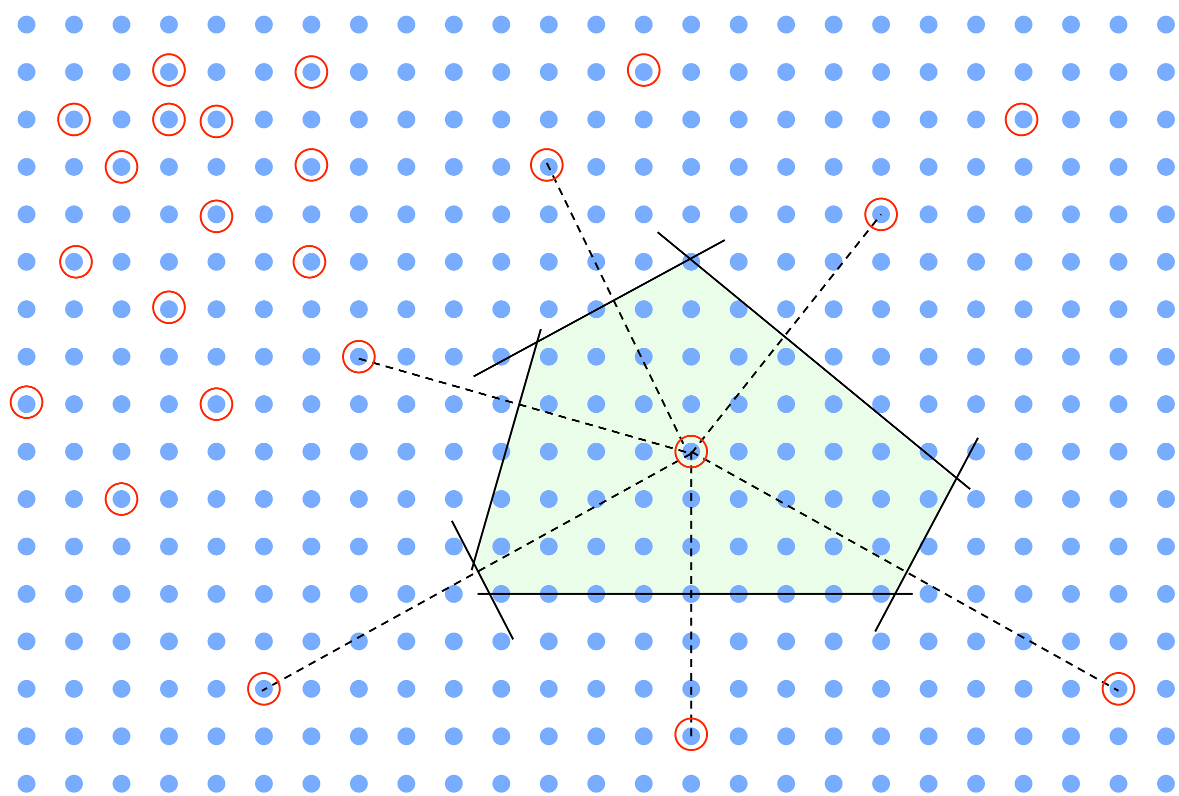


Sequence-Structure Space

sequence

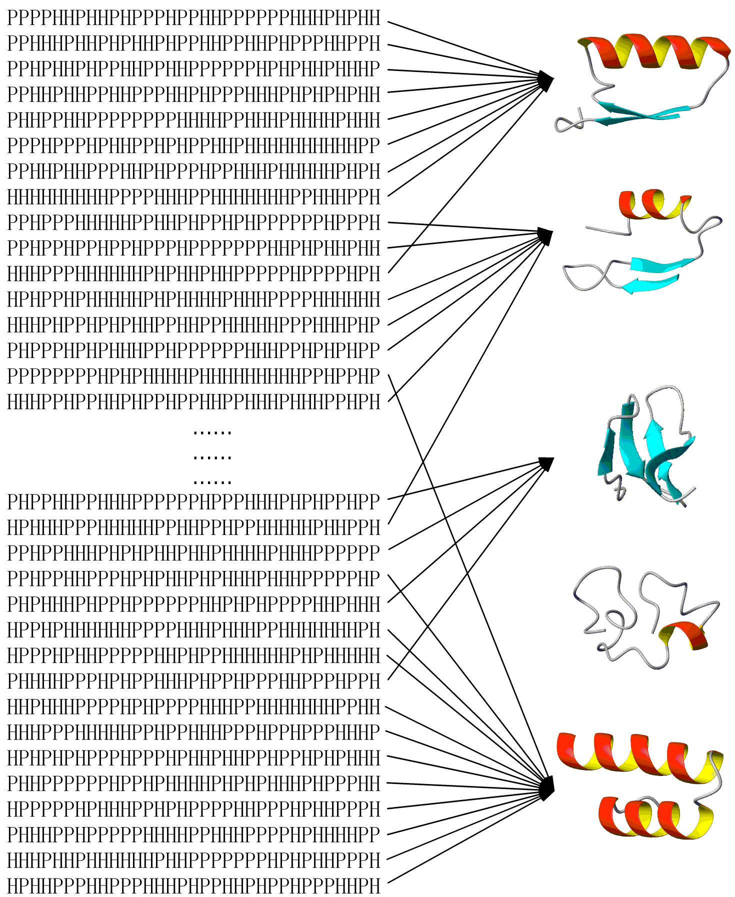
structure

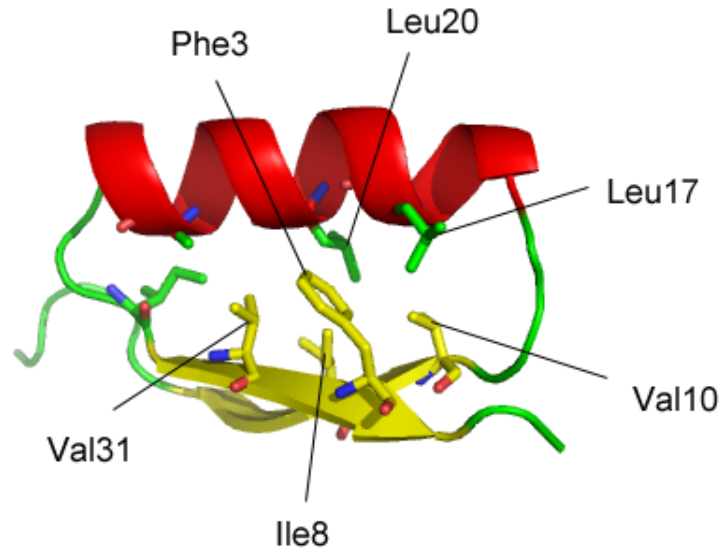
$$H = \sum_i (\sigma_i - s_i)^2$$



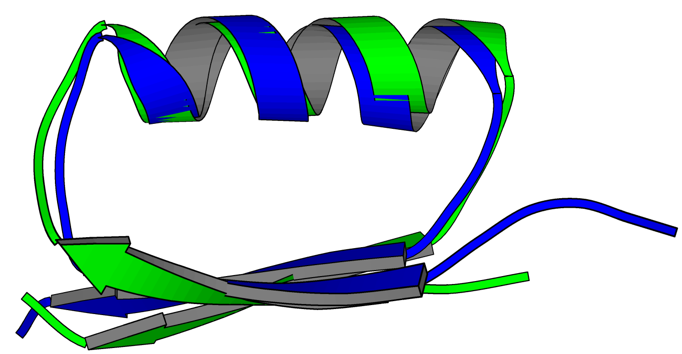
N_S ~ Voronoi volume

β α β 蛋白质全新设计



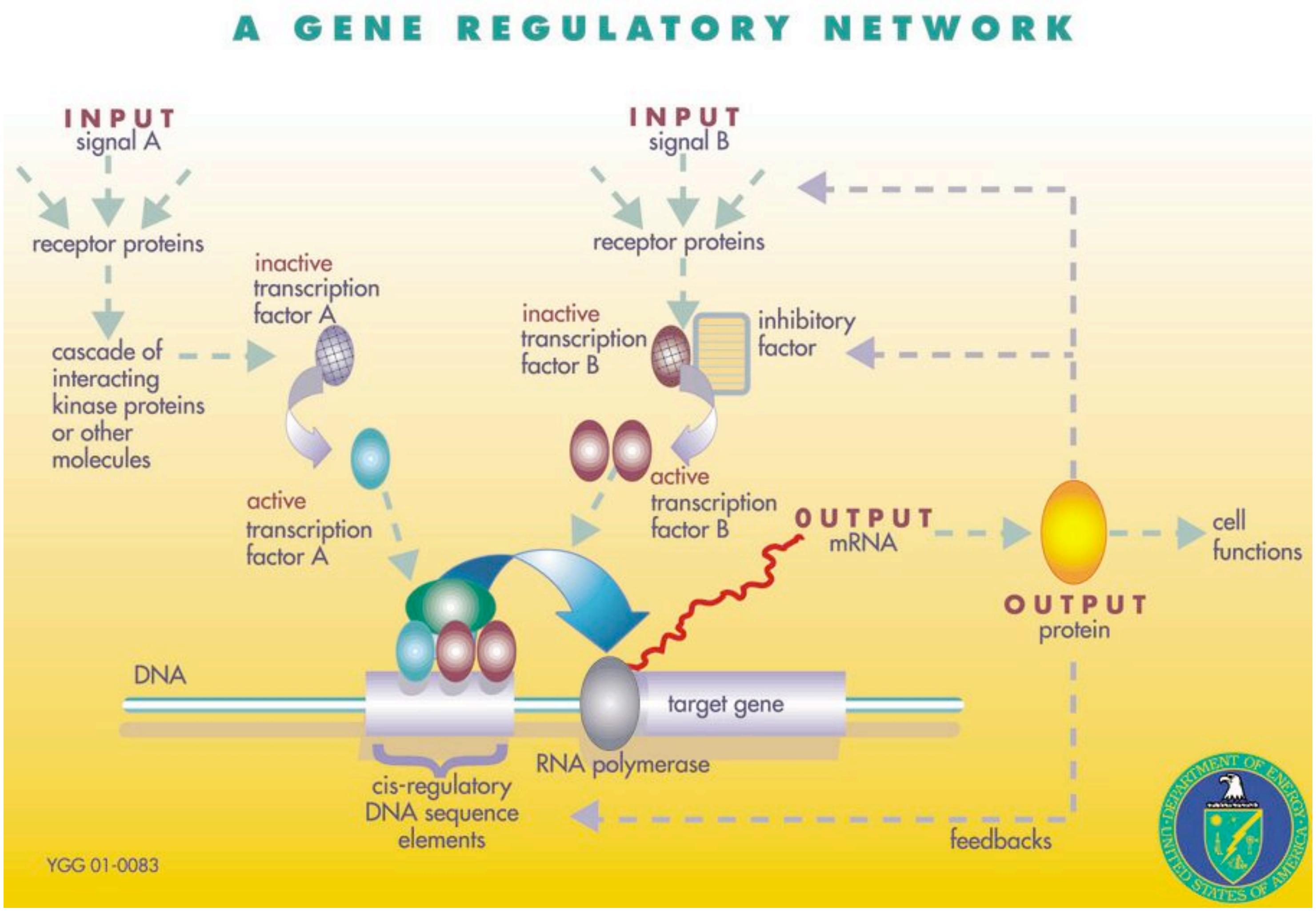


Comparison with the design target

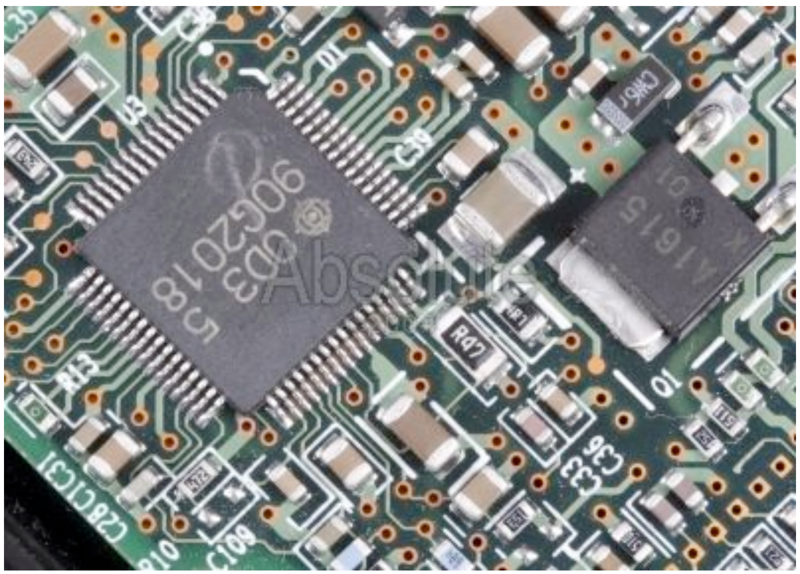


