系统生物学

(Systems Biology)

马彬广

系统生物学大纲

（第一讲）

系统生物学大纲

- 定义 (Definition)
- 学科背景 (Background)
- 内容体系和研究方法 (Contents & Methods)
- 学术组织、会议和刊物 (Research Community)
- 主要参考资料 (References)
- 课程安排和考核 (Plan & Exam)

A confusing concept

支持者说：
- Revolution
- New Paradigm
- 21th Century Biology

反对者说：
- 含混不清
- 新瓶老酒
- 皇帝新装

The Scientist | Volume 17 | Issue 19 | 27 Oct. 6, 2003

那么，究竟什么是“**系统生物学**”呢？

什么是系统生物学
(What is systems biology)

系统生物学 (Systems Biology)

系统　生物学 (Systems　Biology)

Q:　系统生物学 = 系统　+　生物学?

A:　系统生物学 ≠ 系统　+　生物学

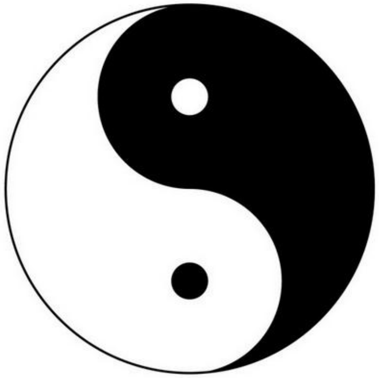
从“系统”的视角，对生物进行研究：

因此，　Systems Biology ≈ Systems（Biology）

$$y = f(x)$$

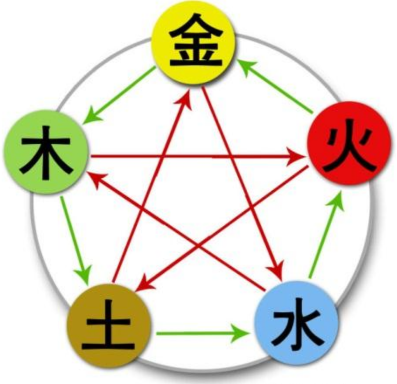
系统的思想（相互作用着的整体）

中国古代哲学



辩证唯物主义：物质世界是由无数相互联系、相互依赖、相互制约、相互作用的事物和过程所形成的统一整体

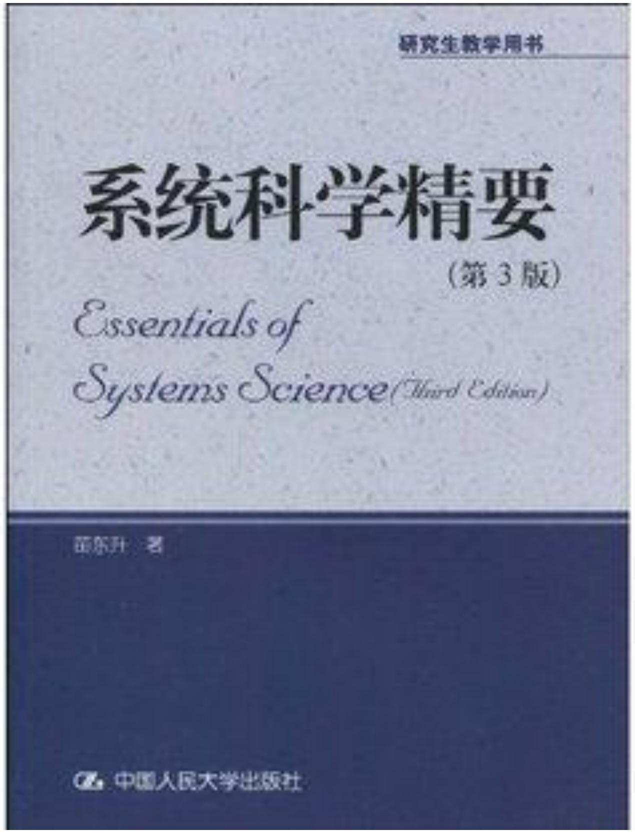
---马克思、恩格斯



五行生尅图

系统特性

- 多元性和差异性的统一
- 相关性：所有元素都不是孤立的
- 涌现性：1+1>2



研究生教学用书

系统科学精要

（第3版）

Essentials of Systems Science (Third Edition)

苗东升 著

中国人民大学出版社

苗东升，《系统科学精要》

What is Systems Biology?

- Systems biology is an emergent field that aims at system-level understanding of biological systems.

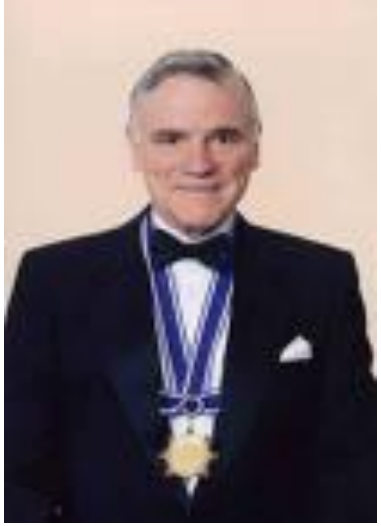
To understand biology at the system level, we must examine the structure and dynamics of cellular and organismal function, rather than the characteristics of isolated parts of a cell or organism.

Science, 295, 1662-1664 (2002).

Hiroaki Kitano（北野宏明）Ph.D
Project Director. Sony Computer Science Laboratories

What is Systems Biology?

Systems biology is a scientific discipline that endeavors to quantify all of the molecular elements of a biological system to assess their interactions and to integrate that information into graphical network models that serve as predictive hypotheses to explain emergent behaviors.



Science, 360, 640-643 (2004).

Leroy Hood （MD PhD） is recognized as one of the world’s leading scientists in molecular biotechnology and genomics. In 2000, Hood co-founded, and is currently President of, the Institute for Systems Biology in Seattle which pioneers systems approaches to biology and medicine.

“Organisms function in an integrated manner - our senses, our muscles, our metabolism and our mind work together seamlessly. But biologists have historically studied organisms part by part and celebrated the modern ability to study them molecule by molecule, gene by gene. Systems biology is devoted to a new science, a critical science of the future that seeks to understand the integration of the pieces to form biological systems.”

-David Baltimore, Nobel Laureate

什么是系统生物学？

系统生物学是在细胞、组织、器官和生物体整体水平上研究结构和功能各异的分子及其相互作用，并通过计算生物学来定量阐明和预测生物功能和行为。

中国科学院院刊

2004, 19（1）：31-34.

杨胜利 院士

定义
(Definition)

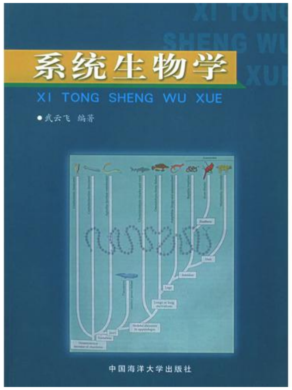
- 系统生物学是研究生命系统各层次组分在时空中发生的相互作用，以发现系统的组织原理、动态行为和涌现属性中规律的学科。

- Systems biology is a discipline to study the spatial-temporal interactions of components in different levels of biological systems, seeking to find the laws in the organization principles, dynamic behaviors and emergent properties of such biological systems.

The meaning of “Systems” in “Systems Biology”

Not: Systematics (系统分类学，种系发生学)

✗



Same as in “Systems Science”

✓

Also called: “New Systems Biology” or

“Contemporary Systems Biology”

An “old” but “new” field

- Alfred Lotka, Elements of Physical Biology (1925)

- Ludwig von Bertalanffy, The Organism Considered as a Physical System (1940)

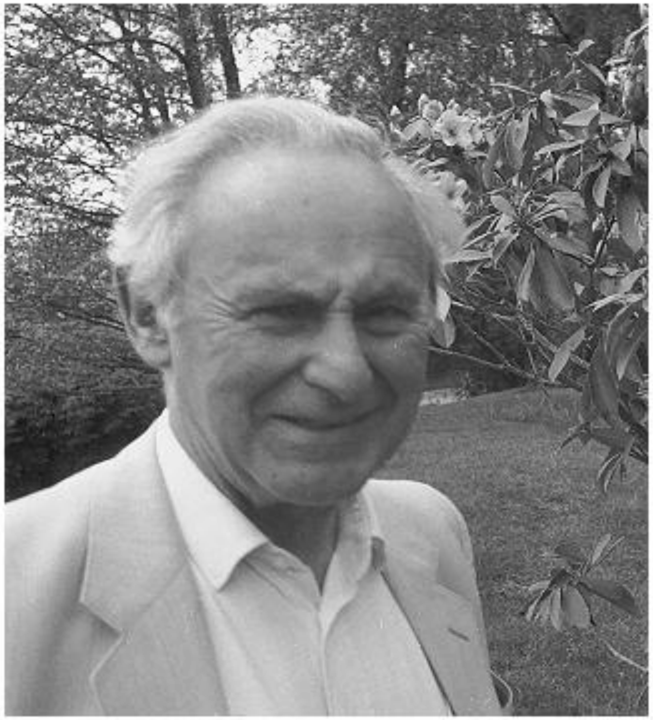
- Erwin Schrodinger, What is life? with mind and matter and autobiographical sketches.

- Norbert Wiener, Cybernetics (1948)

- Claude E. Shannon, A Mathematical Theory of Communication (1948)
- Hodgkin & Huxley, the model of electrical excitability of neurons (1952)

- Henrik Kacser, Metabolic Control Analysis, (1957)
- … and so on.

Henrik Kacser.
Systems Biology. Described in 1957



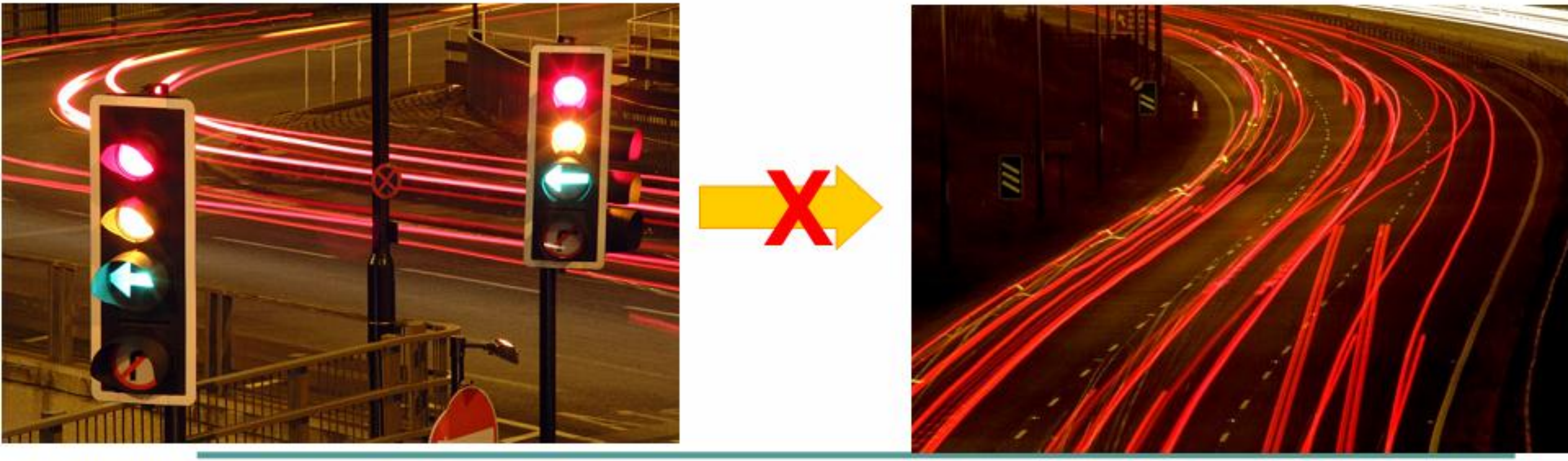
- "The properties of a system are in fact more than (or different from) the sum of the properties of its components, a fact often overlooked in zealous attempts to demonstrate additivity of certain phenomena. It is with these systemic properties that we shall be mainly concerned"
- "There are no concepts in chemistry or physics equivalent to genes\ regulation\ epigenesis precisely because these are properties only possible in systems of greater complexity than have been subjected to detailed analysis by those sciences"

KACSER H 1957 Some physicochemical aspect of biological organisation Appendix to The Strategy of the Genes, (Waddington CH, ed), pp 191-249. London: George Allen and Unwin

Henrik Kacser. The founder of Metabolic Control Analysis

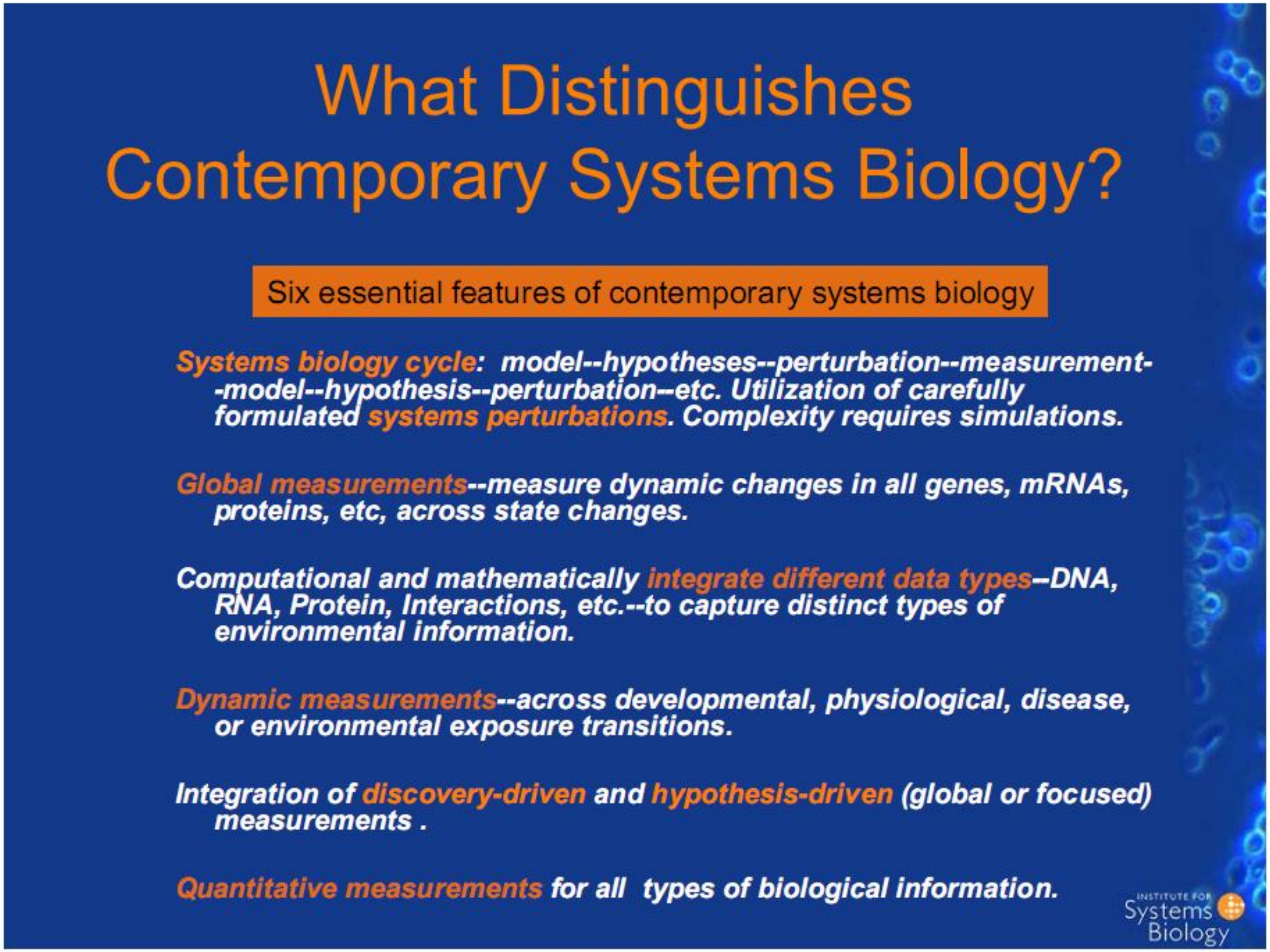
The expectation that a metabolic pathway will be controlled by a single pacemaker reaction is a fallacy,

Most of the experimental criteria used in the supposed identification of such steps are misleading. Instead, varying amounts of control can be distributed over the enzymes of the pathway, but this is a property of the metabolic system as a whole *and cannot be predicted from the characteristics of the enzymes in isolation.*



KACSER, H. & BURNS, J. A. (1973) The control of flux. *Symp. Soc. Exp. Biol.*27, 65-104.

What makes “Systems Biology” new?



What Distinguishes Contemporary Systems Biology?

Six essential features of contemporary systems biology

***Systems biology cycle*: model--hypotheses--perturbation--measurement--model--hypothesis--perturbation--etc. Utilization of carefully formulated *systems perturbations*. Complexity requires simulations.**

***Global measurements*--measure dynamic changes in all genes, mRNAs, proteins, etc, across state changes.**

***Computational and mathematically* *integrate different data types*--DNA, RNA, Protein, Interactions, etc.--to capture distinct types of environmental information.**

***Dynamic measurements*--across developmental, physiological, disease, or environmental exposure transitions.**

Integration of* *discovery-driven* *and* *hypothesis-driven* *(global or focused) measurements .

Quantitative measurements* *for all types of biological information.

Institute for Systems Biology

----by Leroy Hood

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背景学科

- 生理学
- 分子生物学
- 生物信息学及各种组学

生理学

生理学（**physiology**）是生物学的一个分支，是以生物机体的生命活动现象和机体各个组成部分的功能为研究对象的一门科学。

Physiology is the science of studying the functional activities and its mechanisms in biological body.
For example: why can heart automatically beat?

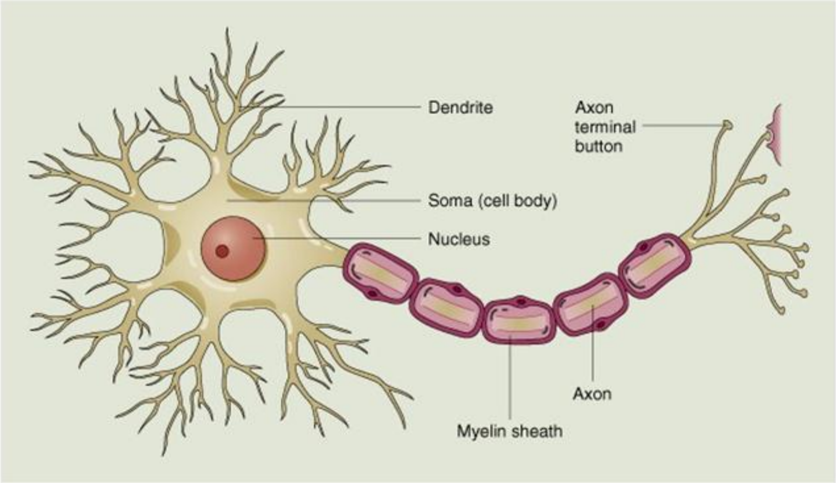
英国人哈维是近代生理学的奠基人

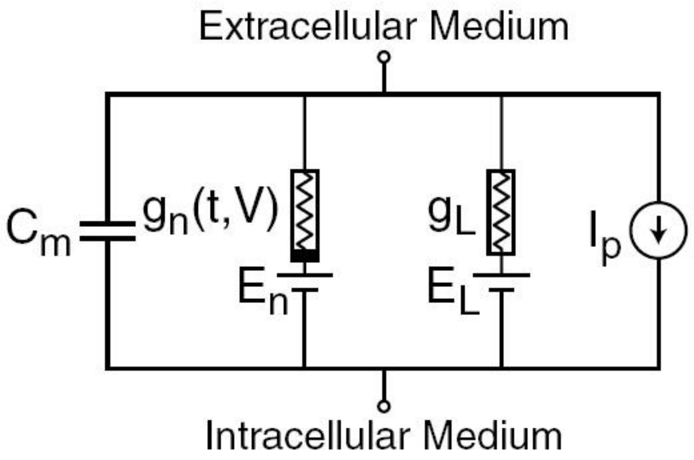
William Harvey (1578-1657)

主要内容：不同系统、器官、组织、细胞、分子的功能及其相互协调；功能调节机制；机体如何适应环境.

艺术家们描绘的Hales做的测量马的血压实验，玻璃管中血液的高度反应了血液循环中的压力。

Hodgkin-Huxley神经传导生理模型



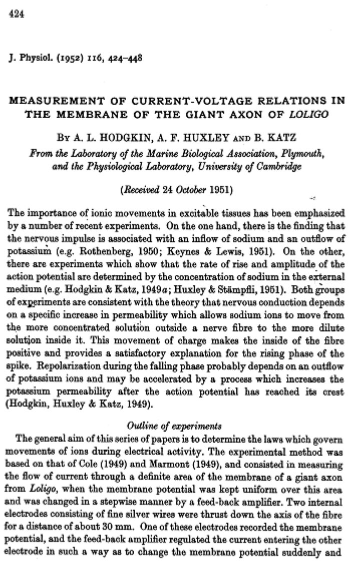


$$I = C_M \frac{dV}{dT} + \bar{g}_K n^4 (V - V_K) + \bar{g}_{Na} m^3 h (V - V_{Na}) + \bar{g}_l (V - V_l)$$

$$\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n$$

$$\frac{dm}{dt} = \alpha_m (1 - m) - B_m m$$

$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h$$



424

J. Physiol. (1952) 116, 424–448

MEASUREMENT OF CURRENT-VOLTAGE RELATIONS IN THE MEMBRANE OF THE GIANT AXON OF *LOLIGO*

BY A. L. HODGKIN, A. F. HUXLEY AND B. KATZ

From the Laboratory of the Marine Biological Association, Plymouth,
and the Physiological Laboratory, University of Cambridge

(*Received 24 October* 1951)

The importance of ionic movements in excitable tissues has been emphasized by a number of recent experiments. On the one hand, there is the finding that the nervous impulse is associated with an inflow of sodium and an outflow of potassium (e.g. Rothenberg, 1950; Keynes & Lewis, 1951). On the other, there are experiments which show that the rate of rise and amplitude of the action potential are determined by the concentration of sodium in the external medium (e.g. Hodgkin & Katz, 1949*a*; Huxley & Stämpfli, 1951). Both groups of experiments are consistent with the theory that nervous conduction depends on a specific increase in permeability which allows sodium ions to move from the more concentrated solution outside a nerve fibre to the more dilute solution inside it. This movement of charge makes the inside of the fibre positive and provides a satisfactory explanation for the rising phase of the spike. Repolarization during the falling phase probably depends on an outflow of potassium ions and may be accelerated by a process which increases the potassium permeability after the action potential has reached its crest (Hodgkin, Huxley & Katz, 1949).

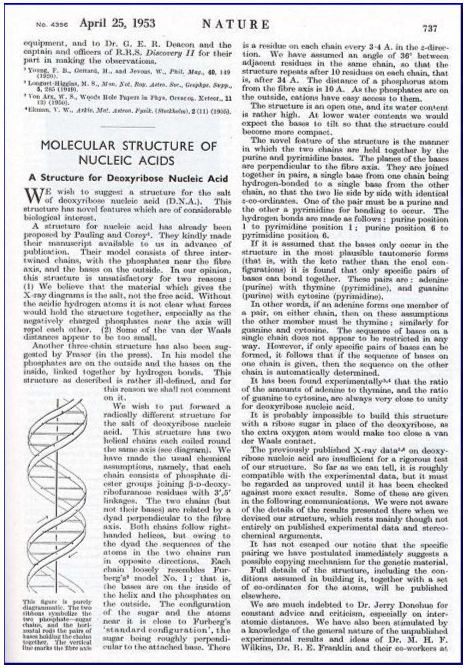
Outline of experiments

The general aim of this series of papers is to determine the laws which govern movements of ions during electrical activity. The experimental method was based on that of Cole (1949) and Marmont (1949), and consisted in measuring the flow of current through a definite area of the membrane of a giant axon from *Loligo*, when the membrane potential was kept uniform over this area and was changed in a stepwise manner by a feed-back amplifier. Two internal electrodes consisting of fine silver wires were thrust down the axis of the fibre for a distance of about 30 mm. One of these electrodes recorded the membrane potential, and the feed-back amplifier regulated the current entering the other electrode in such a way as to change the membrane potential suddenly and

分子生物学

□ **分子生物学**是研究核酸、蛋白质等生物大分子的结构与功能，并从分子水平上阐明蛋白质与蛋白质、蛋白质与核酸之间的互作及其基因表达调控机理的学科。

□ 广义上，分子生物学包括对蛋白质和核酸等生物大分子结构与功能的研究，以及从分子水平上阐明生命现象和生物规律，但目前主要研究基因的结构与功能、复制、转录、表达和调控，确切地应称为分子遗传学。



No. 4356 April 25, 1953 NATURE 737

equipment, and to Dr. G. E. R. Deacon and the captain and officers of R.R.S. *Discovery II* for their part in making the observations.

[1] Young, F. B., Gerrard, H., and Jevons, W., *Phil. Mag.*, **40**, 149 (1920).

[2] Longuet-Higgins, M. S., *Mon. Not. Roy. Astro. Soc., Geophys. Supp.*, **5**, 285 (1949).

[3] Von Arx, W. S., Woods Hole Papers in Phys. Oceanog. Meteor., **11** (3) (1950).

[4] Ekman, V. W., *Arkiv. Mat. Astron. Fysik. (Stockholm)*, **2** (11) (1905).

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey[1]. They kindly made their manuscript available to us in advance of publication. Their model consists of three intertwined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion, this structure is unsatisfactory for two reasons: (1) We believe that the material which gives the X-ray diagrams is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what forces would hold the structure together, especially as the negatively charged phosphates near the axis will repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Fraser (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment on it.

This figure is purely diagrammatic. The two ribbons symbolize the two phosphate—sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis

We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions, namely, that each chain consists of phosphate diester groups joining β-D-deoxyribofuranose residues with 3′,5′ linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to the dyad the sequences of the atoms in the two chains run in opposite directions. Each chain loosely resembles Furberg's[2] model No. 1; that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration of the sugar and the atoms near it is close to Furberg's 'standard configuration', the sugar being roughly perpendicular to the attached base. There is a residue on each chain every 3·4 A. in the z-direction. We have assumed an angle of 36° between adjacent residues in the same chain, so that the structure repeats after 10 residues on each chain, that is, after 34 A. The distance of a phosphorus atom from the fibre axis is 10 A. As the phosphates are on the outside, cations have easy access to them.

The structure is an open one, and its water content is rather high. At lower water contents we would expect the bases to tilt so that the structure could become more compact.

The novel feature of the structure is the manner in which the two chains are held together by the purine and pyrimidine bases. The planes of the bases are perpendicular to the fibre axis. They are joined together in pairs, a single base from one chain being hydrogen-bonded to a single base from the other chain, so that the two lie side by side with identical z-co-ordinates. One of the pair must be a purine and the other a pyrimidine for bonding to occur. The hydrogen bonds are made as follows: purine position 1 to pyrimidine position 1; purine position 6 to pyrimidine position 6.

If it is assumed that the bases only occur in the structure in the most plausible tautomeric forms (that is, with the keto rather than the enol configurations) it is found that only specific pairs of bases can bond together. These pairs are: adenine (purine) with thymine (pyrimidine), and guanine (purine) with cytosine (pyrimidine).

In other words, if an adenine forms one member of a pair, on either chain, then on these assumptions the other member must be thymine; similarly for guanine and cytosine. The sequence of bases on a single chain does not appear to be restricted in any way. However, if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined.

It has been found experimentally[3,4] that the ratio of the amounts of adenine to thymine, and the ratio of guanine to cytosine, are always very close to unity for deoxyribose nucleic acid.

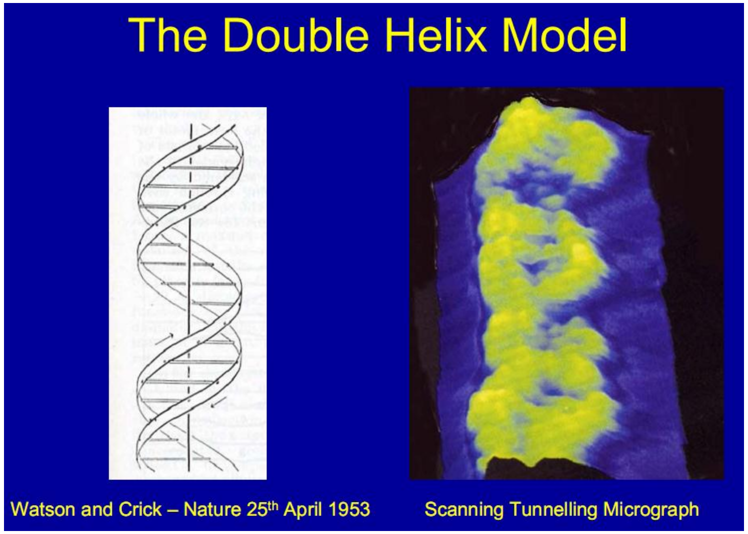
It is probably impossible to build this structure with a ribose sugar in place of the deoxyribose, as the extra oxygen atom would make too close a van der Waals contact.

The previously published X-ray data[5,6] on deoxyribose nucleic acid are insufficient for a rigorous test of our structure. So far as we can tell, it is roughly compatible with the experimental data, but it must be regarded as unproved until it has been checked against more exact results. Some of these are given in the following communications. We were not aware of the details of the results presented there when we devised our structure, which rests mainly though not entirely on published experimental data and stereochemical arguments.

It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

Full details of the structure, including the conditions assumed in building it, together with a set of co-ordinates for the atoms, will be published elsewhere.

We are much indebted to Dr. Jerry Donohue for constant advice and criticism, especially on interatomic distances. We have also been stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. M. H. F. Wilkins, Dr. R. E. Franklin and their co-workers at



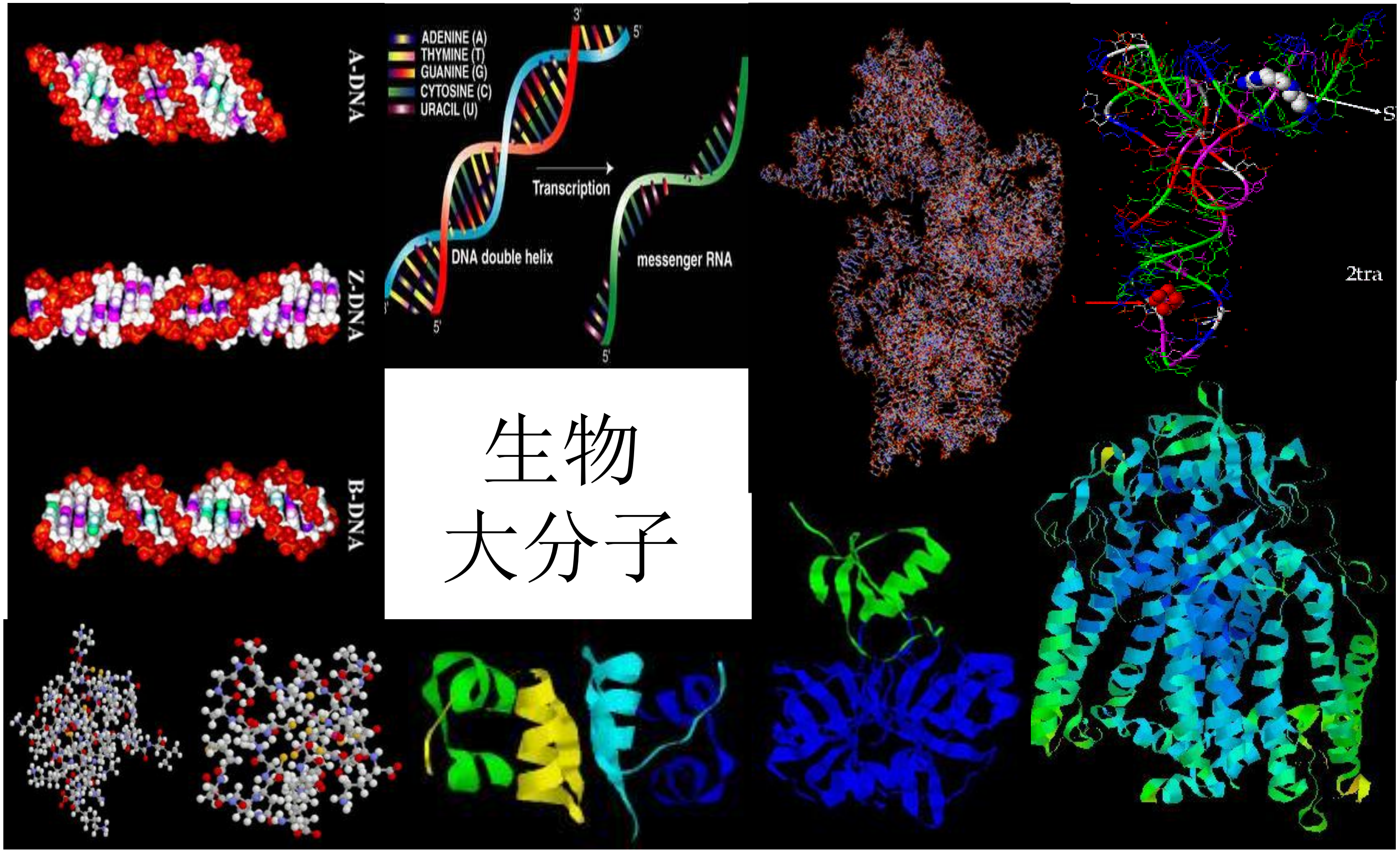
The Double Helix Model

Watson and Crick – Nature 25th April 1953

Scanning Tunnelling Micrograph

生物
大分子

DNA　mRNA　16S rRNA　tRNA



蜘蛛毒素　金属硫蛋白　胰岛素　蛋白酶　光合作用受体

生物信息学

- □ Bioinformatics is the application of statistics and computer science to the field of molecular biology. （from Wiki）
- □ As Science: 从信息的角度，认识生命活动中的规律。
- □ As Technology: 信息技术(IT)在生命科学（特别是）分子生物学中的应用。