Liang, H., H. Chen, K. Fan, P. Wei, X. Guo, J. W. Jin, C. Zeng, C. Tang, L. H. Lai, De Novo Design of a βαβ Motif. *Angew. Chem. Int. Ed.* **48**, 3301 (2009).

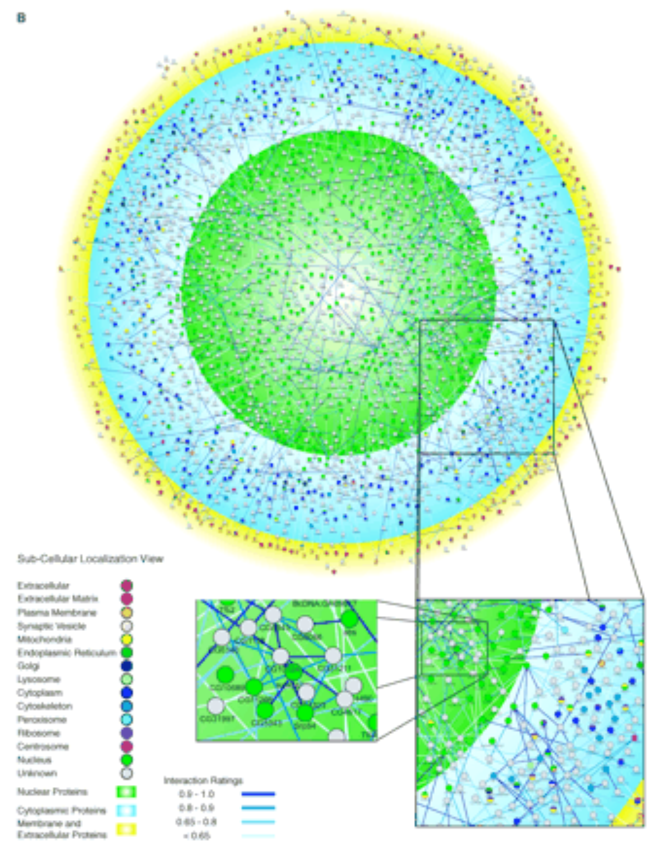
Robustness of biological networks



Design Principle of Biological Networks
--A Computer Chip or a "Brownian Machine"?



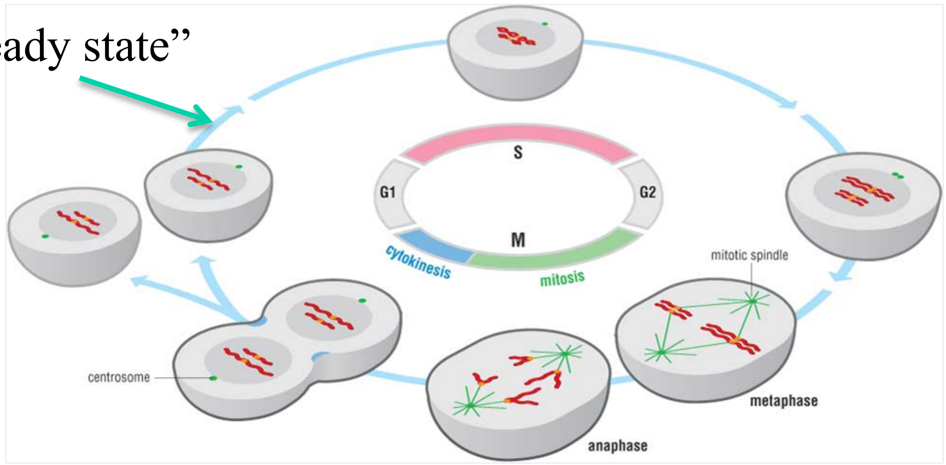
Specifically and reliably wired interactions in a clean and stable environment; No unwanted cross talks