Bioinformatics-- a definition by NIH(1995)

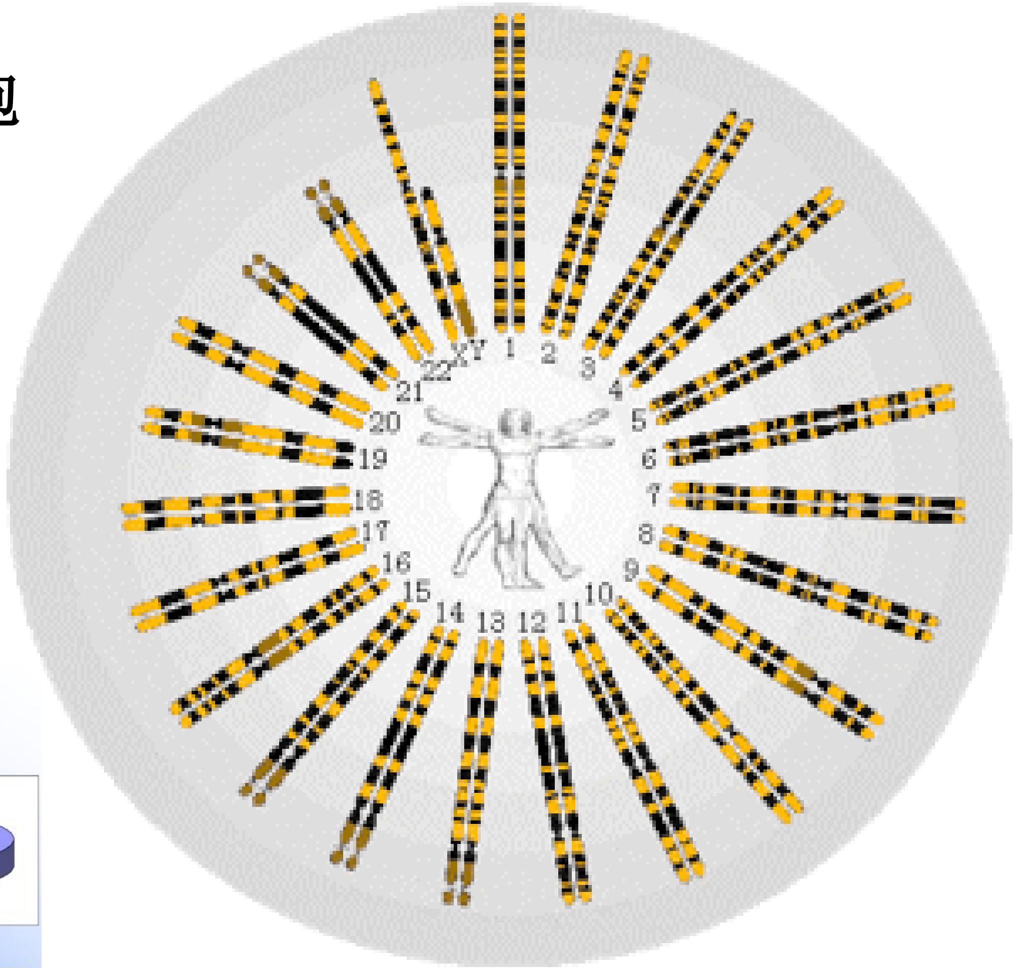
Bioinformatics is defined as a scientific discipline that encompasses all aspects of biological information acquisition, processing, storage, distribution, analysis and interpretation, that combines the tools and techniques of mathematics, computer science and biology with the aim of understanding the biological significance of a variety of data.

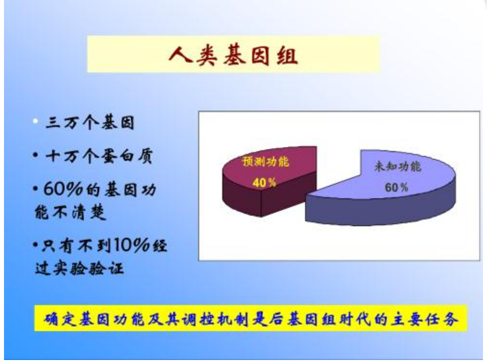
人类基因组计划

- □ 基因组(Genome)：包含细胞或生物体全套的遗传信息的全部遗传物质。

- □ 人类基因组：

  3.2×109 bp





人类基因组

- 三万个基因
- 十万个蛋白质
- 60%的基因功能不清楚
- 只有不到10%经过实验验证

确定基因功能及其调控机制是后基因组时代的主要任务

曼哈顿原子弹计划

阿波罗登月计划

人类基因组计划

为什么提出HGP？

60年代初，美国总统Kennedy提出两个科学计划：

☑登月计划

生物信息资源

🔒攻克肿瘤计划 ← 人类遗传信息的复杂性

↓

人类基因组计划

(HGP，Human Genome Project)

目标：整体上破解人类遗传信息的奥秘

2000.6.26 公共领域和Celera公司同时宣布完成人类基因组工作草图
2001.2.15 《Nature》刊文发表国际公共领域结果
2001.2.16 《Science》刊文发表Celera公司及其合作者结果

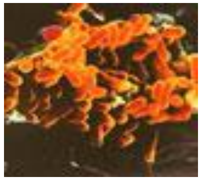
2001年2月15日《Nature》封面

2001年2月16日《Science》封面

Ureaplasma urealyticum

Bacillus subtilis

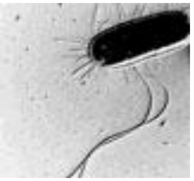
Drosophila melanogaster



Rickettsia prowazekii

Helicobacter pylori

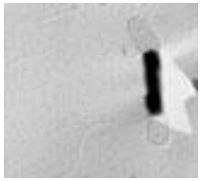
Buchnerasp. APS



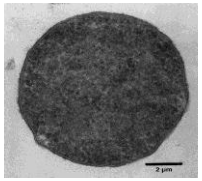
Escherichia coli

human

Arabidopsis



Thermotoga maritima



Thermoplasma acidophilum

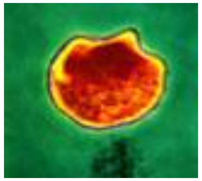
mouse

Caenorhabitis elegans

rat

Borrelia burgorferi

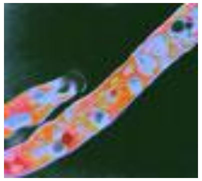
Plasmodium falciparum



Borrelia burgorferi

Aquifex aeolicus

Neisseria meningitidis Z2491



Mycobacterium tuberculosis

模式生物

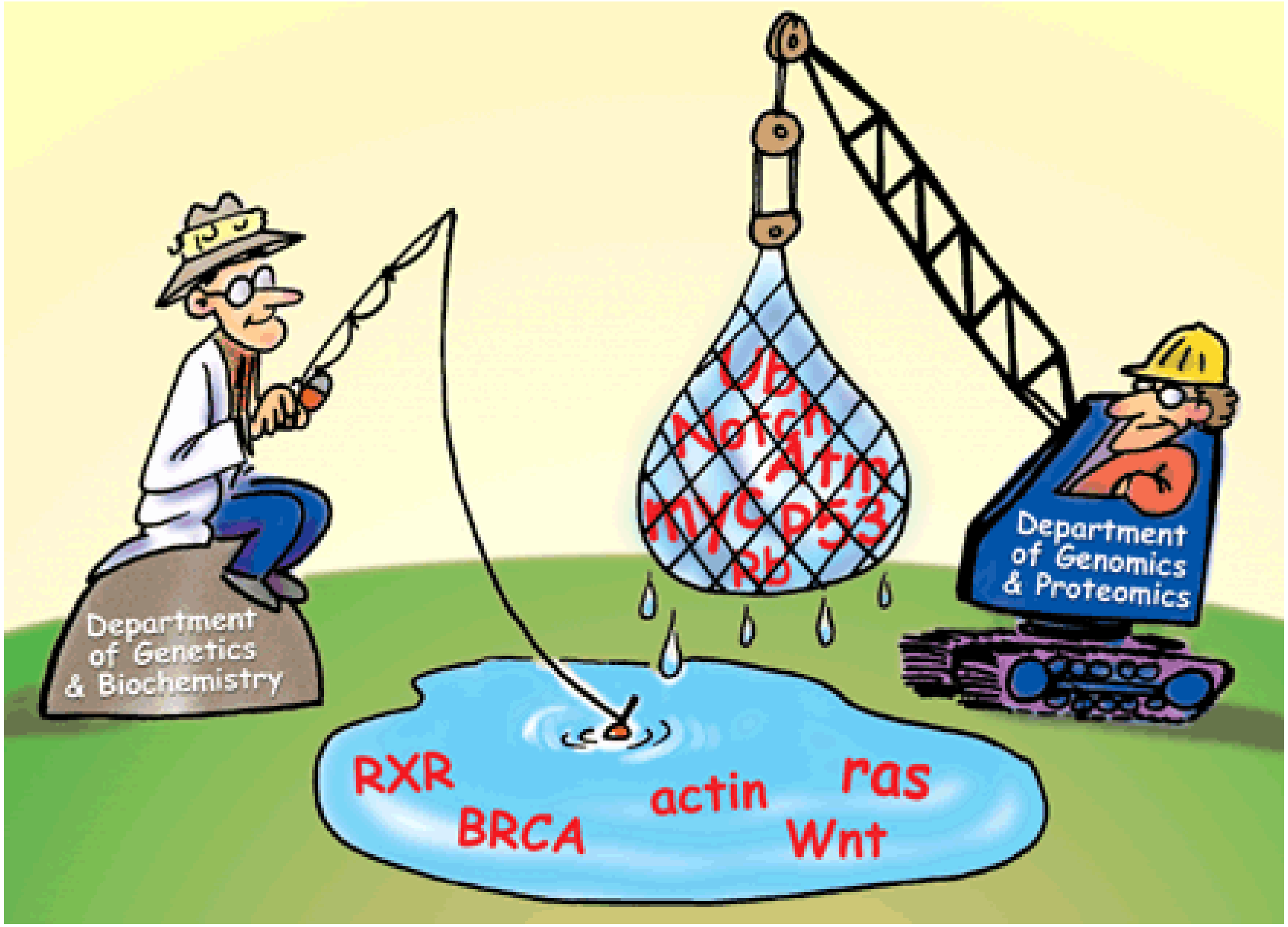
农作物

maize

rice

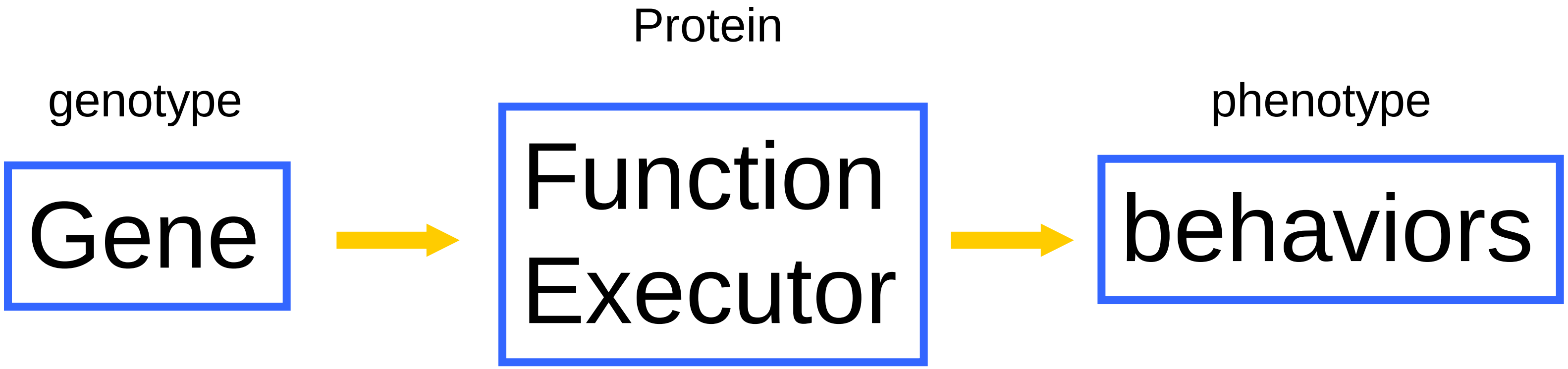
soybean

High throughput experiment



Science, **Vol 291**, 1221-1224 , 16 February 2001

Challenges in decoding genomic information



genotype

Gene

Protein

Function Executor

phenotype

behaviors

Proteomics

Proteomics is the large-scale study of proteins, particularly their structures and functions.
(from Wiki)

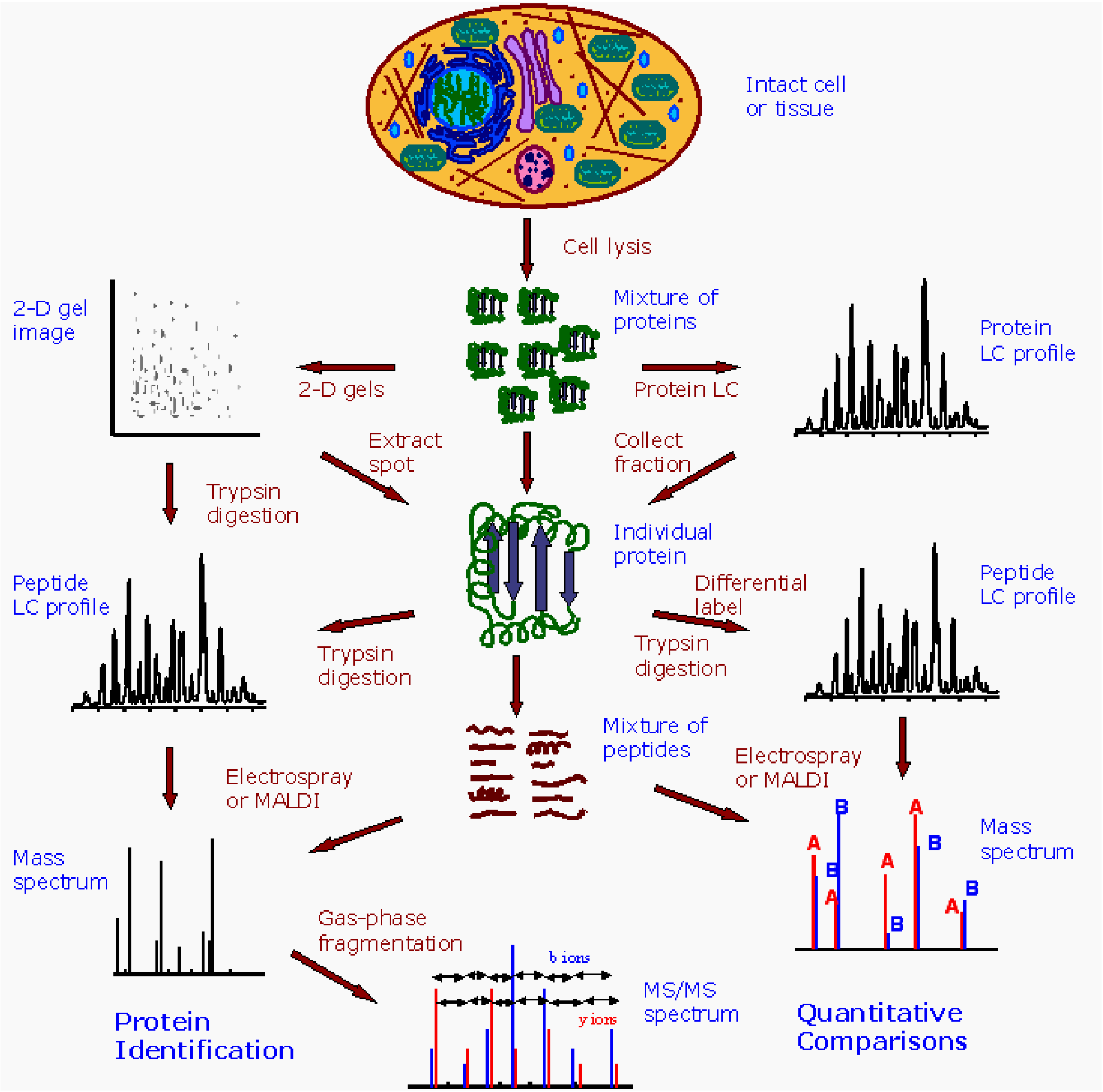
Robotic preparation of MALDI mass spectrometry samples on a sample carrier.

Proteome:

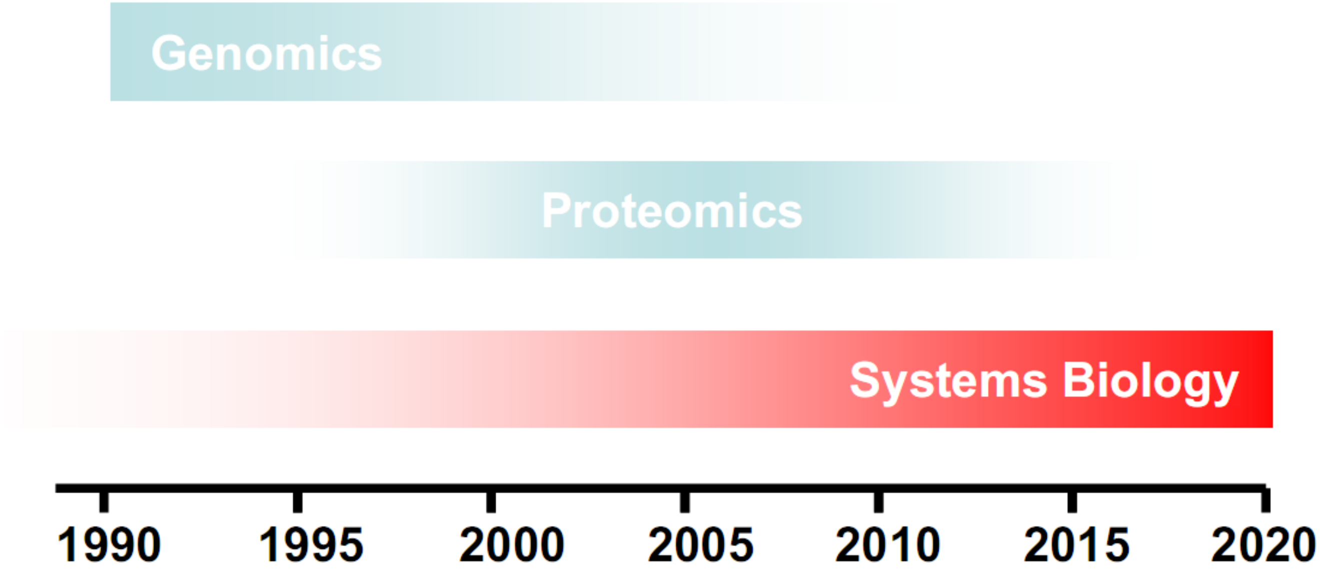
meaning 1: a set of proteins

meaning 2: coded proteins by the whole genome

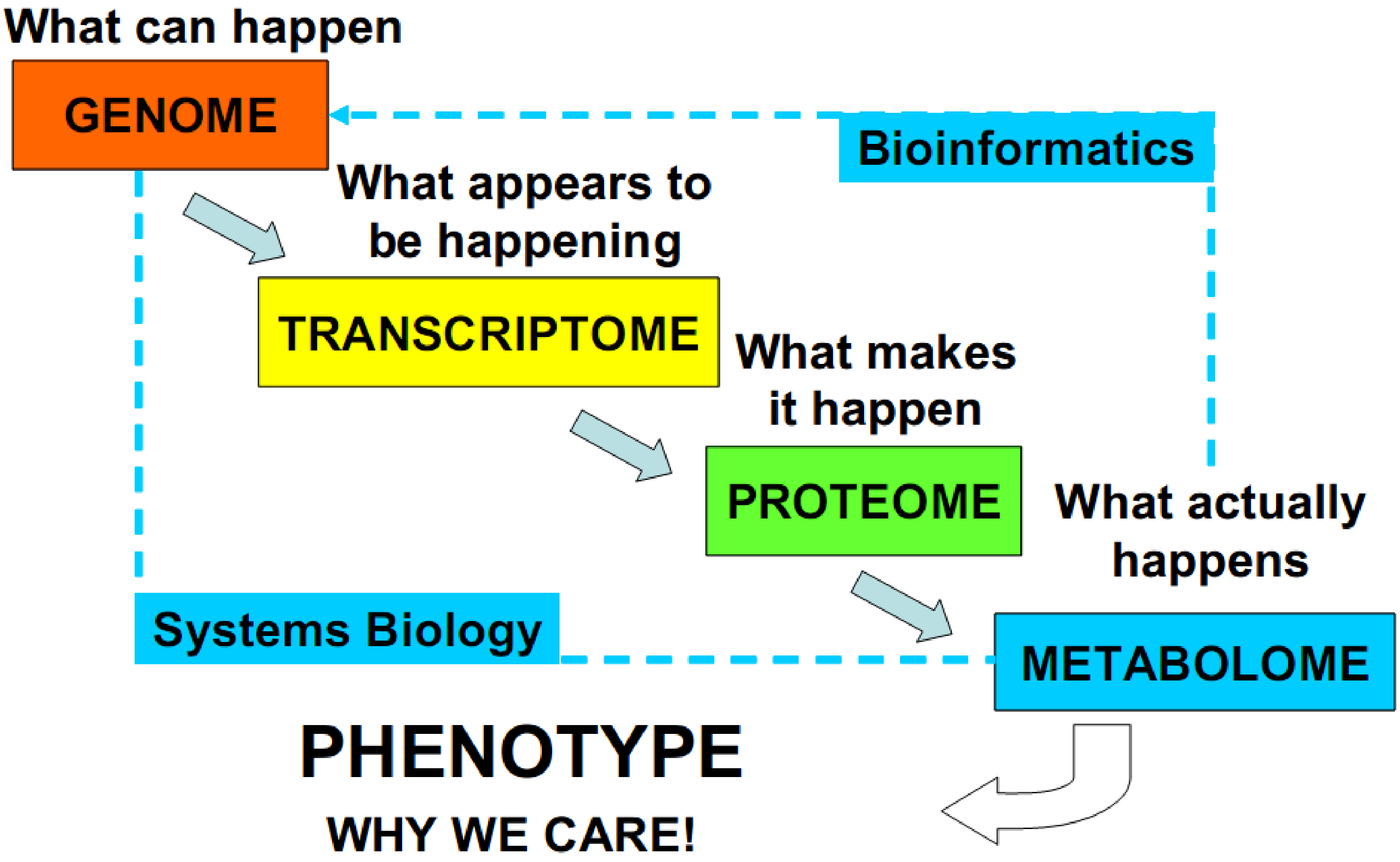
蛋白质组学基本技术路线



Genomics, Proteomics & Systems Biology



The Omics-Cascade



What can happen

GENOME

What appears to be happening

TRANSCRIPTOME

What makes it happen

PROTEOME

What actually happens

METABOLOME

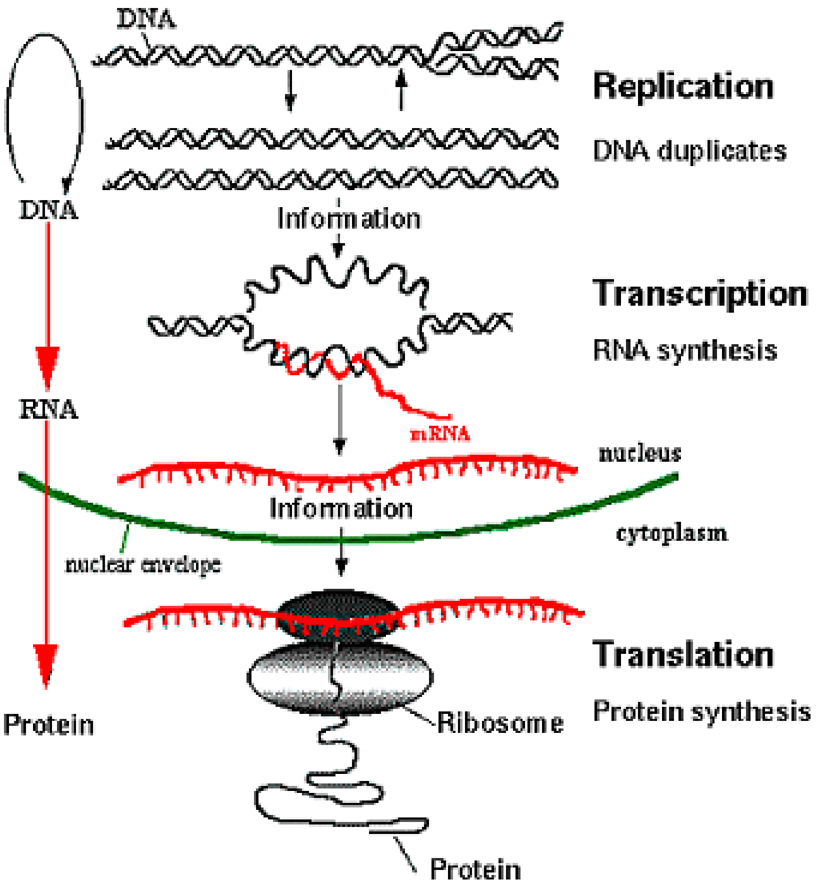
Bioinformatics

Systems Biology

PHENOTYPE

WHY WE CARE!

from http://www.accessexcellence.org/AB/GG/central.html



Gemomics

Transcriptomics

Proteomics

Interactomics

Metabolomics

Dimensionality of Genome Annotation

1D Genome: 基因在基因组上的线性排列

Interaction

2D Genome: 基因及其产物之间的相互关联和作用

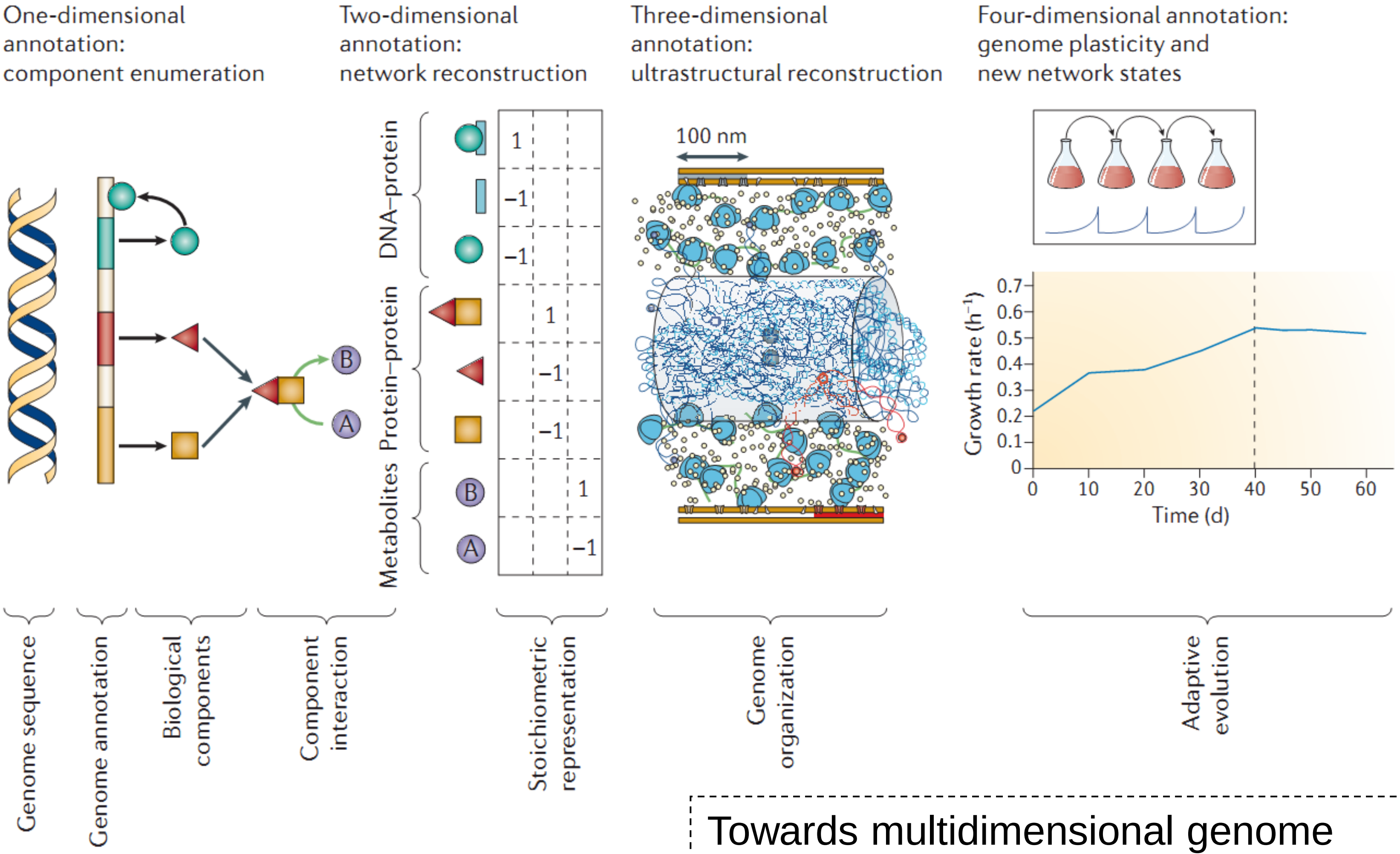
Put contents into context

3D (4D) Genome: 时空中发生的生物分子的动态行为

Two-dimensional annotation of genomes Nature Biotechnology 22, 1218 - 1219 (2004) by Bernhard Palsson

Towards multidimensional genome annotation Nature Reviews Genetics 7, 130-141 (2006) Bernhard O. Palsson

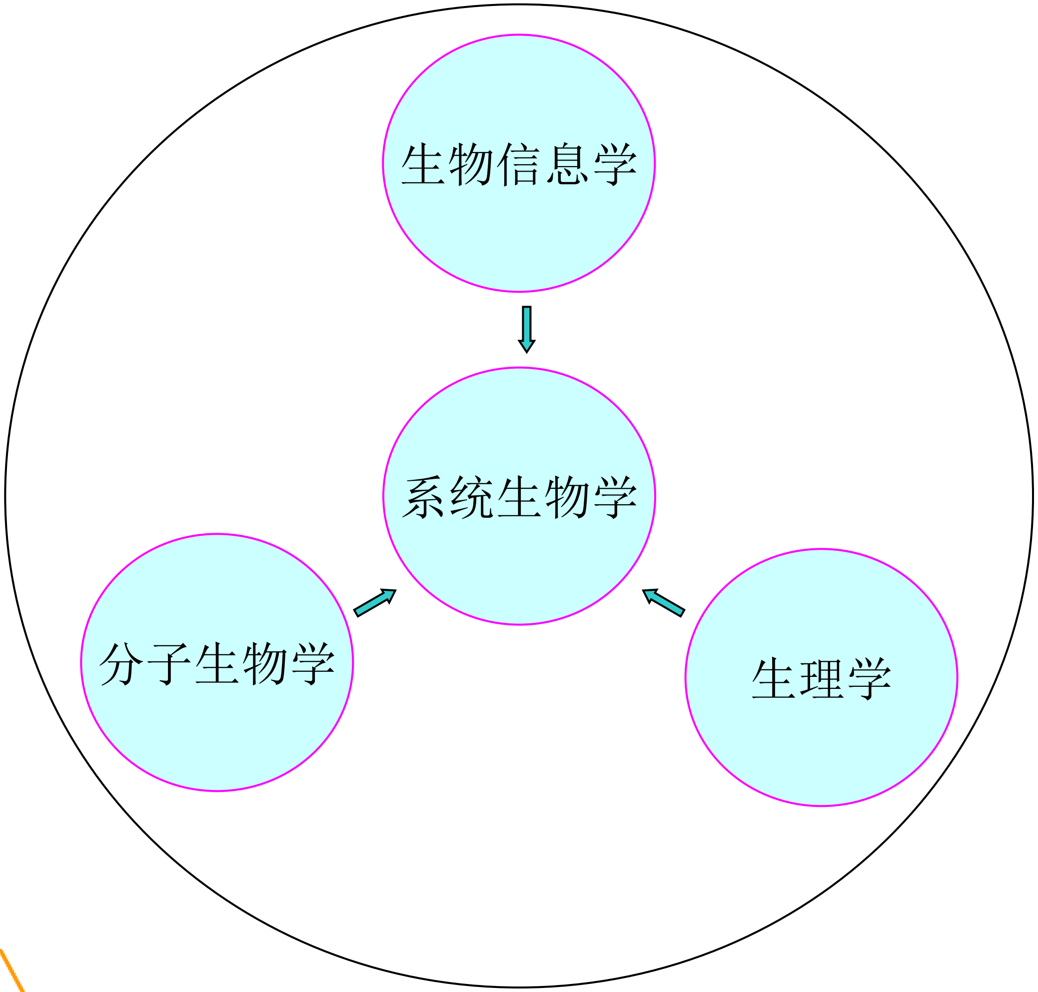
Towards multidimensional genome annotation