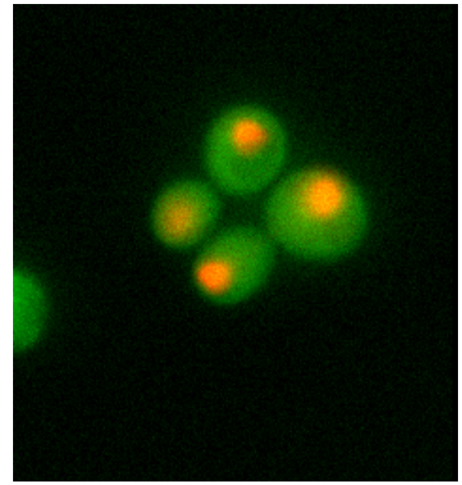


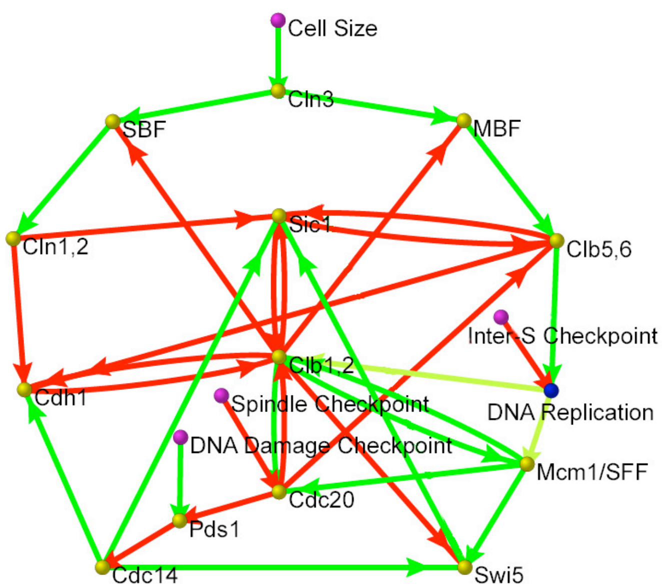
Weak interactions (~kT) in a noisy and fluctuating environment

Network of Cell Cycle Regulators

"Steady state"







Positive regulation:

- •Transcriptional activation
- •Activation by phosphorylation/ dephosphorylation

Negative regulation:

- •Inhibition by binding
- •Deactivation by phosphorylation
- •Mark for degradation

● Checkpoints

Cell Stationary State is a Fixed Point

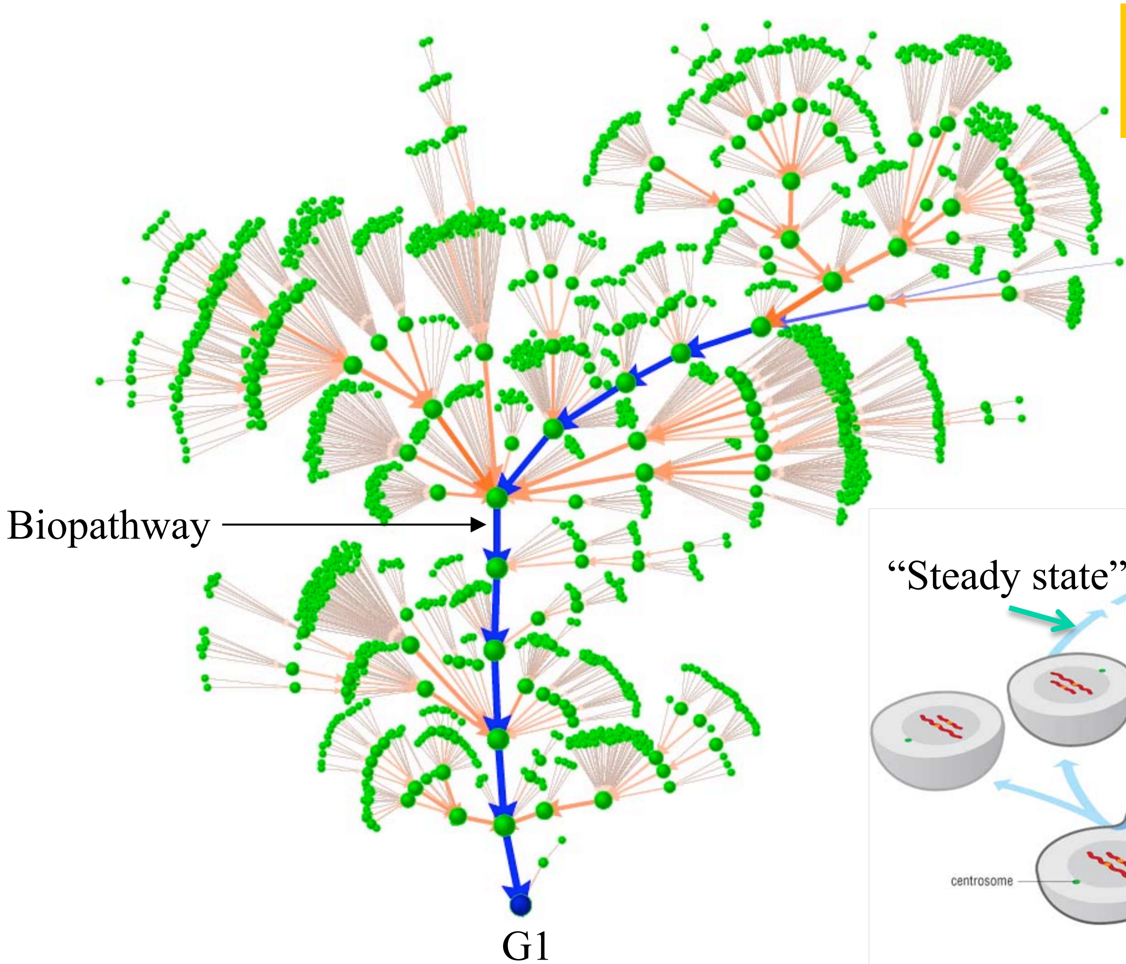
Basin size	Cln3	MBF	SBF	Cln2	Cdh1	Swi5	Cdc20	Clb5	Sic1	Clb2	Mcm1
1764	0	0	0	0	1	0	0	0	1	0	0
151	0	0	1	1	0	0	0	0	0	0	0
109	0	1	0	0	1	0	0	0	1	0	0
9	0	0	0	0	0	0	0	0	1	0	0
7	0	1	0	0	0	0	0	0	1	0	0
7	0	0	0	0	0	0	0	0	0	0	0
1	0	0	0	0	1	0	0	0	0	0	0

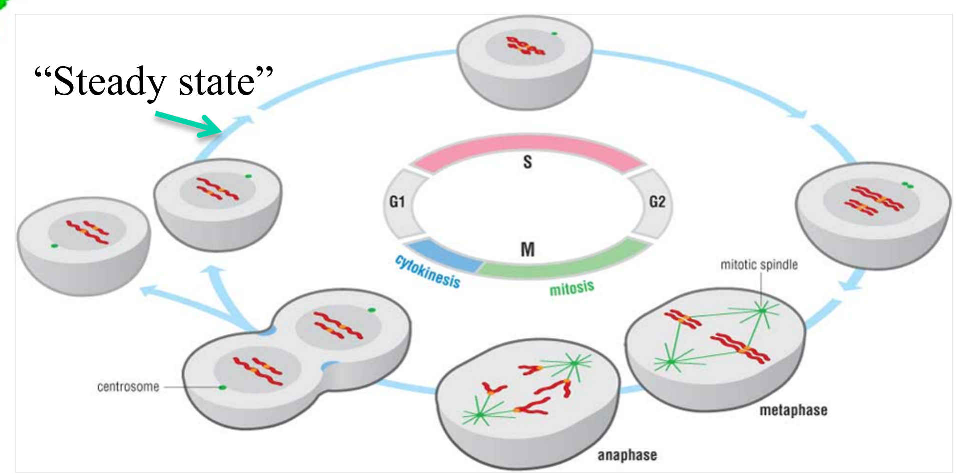
The big fixed point (1764/2048=86%) = G_1 stationary state