Towards multidimensional genome annotation Nature Reviews Genetics 7, 130-141 (2006) Bernhard O. Palsson

系统生物学与相关学科的关系

生命活动三要素：物质、能量、信息



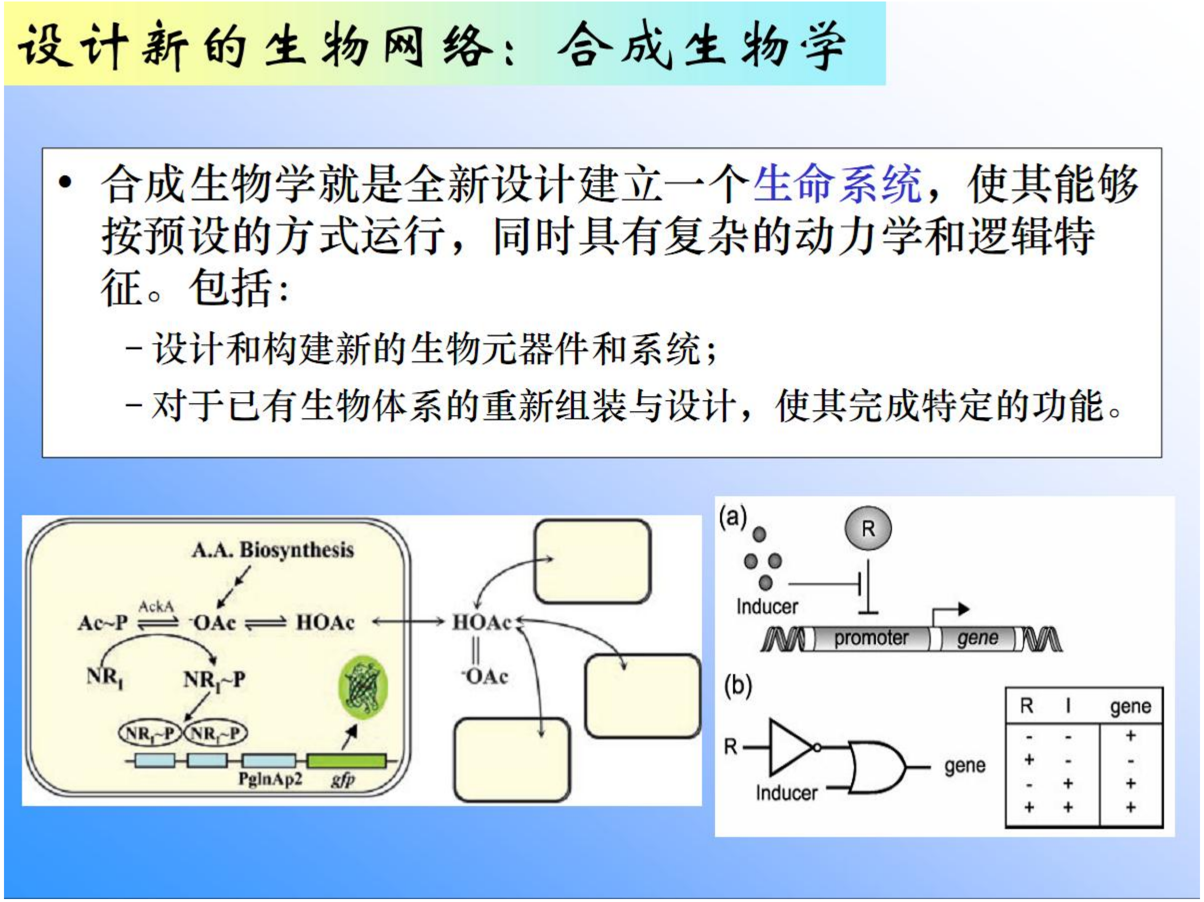
生物信息学

系统生物学

分子生物学

生理学

系统生物学与合成生物学的关系



设计新的生物网络：合成生物学

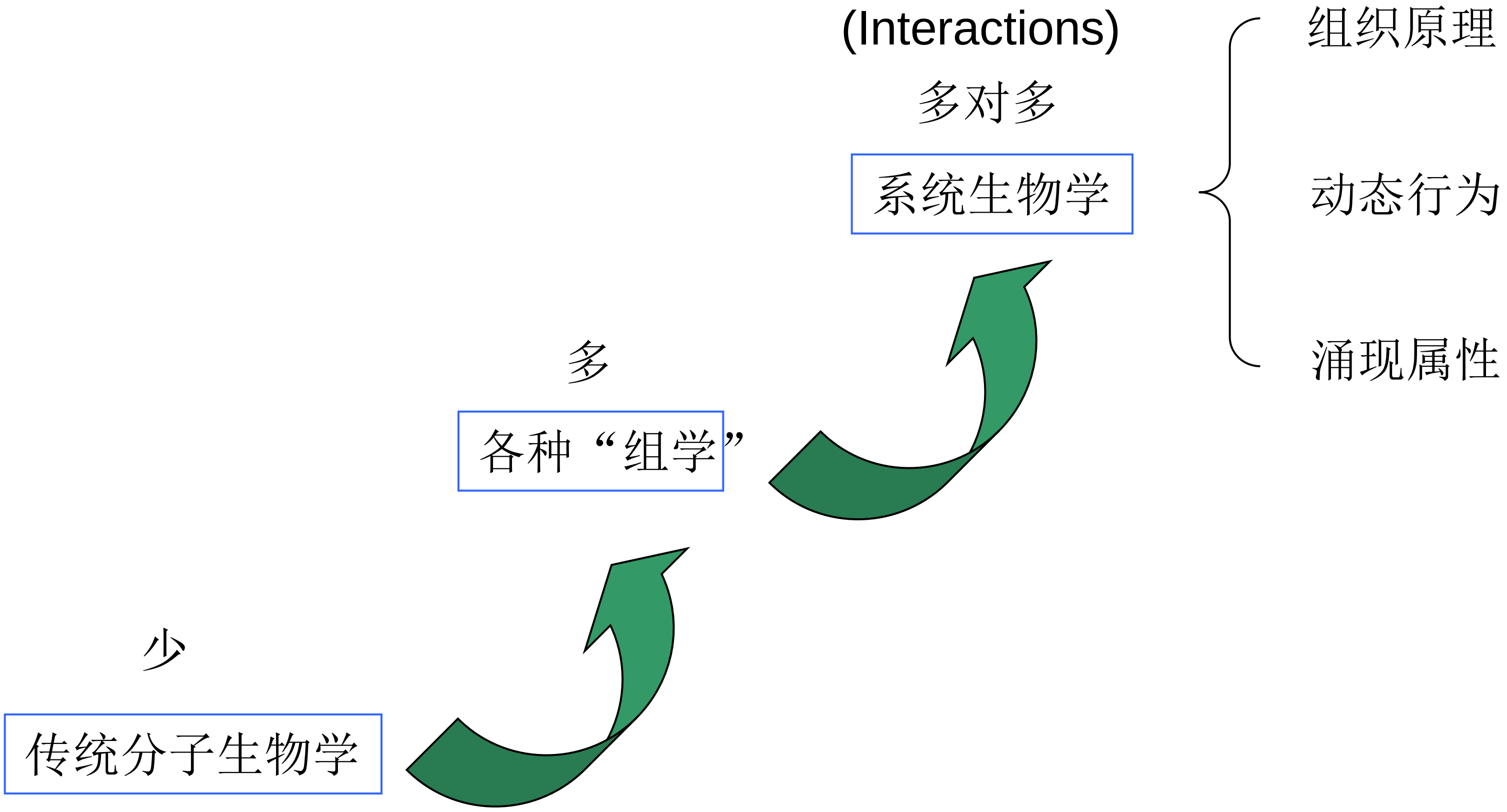
- 合成生物学就是全新设计建立一个生命系统，使其能够按预设的方式运行，同时具有复杂的动力学和逻辑特征。包括：
  - 设计和构建新的生物元器件和系统；
  - 对于已有生物体系的重新组装与设计，使其完成特定的功能。

R	I	gene
-	-	+
+	-	-
-	+	+
+	+	+

“Synthetic Biology”

- □ 系统生物学
  为合成生物学
  提供理论基础
- □ 合成生物学
  为系统生物学
  提供验证手段

研究范式的转变



少

传统分子生物学

多

各种“组学”

(Interactions)

多对多

系统生物学

组织原理

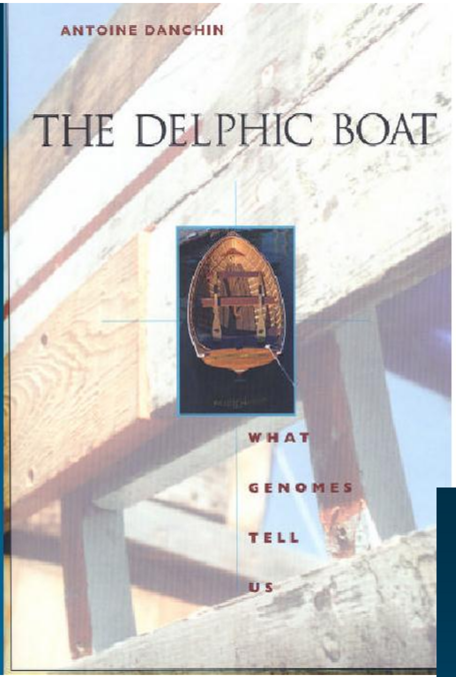
动态行为

涌现属性

系统生物学的哲学思考

The Oracle of Delphi asked:

If every plank in a boat is replaced over time, is it still the same boat?



ANTOINE DANCHIN

THE DELPHIC BOAT

WHAT GENOMES TELL US

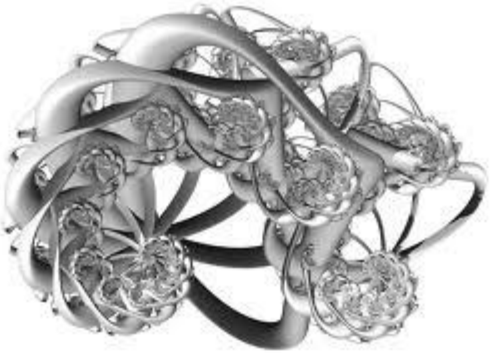
The answer basically is ‘yes’

Thus, the interconnections of biological components--the ‘blueprint,’ the ‘circuit diagrams’--of cells are taking center stage in biology:

and thus... we have the emergence of systems biology

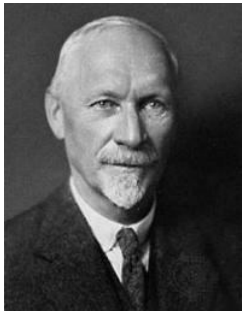
人类认识世界的两种方法论

- ☐ Reductionism



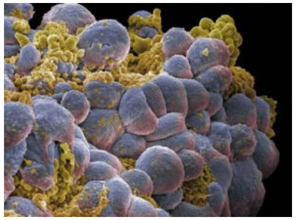
- ☐ Holism

RENE DESCARTES (1595-1650)
"I am thinking therefore I exist."



Jan Smuts (1870-1950)
“Holism and Evolution”

还原论及其局限性



奠基人：笛卡尔
　　分析-重构方法
　　主导地位：分析、分解、还原

400年来，创造了一套可操作的科学方法
面临的巨大问题：复杂系统，用认识的叠加方法，不宜发现整体的“涌现性”

从宇宙、生物圈、动物界、植物界，到个体，器官、组织、细胞、细胞器、DNA、基因片段…还原论的洋葱皮已经剥到“芯”了

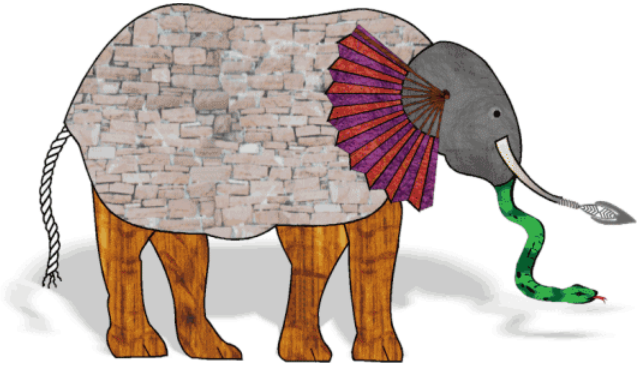
DNA双螺旋结构的发现以及随后的基因突破已经抵达到有机生命与无机物质的拐点，还原论在生命科学领域里所承担的使命大致已经终结

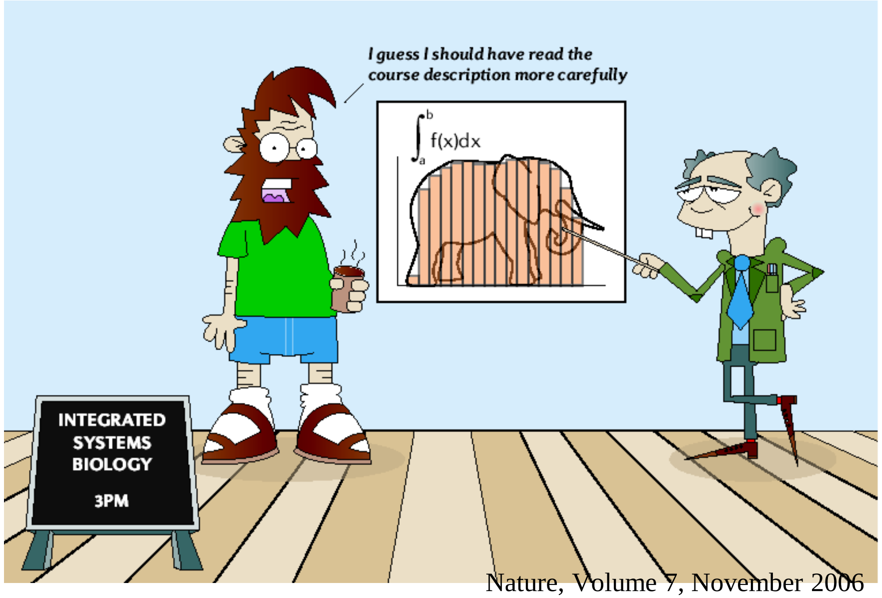
- 科学的分析时代必然划向综合时代——恩格斯

对还原论的超越

“系统论是还原论和整体论的辩证统一”

----- 钱学森





Nature, Volume 7, November 2006

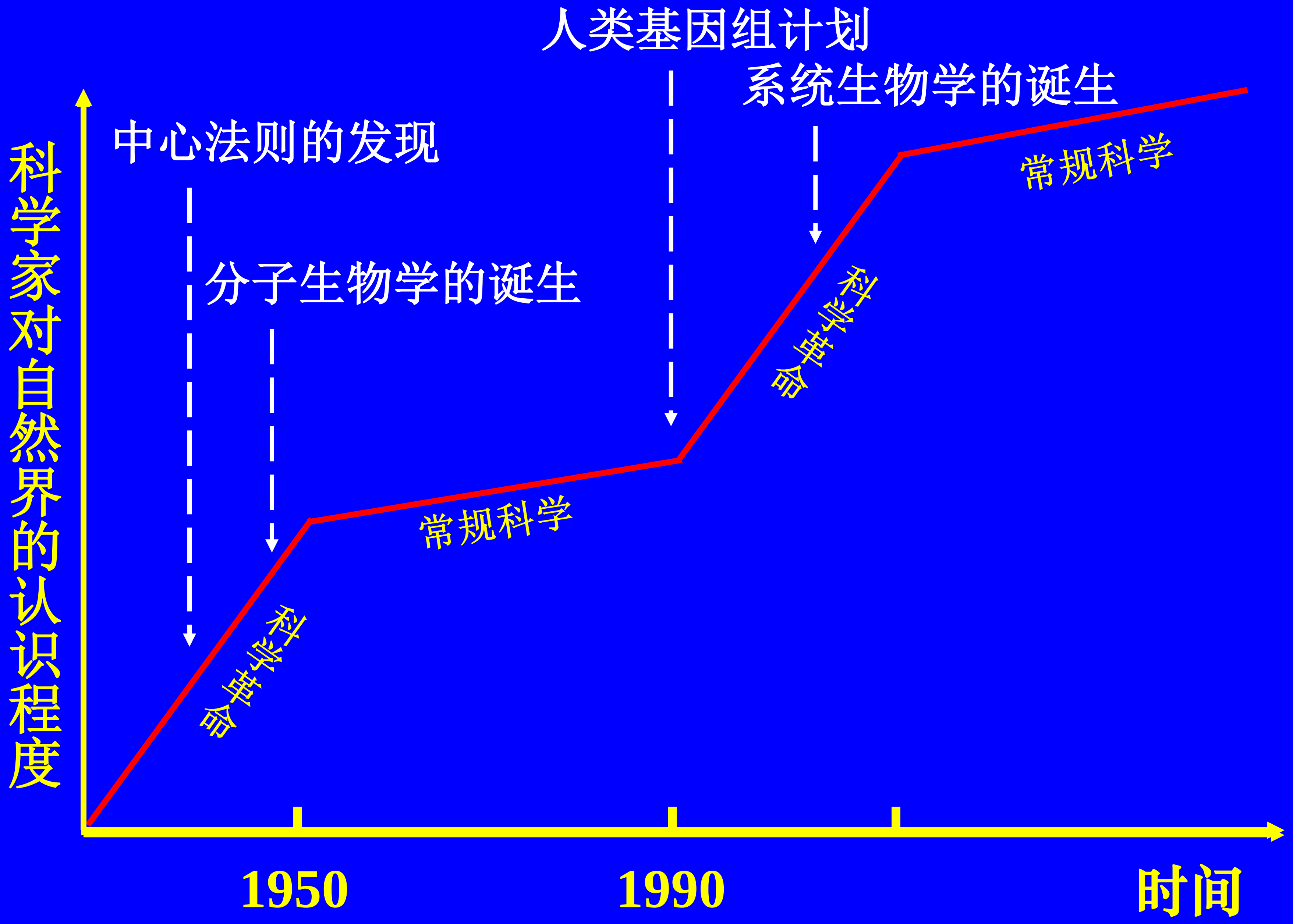
http://www.newvisions.ucsb.edu/background/images/elephant.gif