The lowest point of the landscape

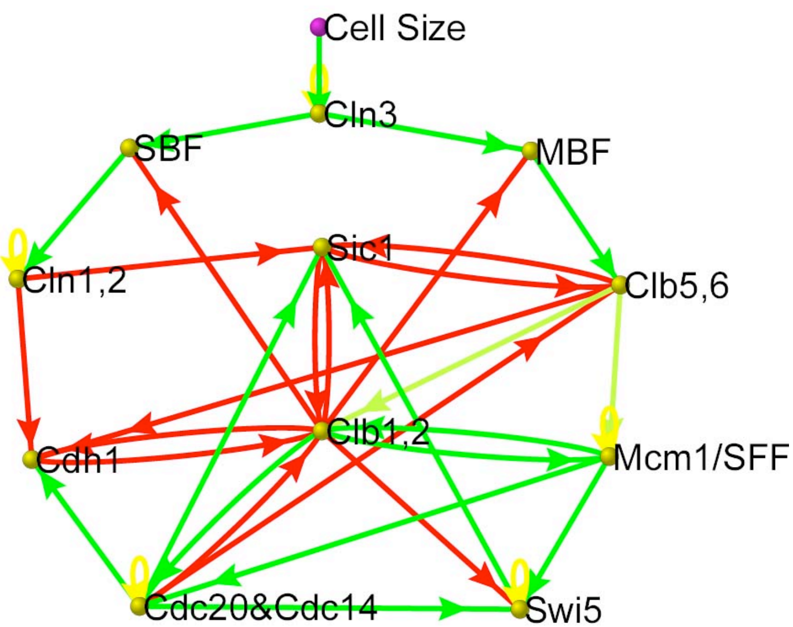
Global Flow Diagram of Trajectories

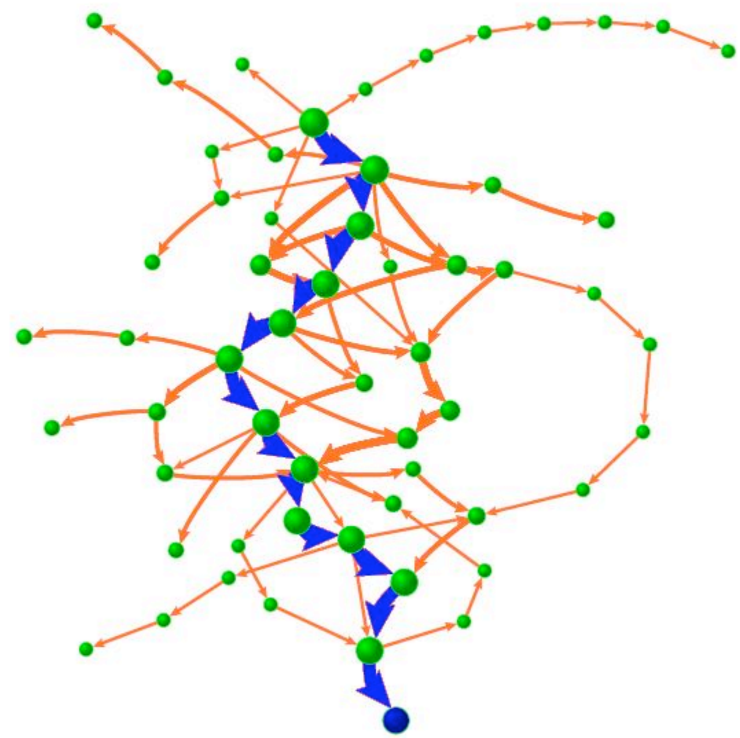
生物定态＝大吸引盆的稳定点
生物路径＝大峡谷





Perturbation
--Stability of the biopathway

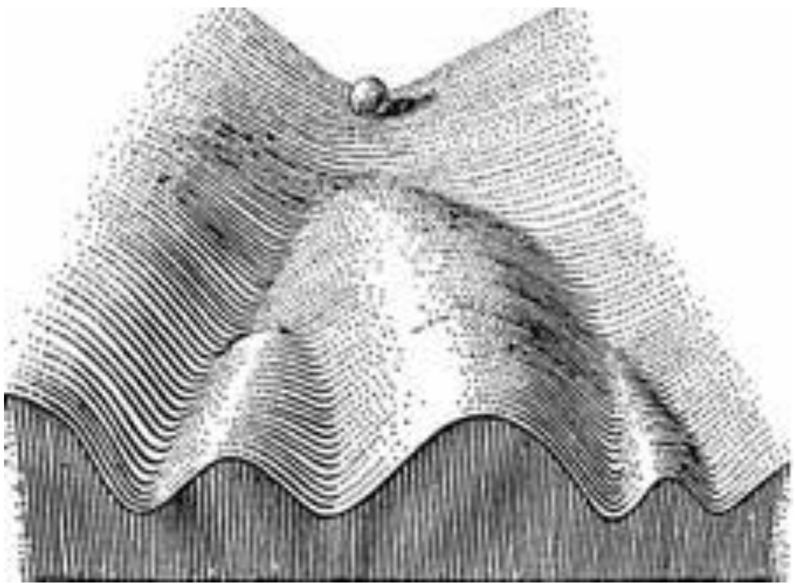


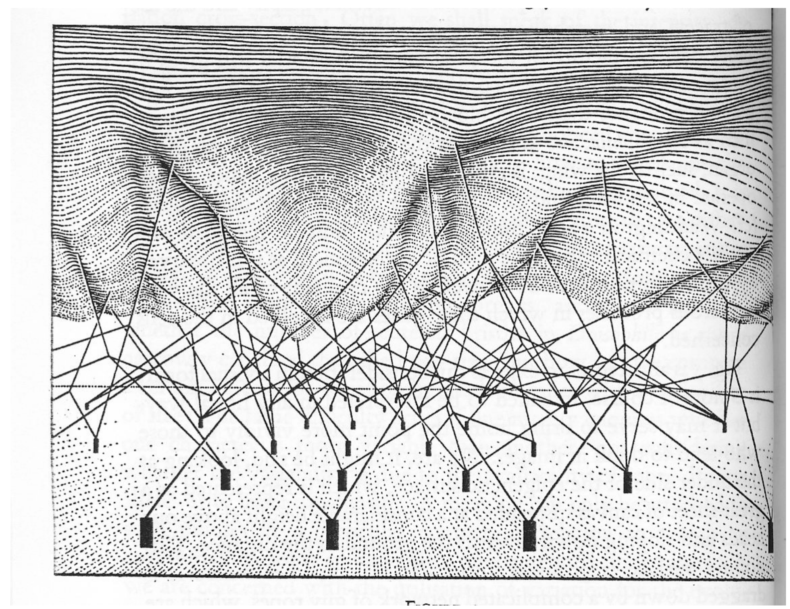


Deletion, addition, color-switching -- 41.2%, 57.4%, 64.7%

The interaction network of biological system is <u>robust</u>

Waddington's metaphor for developmental pathway (1957)



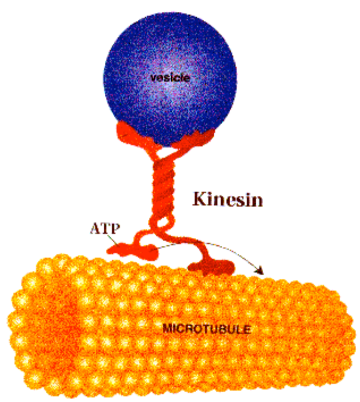


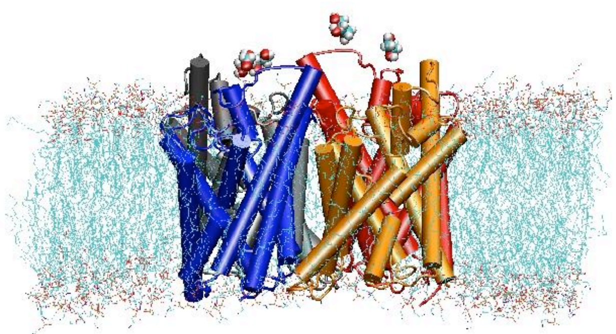
Epigenetic landscape

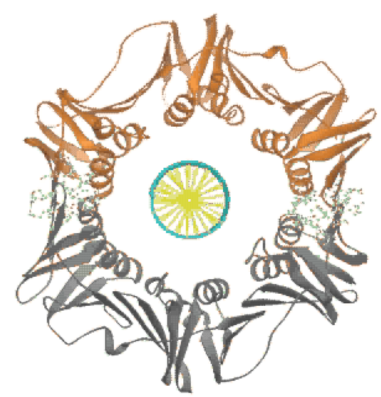
Form follows function
功能决定形式

Macroscopic scale 宏观尺度

Microscopic scale 微观尺度







Function and form on "meso"-scales?

Cellular networks

? ? ? ?