系统生物学是什么

- 是生物学
- 是数据整合
- 是建模仿真
- 是系统科学 (我加的)

教材作者：Edda Klipp

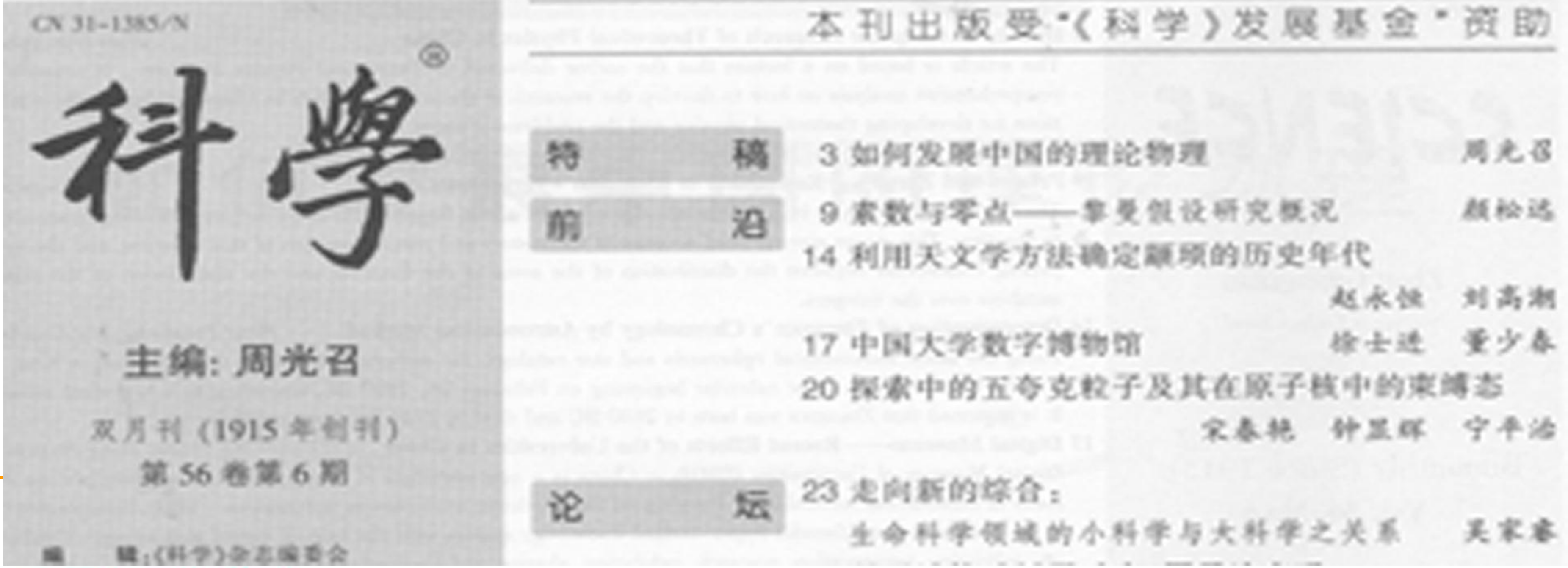
生命科学的第二次革命


人类基因组计划
系统生物学的诞生
中心法则的发现
分子生物学的诞生
科学家对自然界的认识程度
常规科学
科学革命
常规科学
科学革命
1950
1990
时间

"Big Biology" & "Small Biology"

Nature, 2004 432:A18

Daly & Newton / Getty Images



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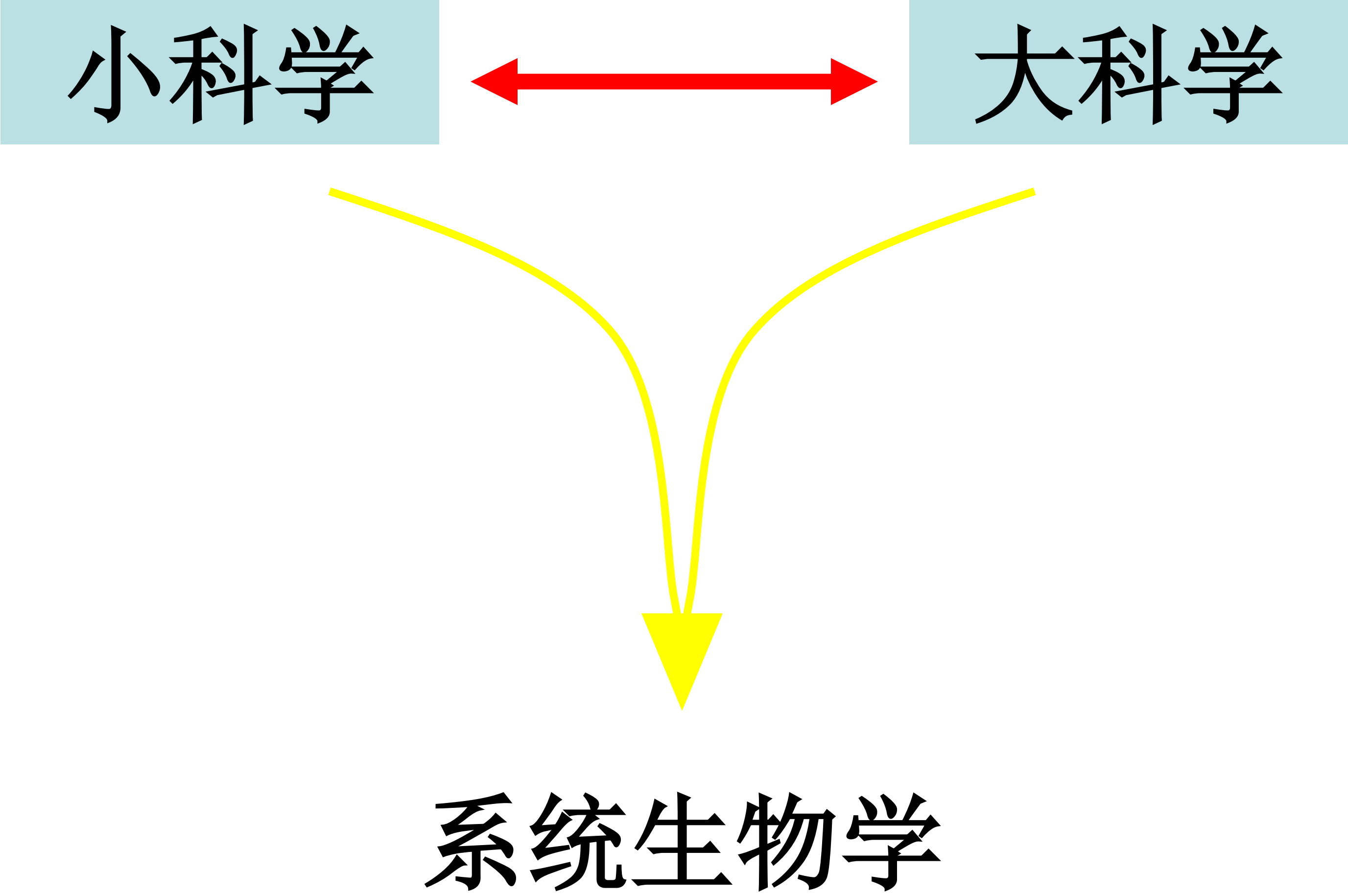
走向新的综合



小科学

大科学

系统生物学

系统生物学大纲

- 定义 (Definition)
- 学科背景 (Background)
- 内容体系和研究方法 (Contents & Methods)
- 学术组织、会议和刊物 (Research Community)
- 主要参考资料 (References)
- 课程安排和考核 (Plan & Exam)

系统生物学研究的四个环节

第一步：对选定的某一生物系统的所有组分进行了解和确定，描绘出该系统的结构，包括基因相互作用网络和代谢途径，以及细胞内和细胞间的作用机理，以此构造出一个初步的系统模型。

第二步：系统地改变被研究对象的内部组成成分（如基因突变）或外部生长条件，然后观测在这些情况下系统组分或结构所发生的相应变化，包括基因表达、蛋白质表达和相互作用、代谢途径等的变化，并把得到的有关信息进行整合。

第三步：把通过实验得到的数据与根据模型预测的情况进行比较，并对初始模型进行修订。

第四步：是根据修正后的模型的预测或假设，设定和实施新的改变系统状态的实验，重复第二步和第三步，不断地通过实验数据对模型进行修订和精练。系统生物学的目标就是要得到一个理想的模型，使其理论预测能够反映出生物系统的真实性。

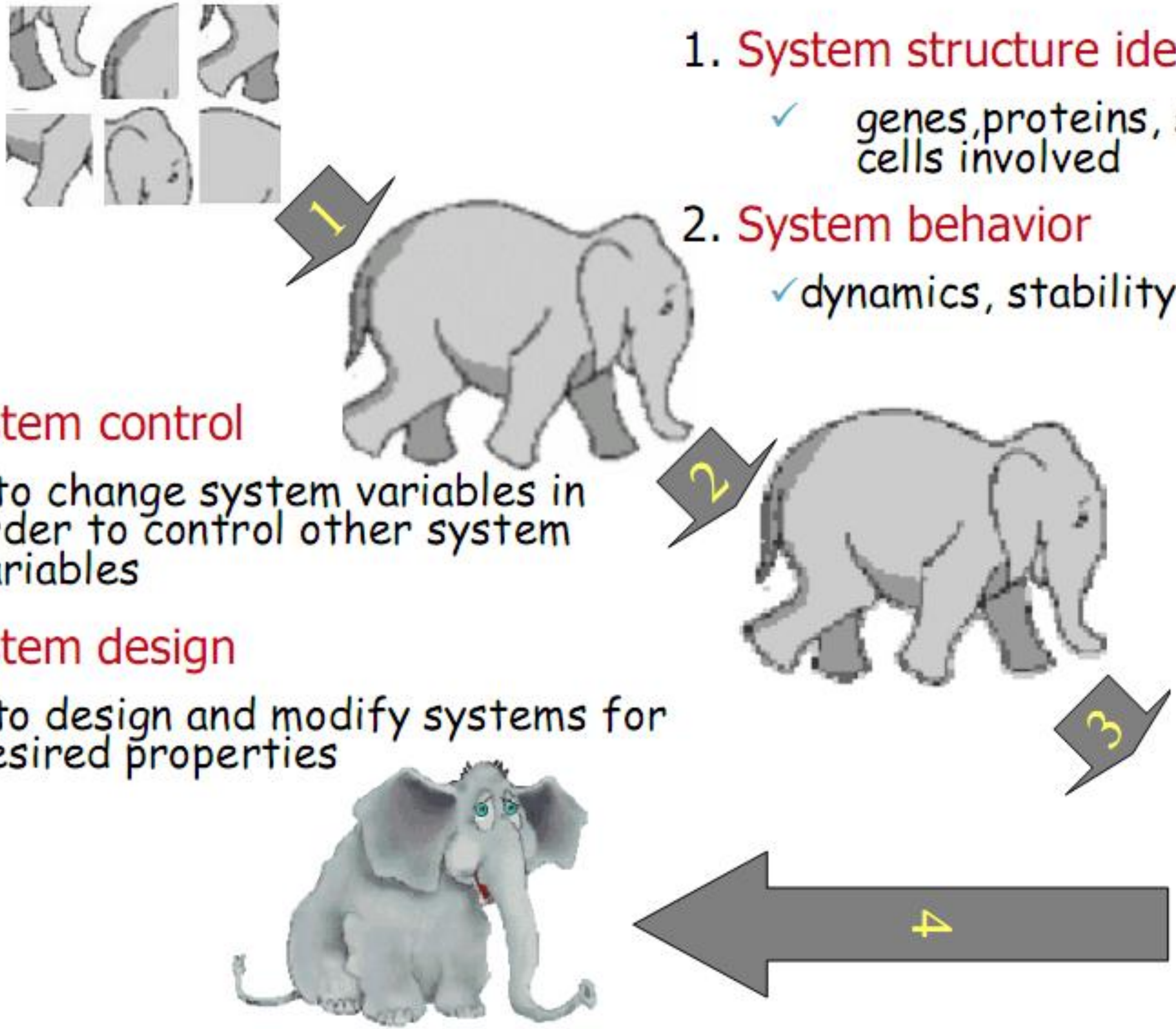
What is Systems Biology?

- **Systems Biology** - ***The study of the mechanisms underlying complex biological processes as integrated systems of many interacting components. Systems biology involves (1) collection of large sets of experimental data (2) proposal of mathematical models that might account for at least some significant aspects of this data set, (3) accurate computer solution of the mathematical equations to obtain numerical predictions, and (4) assessment of the quality of the model by comparing numerical simulations with the experimental data.***
- ***First described in 1999 by Leroy Hood***

Four Aspects

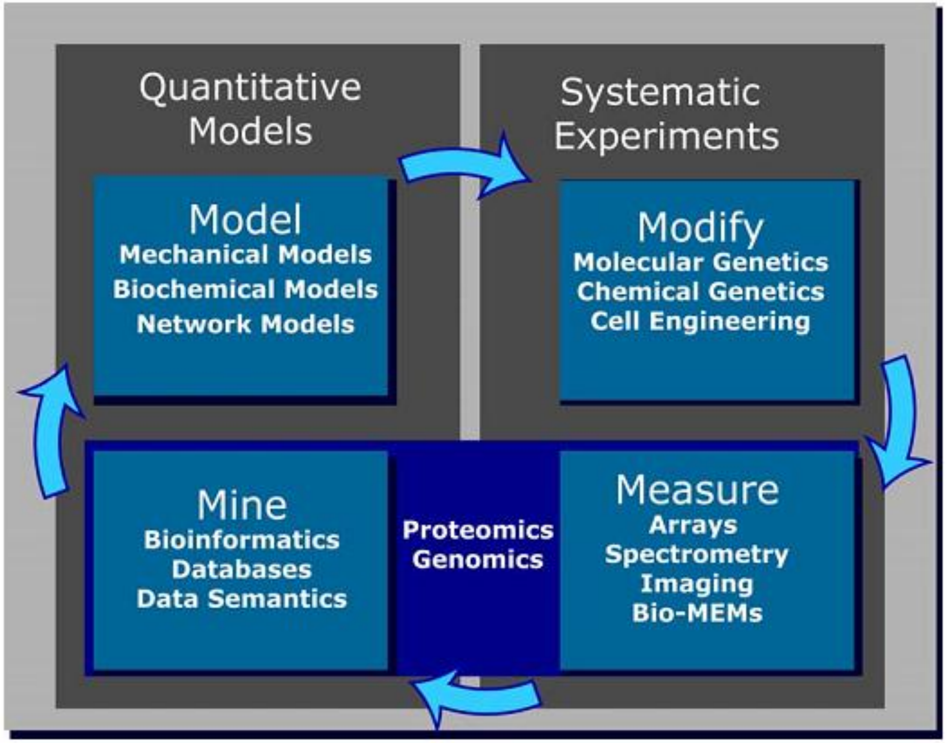
- Understanding of system structure
- Understanding behaviors of the system
- Understanding how to control the system
- Understanding how to design the system

-- by Hiroaki Kitano 2002



1. System structure identification:
   - ✓ genes,proteins, small molecules, cells involved
2. System behavior
   - ✓ dynamics, stability
3. System control
   - ✓ to change system variables in order to control other system variables
4. System design
   - ✓ to design and modify systems for desired properties