Macroscopic — Microscopic

Organismic — Molecular

Bistability

Oscillation

Patterning

Signal transduction

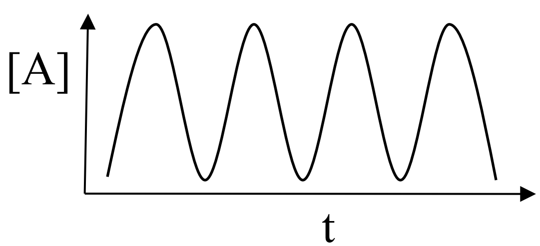
Homeostasis

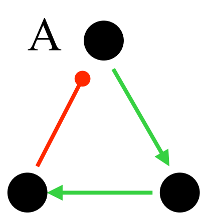
Adaptation

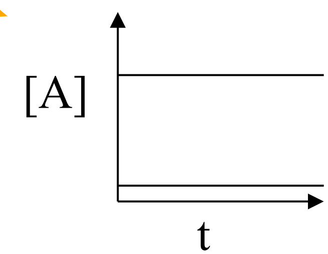
Cell polarization

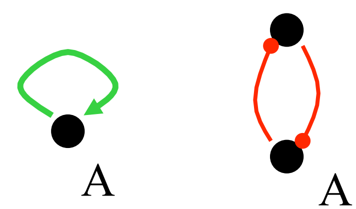
Cell division

… …





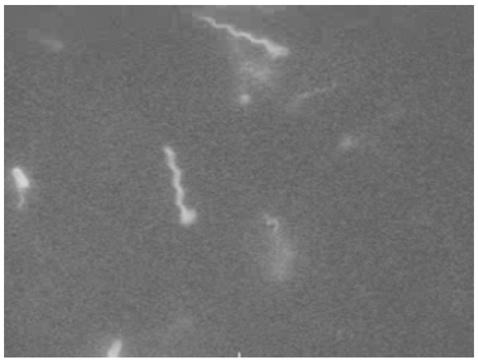


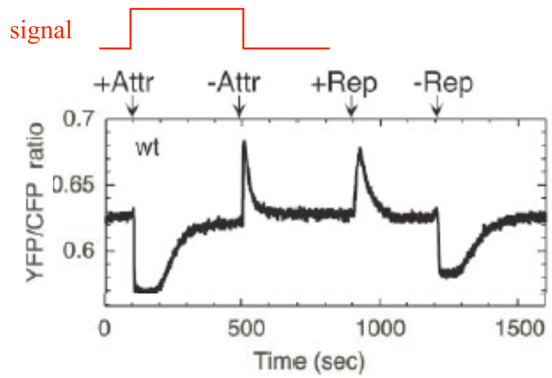


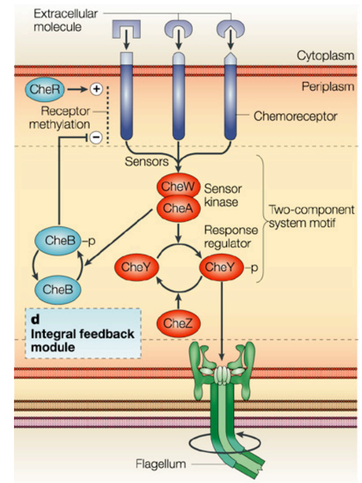
For a given function, are there preferred network topologies (form)?

Biochemical adaptation

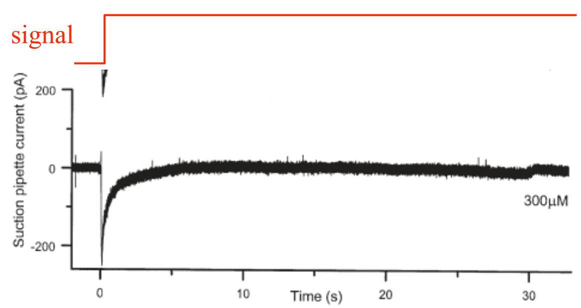
E coli chemotaxis

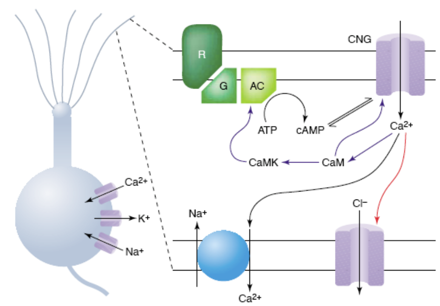






Olfactory sensing

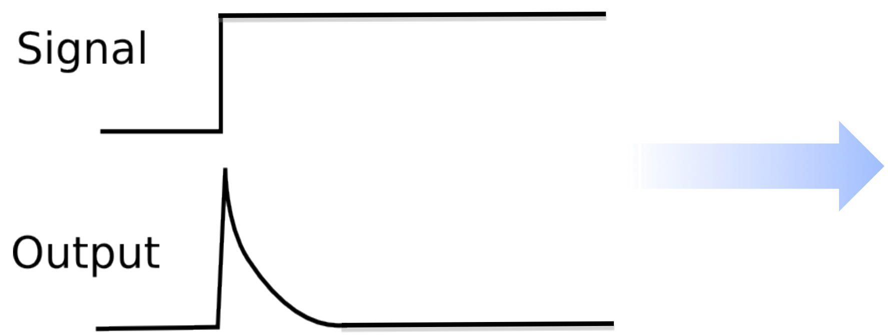




A common feature in sensory and other pathways

Biochemical adaptation

Function

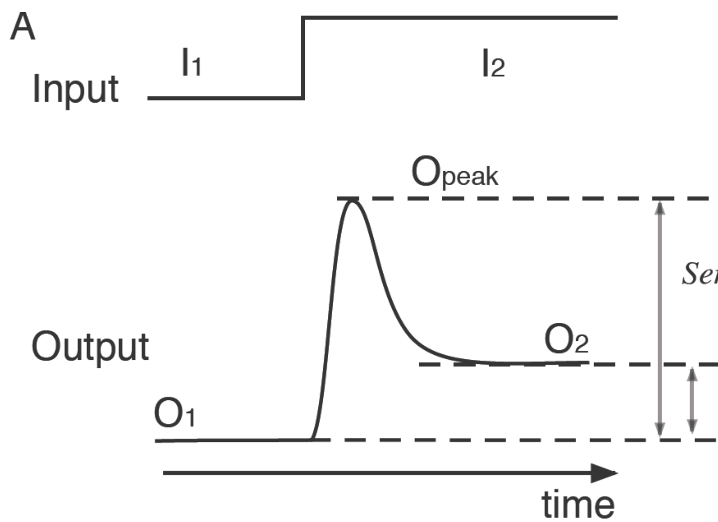


Circuit topology ?

Design principles ?

Function and network space

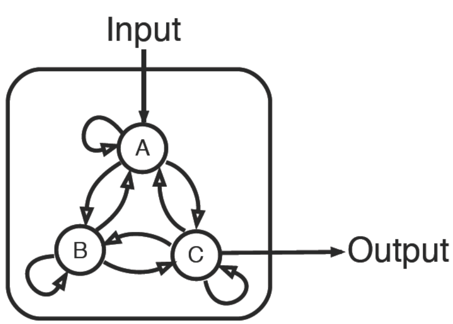
Function



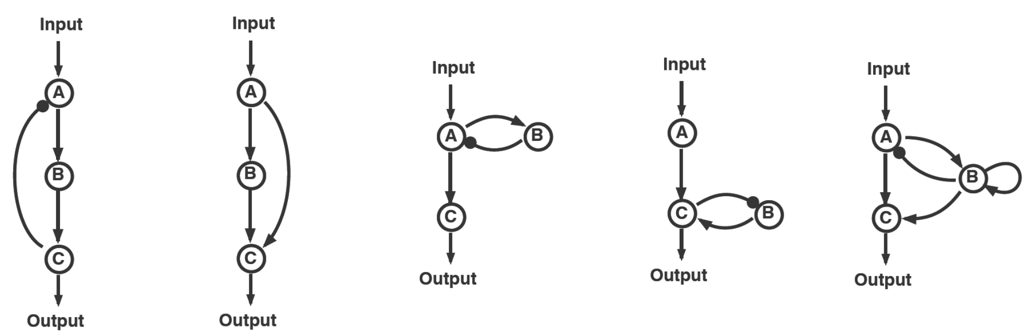
$$Sensitivity = \left|\frac{(O_{peak} - O_1)/O_1}{(I_2 - I_1)/I_1}\right|$$

$$Precision = \left|\frac{(O_2 - O_1)/O_1}{(I_2 - I_1)/I_1}\right|^{-1}$$

Network Topology

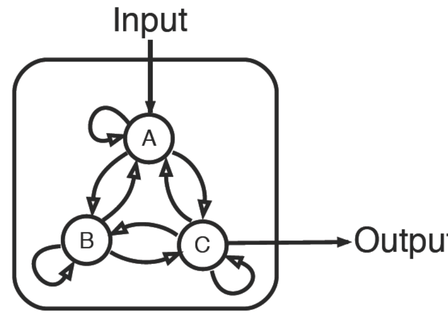


16038 networks



Examples

Linear analysis



Adaptation precision: steady state property

$$\begin{cases} \frac{dA}{dt} = f_A(A,B,C,I) = 0 \\ \frac{dB}{dt} = f_B(A,B,C) = 0 \\ \frac{dC}{dt} = f_C(A,B,C) = 0 \end{cases} \Rightarrow \begin{bmatrix} \frac{\partial f_A}{\partial A} & \frac{\partial f_A}{\partial B} & \frac{\partial f_A}{\partial C} \\ \frac{\partial f_B}{\partial A} & \frac{\partial f_B}{\partial B} & \frac{\partial f_B}{\partial C} \\ \frac{\partial f_C}{\partial A} & \frac{\partial f_C}{\partial B} & \frac{\partial f_C}{\partial C} \end{bmatrix} \begin{bmatrix} \Delta A^* \\ \Delta B^* \\ \Delta C^* \end{bmatrix} + \begin{bmatrix} \frac{\partial f_A}{\partial I} \\ 0 \\ 0 \end{bmatrix} \Delta I = 0$$

$$\begin{bmatrix} \Delta A^* \\ \Delta B^* \\ \Delta C^* \end{bmatrix} = - \begin{bmatrix} \frac{\partial f_A}{\partial A} & \frac{\partial f_A}{\partial B} & \frac{\partial f_A}{\partial C} \\ \frac{\partial f_B}{\partial A} & \frac{\partial f_B}{\partial B} & \frac{\partial f_B}{\partial C} \\ \frac{\partial f_C}{\partial A} & \frac{\partial f_C}{\partial B} & \frac{\partial f_C}{\partial C} \end{bmatrix}^{-1} \begin{bmatrix} \frac{\partial f_A}{\partial I} \\ 0 \\ 0 \end{bmatrix} \Delta I$$

$$\Delta C^* = \Delta I \frac{\partial f_A}{\partial I} \frac{|N|}{|J|}$$

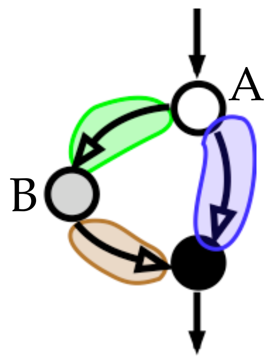
$$N = \begin{bmatrix} \frac{\partial f_B}{\partial A} & \frac{\partial f_B}{\partial B} \\ \frac{\partial f_C}{\partial A} & \frac{\partial f_C}{\partial B} \end{bmatrix}$$

$\Delta C = 0$ requires $|N|=0$ *AND* $|J|\neq 0$

Correspondence between matrix terms and regulations

links ➔ off diagonal terms

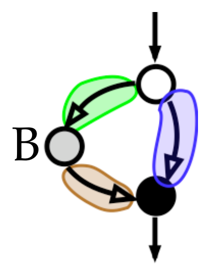
$$|J| = \begin{vmatrix} \frac{\partial f_A}{\partial A} & \frac{\partial f_A}{\partial B} & \frac{\partial f_A}{\partial C} \\ \frac{\partial f_B}{\partial A} & \frac{\partial f_B}{\partial B} & \frac{\partial f_B}{\partial C} \\ \frac{\partial f_C}{\partial A} & \frac{\partial f_C}{\partial B} & \frac{\partial f_C}{\partial C} \end{vmatrix}$$



loops ➔ terms in the determinant

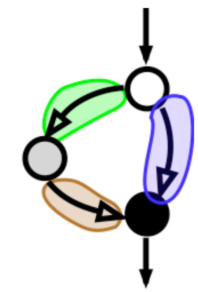
$$|J| = \begin{vmatrix} \frac{\partial f_A}{\partial A} & \frac{\partial f_A}{\partial B} & \frac{\partial f_A}{\partial C} \\ \frac{\partial f_B}{\partial A} & \frac{\partial f_B}{\partial B} & \frac{\partial f_B}{\partial C} \\ \frac{\partial f_C}{\partial A} & \frac{\partial f_C}{\partial B} & \frac{\partial f_C}{\partial C} \end{vmatrix}$$

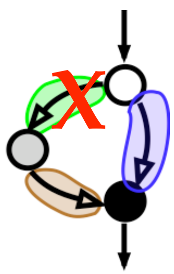
$$|N| = \begin{vmatrix} \frac{\partial f_B}{\partial A} & \frac{\partial f_B}{\partial B} \\ \frac{\partial f_C}{\partial A} & \frac{\partial f_C}{\partial B} \end{vmatrix} = \underbrace{\frac{\partial f_B}{\partial A}\frac{\partial f_C}{\partial B}}_{①} - \underbrace{\frac{\partial f_B}{\partial B}\frac{\partial f_C}{\partial A}}_{②}$$



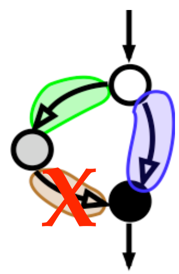
$$|N| = \frac{\partial f_B}{\partial A}\frac{\partial f_C}{\partial B} - \frac{\partial f_B}{\partial B}\frac{\partial f_C}{\partial A} = 0$$

① = ② = 0





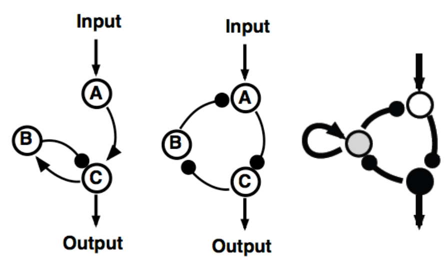
or



$$\frac{\partial f_C}{\partial A} \neq 0 \Rightarrow \frac{\partial f_B}{\partial B} = 0 \rightarrow f_B = g(A,C) \text{ or } f_B = B \cdot g(A,C)$$

No feedforward loop

B is a buffer node



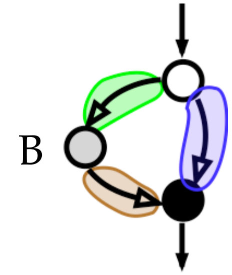
NFBLB class

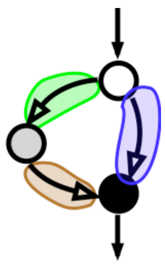
$$|J| = \begin{vmatrix} \frac{\partial f_A}{\partial A} & \frac{\partial f_A}{\partial B} & \frac{\partial f_A}{\partial C} \\ \frac{\partial f_B}{\partial A} & 0 & \frac{\partial f_B}{\partial C} \\ \frac{\partial f_C}{\partial A} & \frac{\partial f_C}{\partial B} & \frac{\partial f_C}{\partial C} \end{vmatrix} < 0$$

At least one negative feedback loop

$$|N| = \frac{\partial f_B}{\partial A}\frac{\partial f_C}{\partial B} - \frac{\partial f_B}{\partial B}\frac{\partial f_C}{\partial A} = 0$$

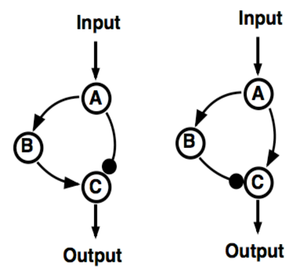
① = ② ≠ 0





Robustly achieving $|N|=0$

$$f_B = \alpha A + g(C)B$$



IFFLP class

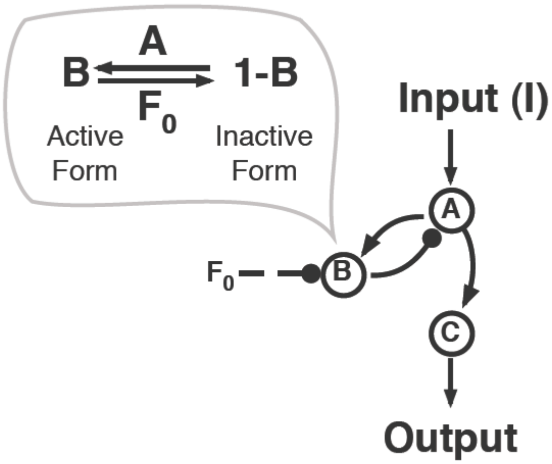
Feedforward loop

B is a proportioner node

$$\frac{\frac{\partial f_B}{\partial A}\frac{\partial f_C}{\partial B}}{\frac{\partial f_C}{\partial A}} = \frac{\partial f_B}{\partial B} < 0$$