Scientific Approach:
The “4 M’s” of Systems Biology at MIT



Quantitative Models

Systematic Experiments

Model
Mechanical Models
Biochemical Models
Network Models

Modify
Molecular Genetics
Chemical Genetics
Cell Engineering

Mine
Bioinformatics
Databases
Data Semantics

Proteomics
Genomics

Measure
Arrays
Spectrometry
Imaging
Bio-MEMs

Mathematical Analysis:
- elucidate hypotheses *(mining)*
- facilitate predictions *(modeling)*

Systematic experimentation:
- pathway focused- multi-variate
- resolved in time and space

主要研究策略

- 自上而下 (Top-down，以Hood为代表)
- 自下而上 (Bottom-up，以Kitano为代表)
- 整合 (Integration)
- 扰动法 (Perturbation)

整合—系统生物学的核心

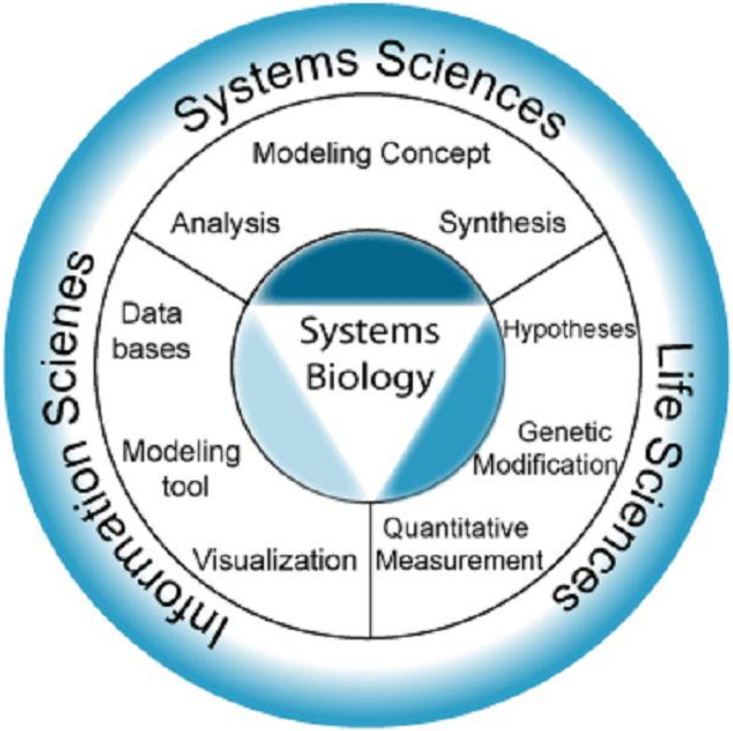
- 系统内不同性质的构成要素（基因、mRNA、蛋白质、生物小分子等）的整合。
- 从基因到细胞、到组织、到个体的各个层次的整合。
- 研究思路和方法的整合。

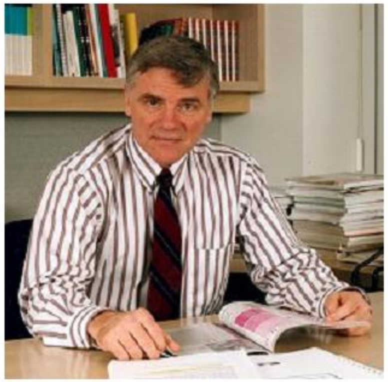
需要生命科学、信息科学、数学、计算机科学等各种学科的共同参与，真正实现这种整合还有很长的路要走。

系统生物学三大学科基础

System Biology

- 生命科学
- 信息科学
- 系统科学

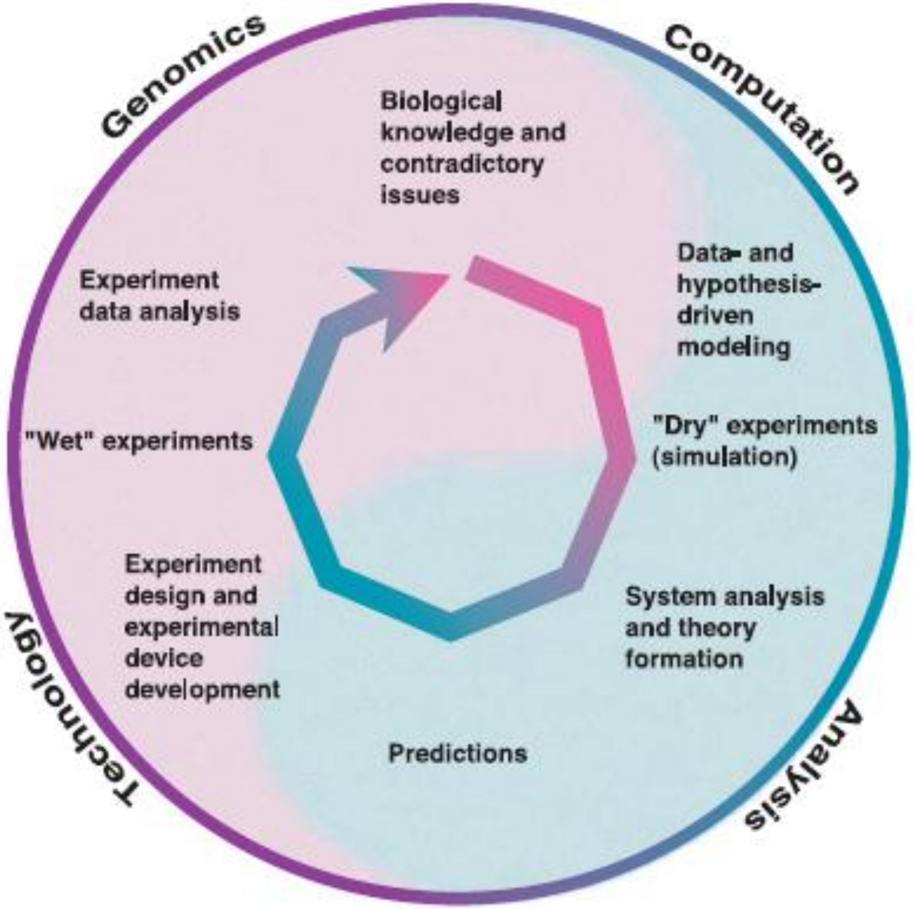




Lee Hood – director of the Institute for System Biology

系统生物学的学科交叉特性

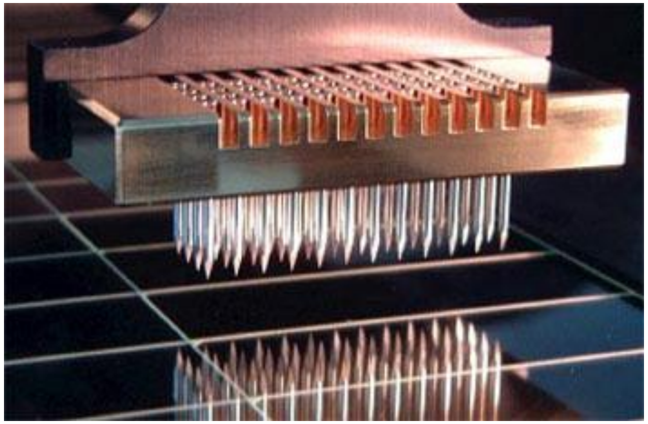
- 生物学
- 物理学
- 化学
- 工程学
- 数学
- 计算科学



系统生物学，是把孤立的在基因水平、蛋白水平的各种相互作用、各种代谢途径、调控途径等融合起来，用以说明 生物整体，高通量的组学实验平台构成了系统生物学的大科学工程.

两大技术支撑

- 实验技术 （Wet Part）

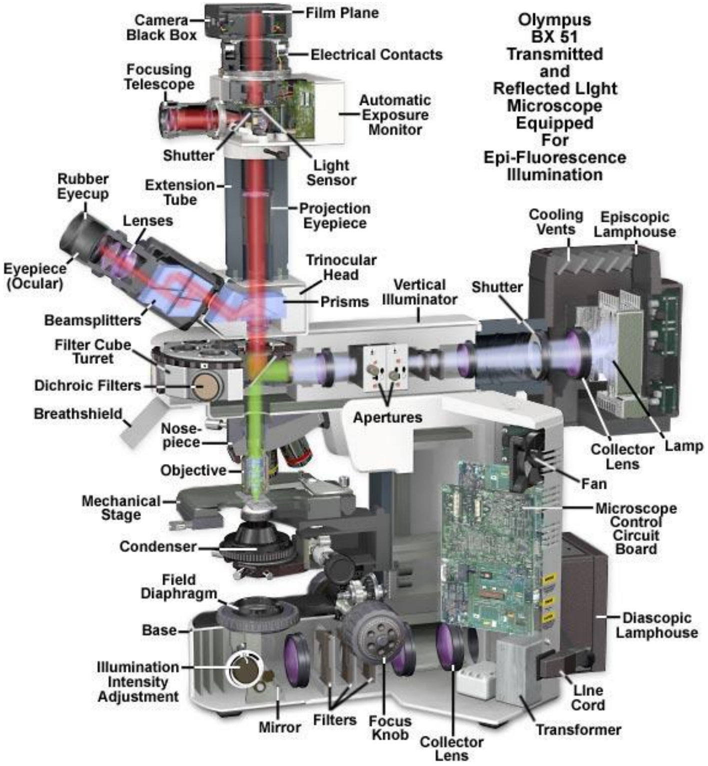


- 信息技术 （Dry Part）

实验技术

- 基本技术
  - 离心与层析
  - 酶切与电泳
  - PCR技术
  - 杂交和印迹技术
- 高通量技术
  - 新DNA测序技术
  - 克隆载体与DNA文库
  - DNA和蛋白质芯片
  - 酵母双杂交
  - 质谱技术
  - ChIP-chip和ChIP-PET技术
- 转基因生物、RNA干扰
- 各种显微示踪技术
- 等

Fluorescence Microscope



http://www.olympusmicro.com/

计算技术

- 程序设计技术
  - 程序设计语言
  - 面向过程与面向对象的程序设计
  - 常用的编程工具
- 数据库技术
  - 数据管理方式的演变
  - 关系型数据库与SQL语言
  - 数据的集成与交换
- 网络技术
  - 计算机网络概述
  - 服务器-客户端结构
  - 网络开发的LAMP体系
- 平行计算技术
  - 并行计算与串行计算的比较
  - 微机集群的架构与应用
  - 并行计算的新趋势：基于多核CPU与GPGPU的程序设计

三种类型的工作

计算具有实验和理论双重属性：

---相对于实验，它是理论；

---相对于理论，它是实验。

数学的运用

一门科学只有当它充分利用数学之后，才能成为一门精确的科学

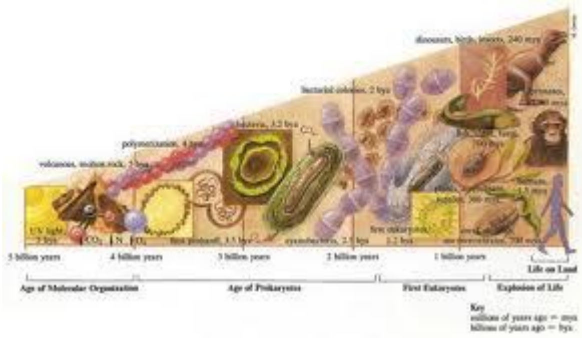
----- 马克思

用到的数学知识：

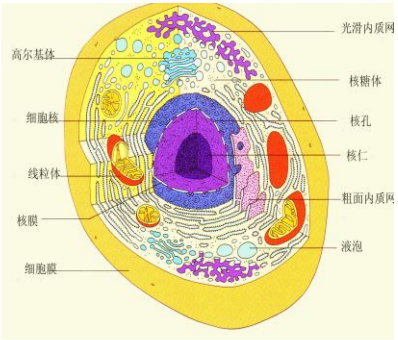
- 线性代数
- 微分方程（常微分方程、偏微分方程、差分方程）
- 图与网络的理论
- 统计学理论
- 随机过程理论

涉及的生物学知识

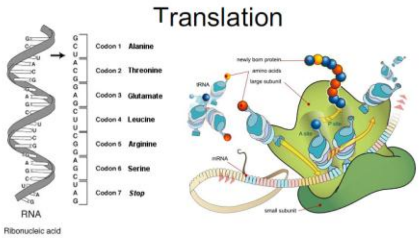
- 生命的起源与进化
    - 生命起源的学说
    - 生命的化学进化
    - 生命的生物进化



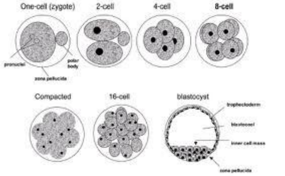
- 细胞结构与物质代谢
    - 细胞的构成
    - 生物分子的合成与分解
    - 生物分子中的化学键和重要作用力

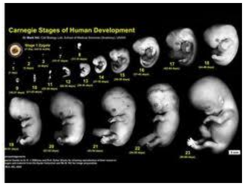


- 分子生物学中心法则
    - 基因表达的信息流向
    - 基因表达的调控
    - 表达后蛋白的修饰



- 细胞周期与胚胎发育
    - 细胞的分裂过程
    - 胚胎的发育过程





生物信息资源

- 常用数据库
  - 序列和结构数据库
  - 基因表达数据库
  - 蛋白相互作用数据库
  - 代谢途径数据库
  - 动力学和模型数据库

- 常用的算法和网络服务
  - 序列和结构比对算法
  - 进化树构建方法
  - 网络建模、比对和分析的方法

- 常用的建模工具
  - 通用建模工具MatLab, Maple, Mathematica
  - Dizzy仿真工具
  - SBW平台
  - 网上建模环境 （ PyBioS）
  - 建模程序包 （PySCeS）

各种组学的研究进展

- 基因组学、转录组学、蛋白质组学、糖组学
- 相互作用组学
- 代谢物组学
- 表型组学、系统组学

- 单基因敲除突变体库的构建
- 微生物的实验室进化
- 最小或必需基因组识别与构造
- 药品分子（如青蒿素）的生物合成
- 遗传逻辑回路设计与改良
- 体内体外振荡子构建与反馈机制研究
- 基因网络中的自调控与网络稳定性
- 单细胞水平基因调控
- 基因表达中的随机性
- 系统病（如癌症）的系统生物学研究
- 免疫系统的系统生物学
- 神经系统中的系统生物学
- 组织和器官发育中稳定性
- microRNA跨界调控
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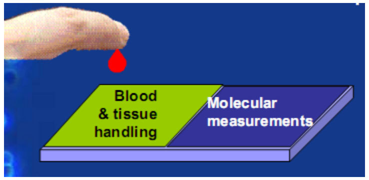

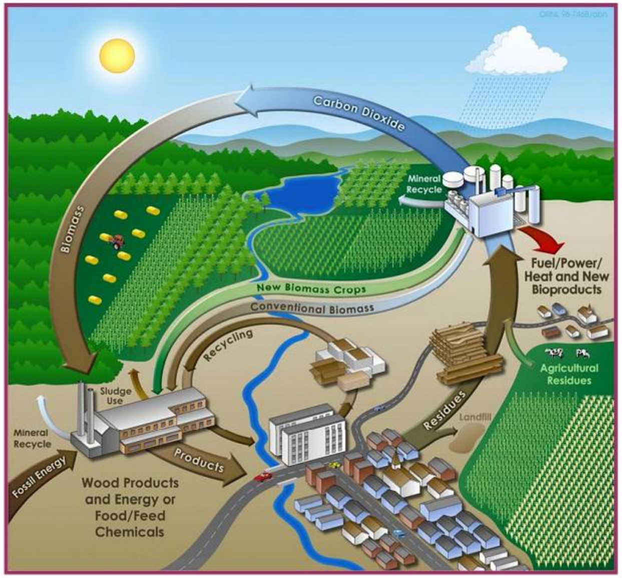

科学前沿

系统生物学

——21 世纪医学和生物学发展的核心驱动力

□陈　竺

世界是复杂的，生命系统和医学同样具有复杂性。我着重从医学的角度出发，谈谈系统生物学与医学的关系。

根据韦伯词典的解释：医学是维持健康，缓解、治愈疾病的一门科学和艺术。新牛津词典对医学的定义则为：医学是对疾病进行诊断、治疗和预防的科学或实践。更有意思的是，著名的内科学教材（CECIL TEXTBOOK）则认为：医学是包涵了个体化、人文化和职业化的一门科学。