Incoherent feedforward

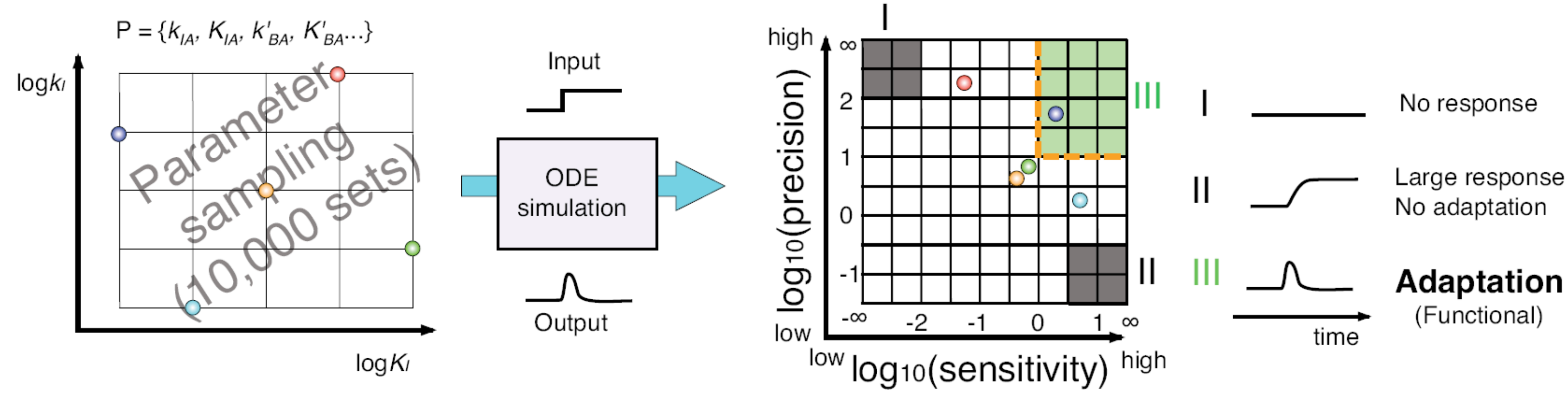
Topology-function mapping



$$\frac{dA}{dt} = k_{IA} I \frac{(1-A)}{(1-A)+K_{IA}} - k'_{BA} B \frac{A}{A+K'_{BA}}$$

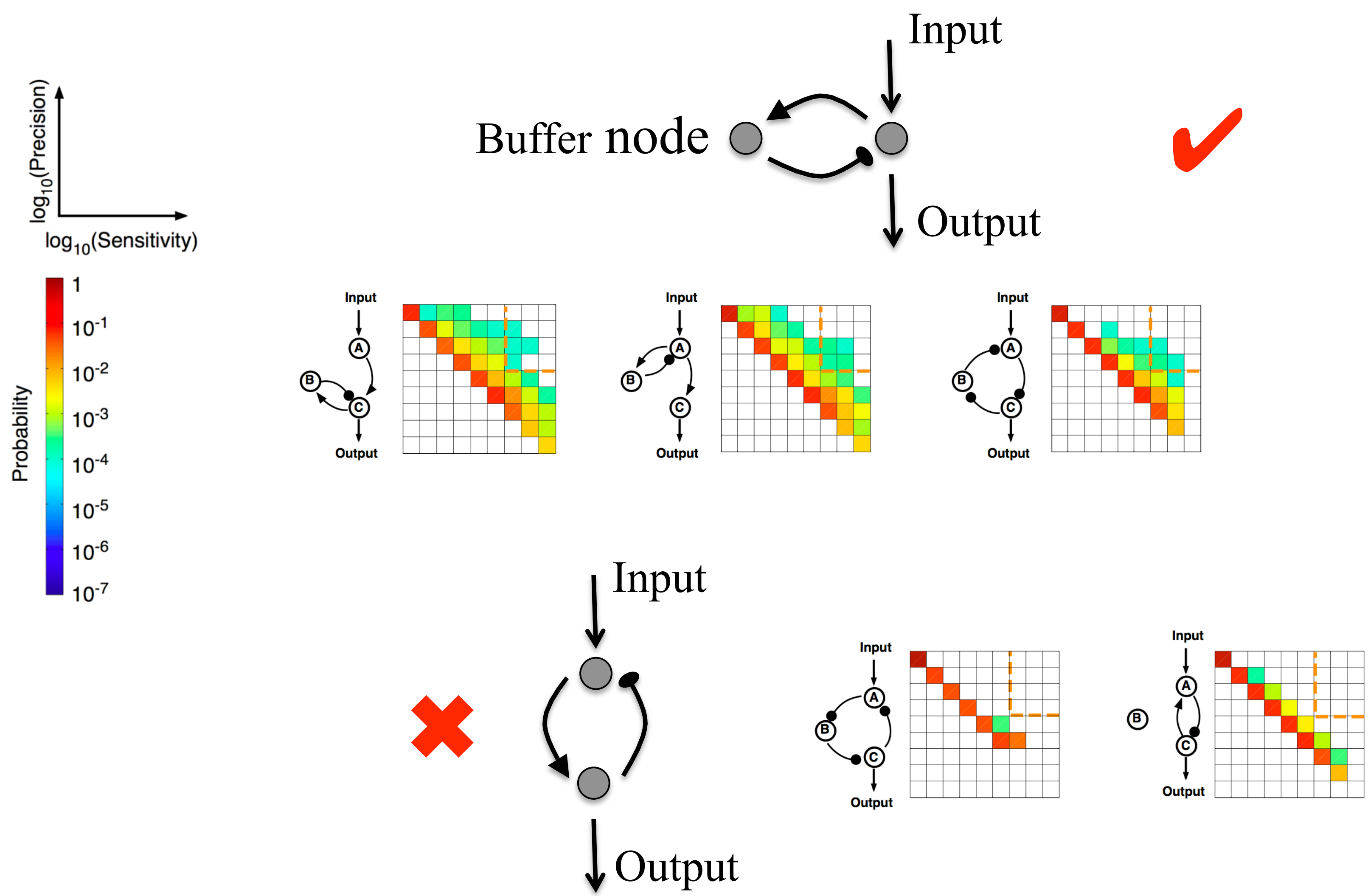
$$\frac{dB}{dt} = k_{AB} A \frac{(1-B)}{(1-B)+K_{AB}} - k'_{F_0B} F_0 \frac{B}{B+K'_{F_0B}}$$

$$\frac{dC}{dt} = k_{AC} A \frac{(1-C)}{(1-C)+K_{AC}} - k'_{F_0C} F_0 \frac{C}{C+K'_{F_0C}}$$



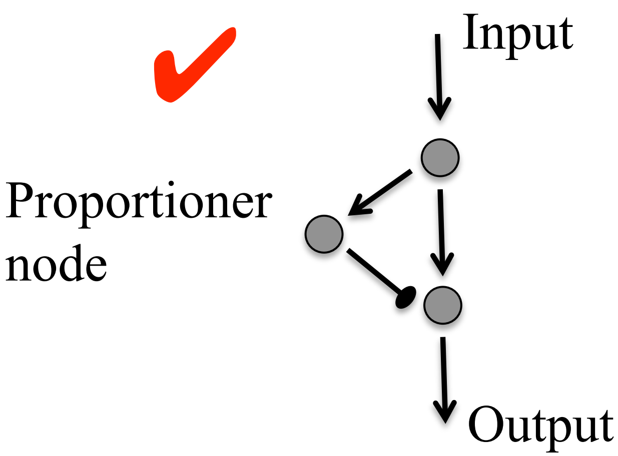
k_{cat}: 0.1~10
K_m: 0.001~100

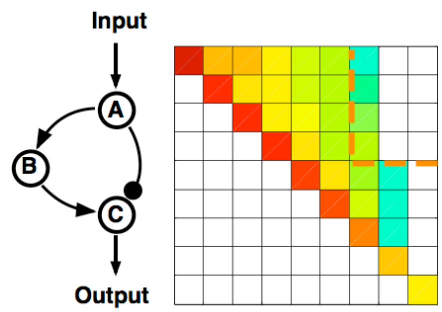
Core adaptive topology
--Negative feedback loop with a buffer

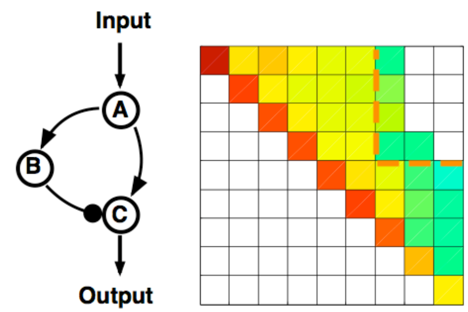


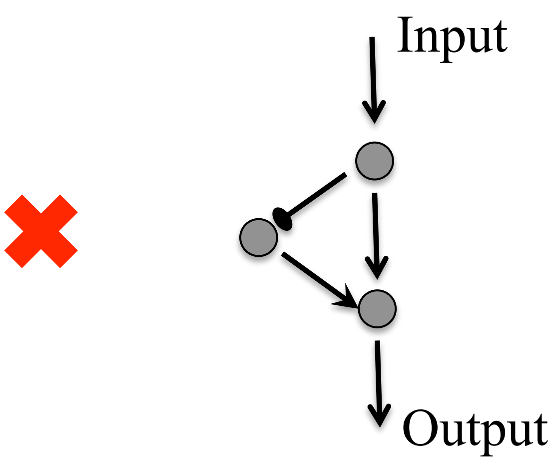
Core adaptive topology

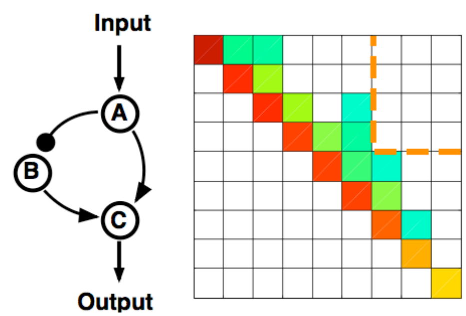
--Incoherent feed-forward loop with a proportioner node





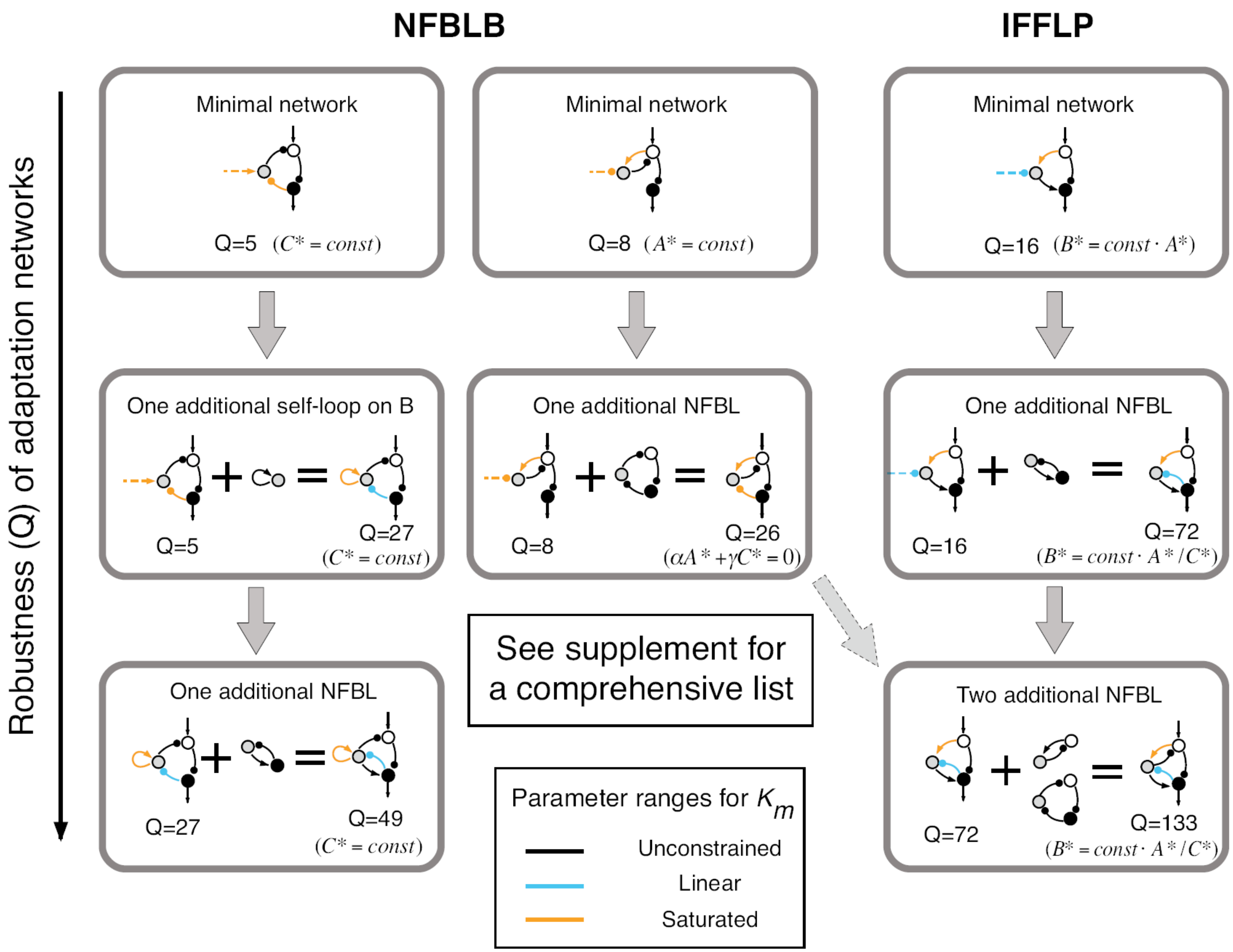




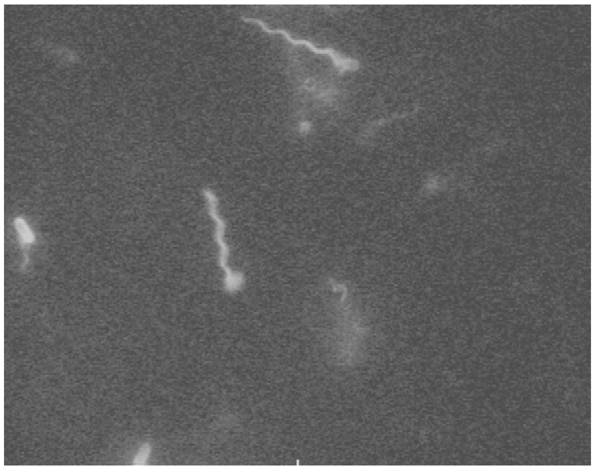


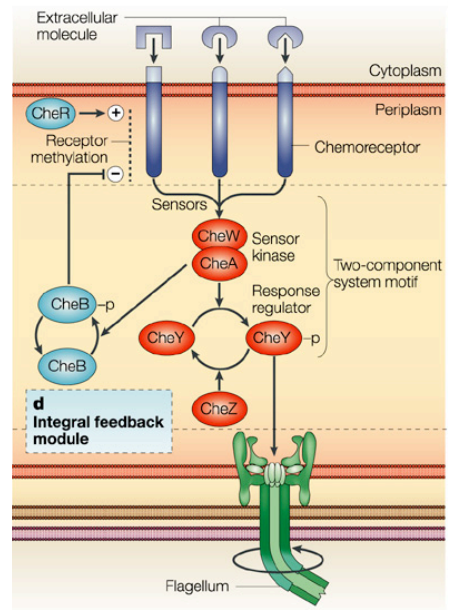
Design table of adaptation circuits

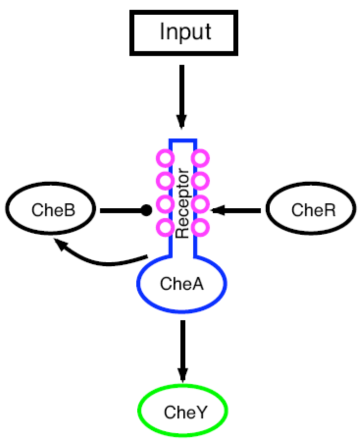
Combinations that improve the performance (Examples)

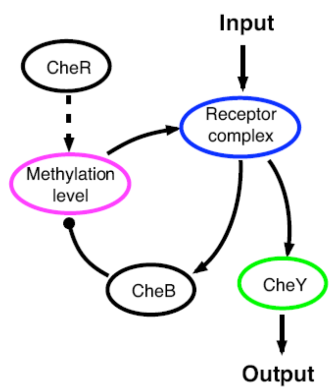


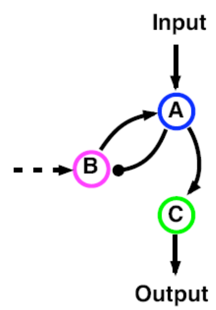
Adaptation circuit of E coli











NFBLB

结束语

•生物世界不仅给物理学提供了一个“应用”的场所，更给物理学的发展带来了新了机遇和挑战。

•技术的进步－－更小（单分子）、更多（高通量）、更准确（荧光标记）、更可控（微流）、等等－－ 正在以前所未有的速度产生大量的，高分辨率的数据。为研究生物体系提供了新的方法和思路。

•生命科学与其它自然及工程学科的融合即将或正在导致一场深刻的革命。这场革命将对本世纪的科学、社会、环境、人类健康等许多领域产生深远的影响。

•物理学在其中也将产生一个新的飞跃，“生命的物理”将不再是梦。

Acknowledgments

(Former) students and postdocs:

Hao Li (NEC->UCSF)

Ying Lv (PKU->Rockefeller->HMS)

Tao Long (PKU->Princeton->Stanford)

Fangting Li (PKU)

Wenzhe Ma (PKU->UCSF->HMS)

Ala Trusina (UCSF->NBI)

Collaborators:

Ned Wingreen (NEC->Princeton)

Luhua Lai (PKU)

Chen Zeng (GWU)

Qi Ouyang (PKU)

Hana El-Samad (UCSF)

Wendell Lim (UCSF)

Protein designability Robustness of cell cycle network Biochemical adaptation

谢谢大家！