我们再来看看医学的演进，以中医药为代表的传统医学是以经验为基础的医学，其优势在于把机体看作

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- 定义 (Definition)
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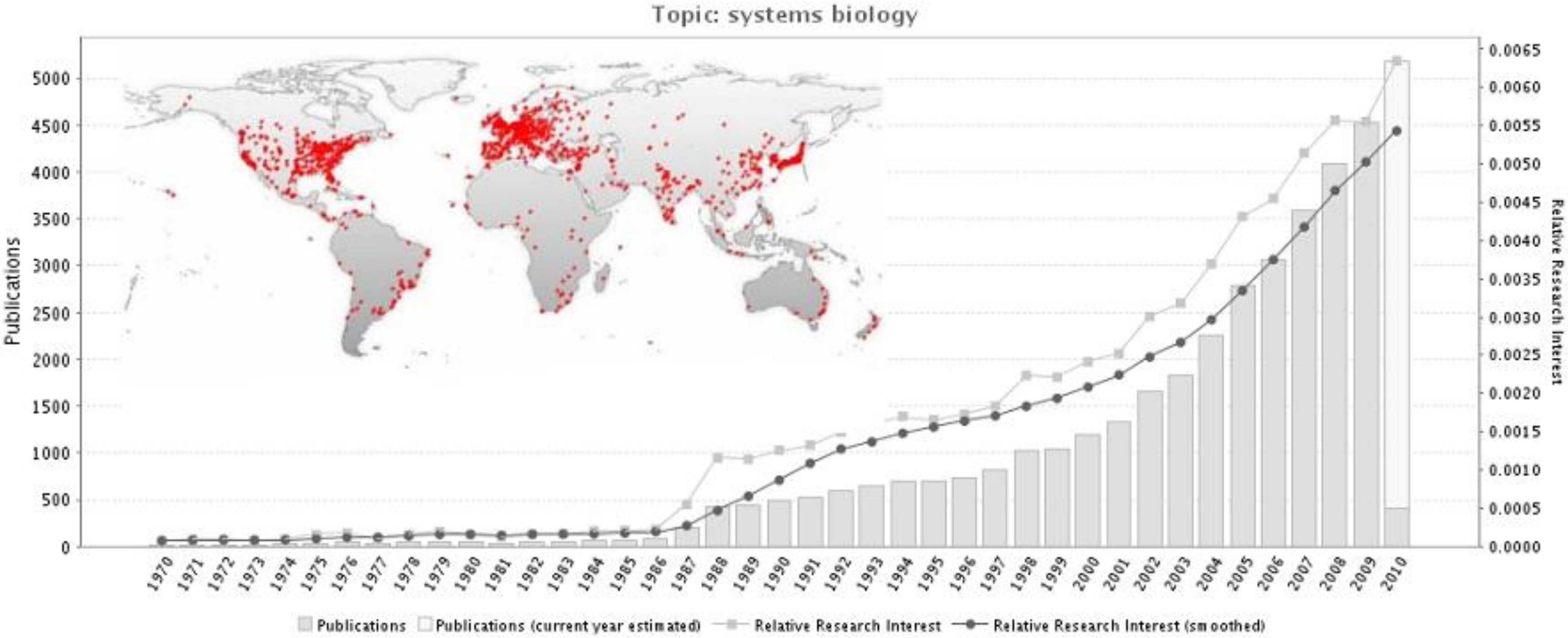

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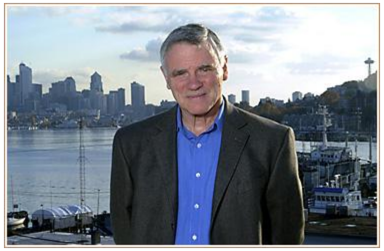
国内外有关计算与系统生物学建设情况

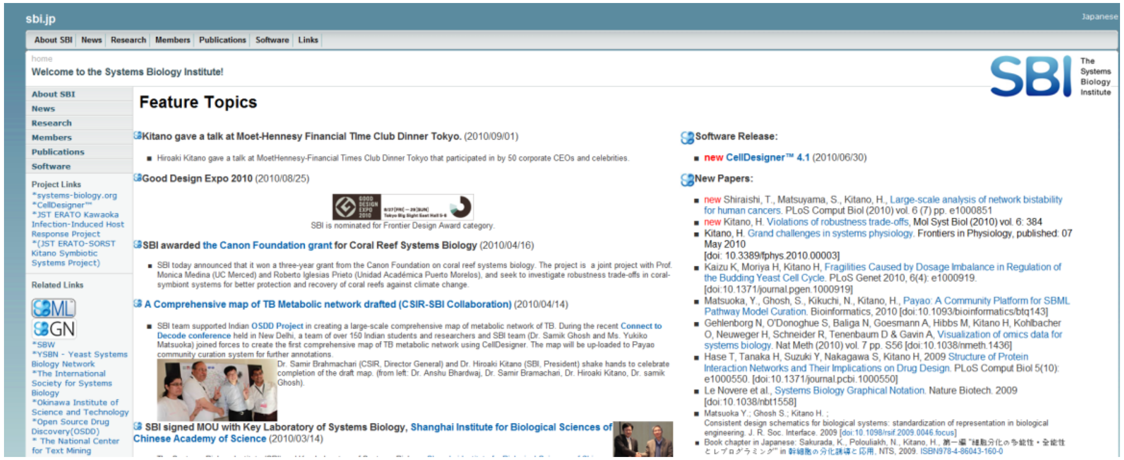
- 2000年2月在美国西雅图成立了第一个系统生物学研究所(L. Hood)。
- 日本的Kinato博士2001年6月建立系统生物学实验室 。
- 哈佛大学于2003年9月新成立了系统生物学系，预计在10年中招聘25个教授。
- MIT于2003年启动了计算与系统生物学计划，各学科的相关实验室参加。
- 美国NIH、NSF及DOE都启动了计算与系统生物学相关的研究计划。
- 中科院生物物理所在2003年3月成立了系统生物学研究中心。
- 中国科技大学成立了系统生物学系。
- 上海交通大学与中科院上海生命科学研究院合作成立了系统生物研究中心。
- 上海交通大学与上海市2007年初合作成立了系统生物医学研究中心。

研究机构与研究组织



Institute for Systems Biology
founded by Leroy Hood in 1999

http://www.systemsbiology.org/



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*CellDesigner™
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*YSBN - Yeast Systems Biology Network
*The International Society for Systems Biology
*Okinawa Institute of Science and Technology
*Open Source Drug Discovery(OSDD)
* The National Center for Text Mining

Feature Topics

Kitano gave a talk at Moet-Hennesy Financial TIme Club Dinner Tokyo. (2010/09/01)

- Hiroaki Kitano gave a talk at MoetHennesy-Financial Times Club Dinner Tokyo that participated in by 50 corporate CEOs and celebrities.

Good Design Expo 2010 (2010/08/25)

SBI is nominated for Frontier Design Award category.

SBI awarded the Canon Foundation grant for Coral Reef Systems Biology (2010/04/16)

- SBI today announced that it won a three-year grant from the Canon Foundation on coral reef systems biology. The project is a joint project with Prof. Monica Medina (UC Merced) and Roberto Iglesias Prieto (Unidad Académica Puerto Morelos), and seek to investigate robustness trade-offs in coral-symbiont systems for better protection and recovery of coral reefs against climate change.

A Comprehensive map of TB Metabolic network drafted (CSIR-SBI Collaboration) (2010/04/14)

- SBI team supported Indian OSDD Project in creating a large-scale comprehensive map of metabolic network of TB. During the recent Connect to Decode conference held in New Delhi, a team of over 150 Indian students and researchers and SBI team (Dr. Samik Ghosh and Ms. Yukiko Matsuoka) joined forces to create the first comprehensive map of TB metabolic network using CellDesigner. The map will be up-loaded to Payao community curation system for further annotations.

Dr. Samir Brahmachari (CSIR, Director General) and Dr. Hiroaki Kitano (SBI, President) shake hands to celebrate completion of the draft map. (from left: Dr. Anshu Bhardwaj, Dr. Samir Bramachari, Dr. Hiroaki Kitano, Dr. samik Ghosh).

SBI signed MOU with Key Laboratory of Systems Biology, Shanghai Institute for Biological Sciences of Chinese Academy of Science (2010/03/14)

Software Release:

- new CellDesigner™ 4.1 (2010/06/30)

New Papers:

- new Shiraishi, T., Matsuyama, S., Kitano, H., Large-scale analysis of network bistability for human cancers. PLoS Comput Biol (2010) vol. 6 (7) pp. e1000851
- new Kitano, H. Violations of robustness trade-offs, Mol Syst Biol (2010) vol. 6: 384
- Kitano, H. Grand challenges in systems physiology. Frontiers in Physiology, published: 07 May 2010 [doi: 10.3389/fphys.2010.00003]
- Kaizu K, Moriya H, Kitano H, Fragilities Caused by Dosage Imbalance in Regulation of the Budding Yeast Cell Cycle. PLoS Genet 2010, 6(4): e1000919. [doi:10.1371/journal.pgen.1000919]
- Matsuoka, Y., Ghosh, S., Kikuchi, N., Kitano, H., Payao: A Community Platform for SBML Pathway Model Curation. Bioinformatics, 2010 [doi:10.1093/bioinformatics/btq143]
- Gehlenborg N, O'Donoghue S, Baliga N, Goesmann A, Hibbs M, Kitano H, Kohlbacher O, Neuweger H, Schneider R, Tenenbaum D & Gavin A, Visualization of omics data for systems biology. Nat Meth (2010) vol. 7 pp. S56 [doi:10.1038/nmeth.1436]
- Hase T, Tanaka H, Suzuki Y, Nakagawa S, Kitano H, 2009 Structure of Protein Interaction Networks and Their Implications on Drug Design. PLoS Comput Biol 5(10): e1000550. [doi:10.1371/journal.pcbi.1000550]
- Le Novere et al., Systems Biology Graphical Notation. Nature Biotech. 2009 [doi:10.1038/nbt1558]
- Matsuoka Y.; Ghosh S.; Kitano H. ; Consistent design schematics for biological systems: standardization of representation in biological engineering. J. R. Soc. Interface. 2009 [doi:10.1098/rsif.2009.0046.focus]
- Book chapter in Japanese: Sakurada, K., Polouliakh, N., Kitano, H., 第一編 "細胞分化の多能性・全能性とレプログラミング" in 幹細胞の分化誘導と応用, NTS, 2009. ISBN978-4-86043-160-0

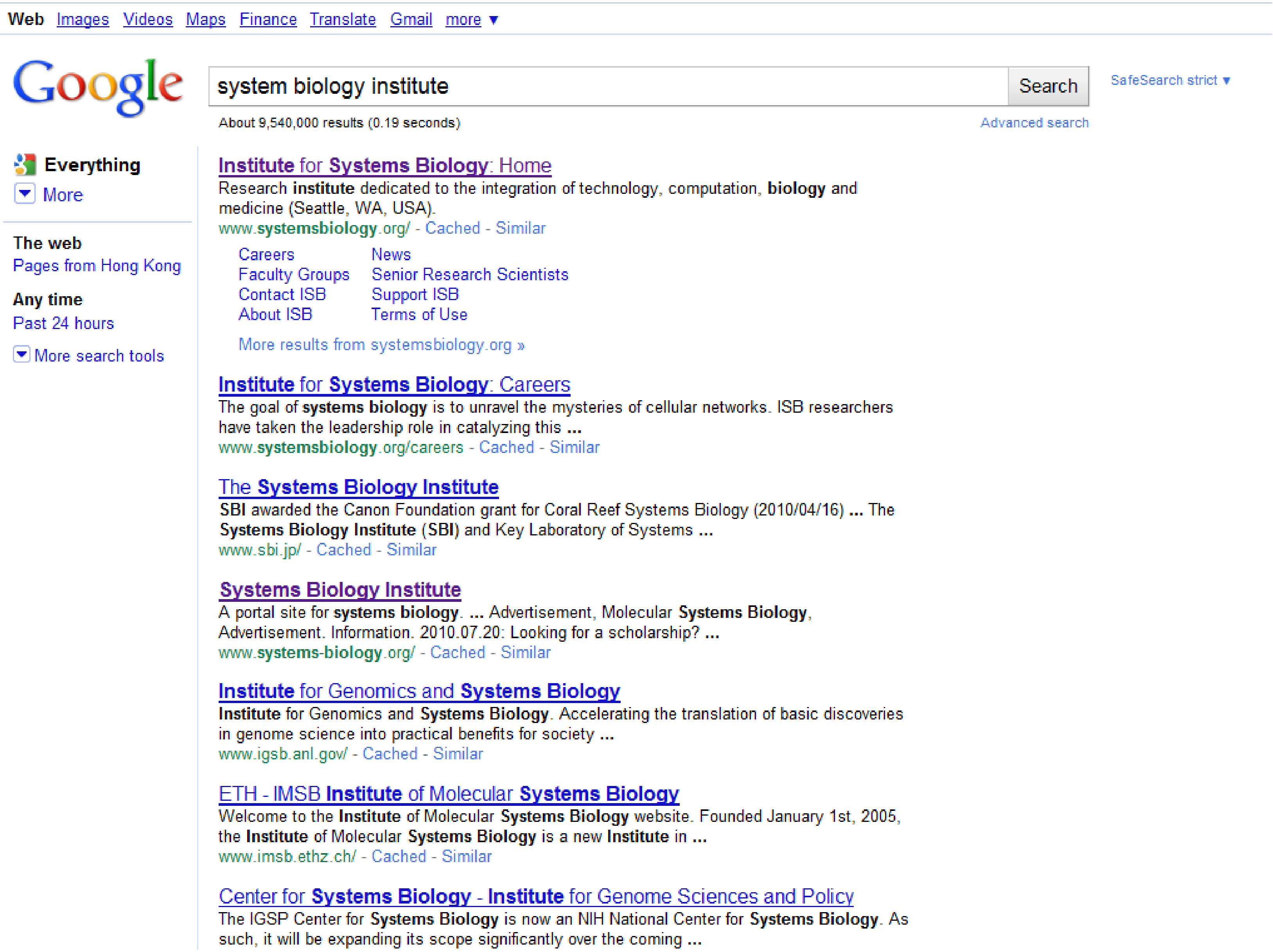
Hiroaki Kitano

http://systems-biology.org/

Other famous institutes

- Systems Biology Department at Harvard Medical School
- Computational and Systems Biology Initiative at MIT
- Bio-X at Stanford University
- BioSPI Project at Weizmann, Israel
- SystemsX.ch, The Swiss Initiative in Systems Biology

- Caltech, USA
- University of Edinburgh, UK
- University of Gotenberg, Sweden
- Humboldt University Berlin, Institute for Biology, Theoretical Biophysics, Berlin, Germany



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国内机构

- 中科院系统生物学重点实验室，http://www.sysbio.ac.cn/
- 复旦大学数学学院，系统生物学研究室
- 中科院生物物理所，系统生物学研究组
- 中科院数学与系统科学研究院，生物信息学组
- 苏州大学系统生物学研究中心，http://www.sysbio.org.cn/
- 西南大学蚕学与系统生物学研究所
- 等

重要学术会议

- ICSB: International Conference on Systems Biology
- 11th, Edingburgh, UK, October 10-15, 2010
- http://www.icsb2010.org.uk

- WCSB: International Workshop on Computational Systems Biology, 7th. (Luxembourg, June 16-18, 2010)

- ICCSB: International Conference on Computational and Systems Biology, 2011 (Manila, Philippines, March 29-31, 2011)

主要学术刊物

- Molecular Systems Biology
- PLoS Computational Biology
- Bioinformatics (SB section)
- BMC Systems Biology
- BMC Bioinformatics
- Journal of Theoretical Biology
- Journal of Computational Biology
- *in silico* Biology
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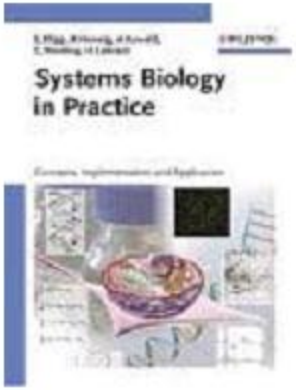
主要教学参考资料

- 教材
- 《系统生物学的理论、方法和应用》［德］柯利普等著；贺福初 等译，复旦大学出版社，2007。



Systems Biology in Practice

- Klipp E. etc. Systems Biology: A Textbook, Wiley-VCH, 2009.

Systems Biology

A Textbook

其他中文参考书

- 《系统生物学基础》［日］北野宏明 编；刘笔锋，周艳红等译，化学工业出版社，2007。
- 《系统生物学：哲学基础》［荷］布杰德 等编著；孙之荣等译，科学出版社，2008。
- 《系统生物学》，张自立，王振英 编著，科学出版社，2009。
- 《系统生物学导论：生物回路的设计原理》尤. 阿隆 著，王翼飞 等译， 化学工业出版社，2010。
- 《合成生物学》，宋凯，科学出版社，2010。
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- 《系统生物学》，林标扬 编著，浙江大学出版社，2012。

- 苗东升，《系统科学精要（第3版）》，中国人民大学出版社，2010。
- 高隆昌，《系统学原理》，科学出版社，2005。
- 岑沛霖 等 编著，《生物反应工程》，高等教育出版社，2005。

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Other English Books

- Alberghina L. & Westerhoff H.V. (Eds.) Systems Biology: Definitions and Perspectives (Topics in Current Genetics), Springer-Verlag Berlin Heidelberg, 2005.
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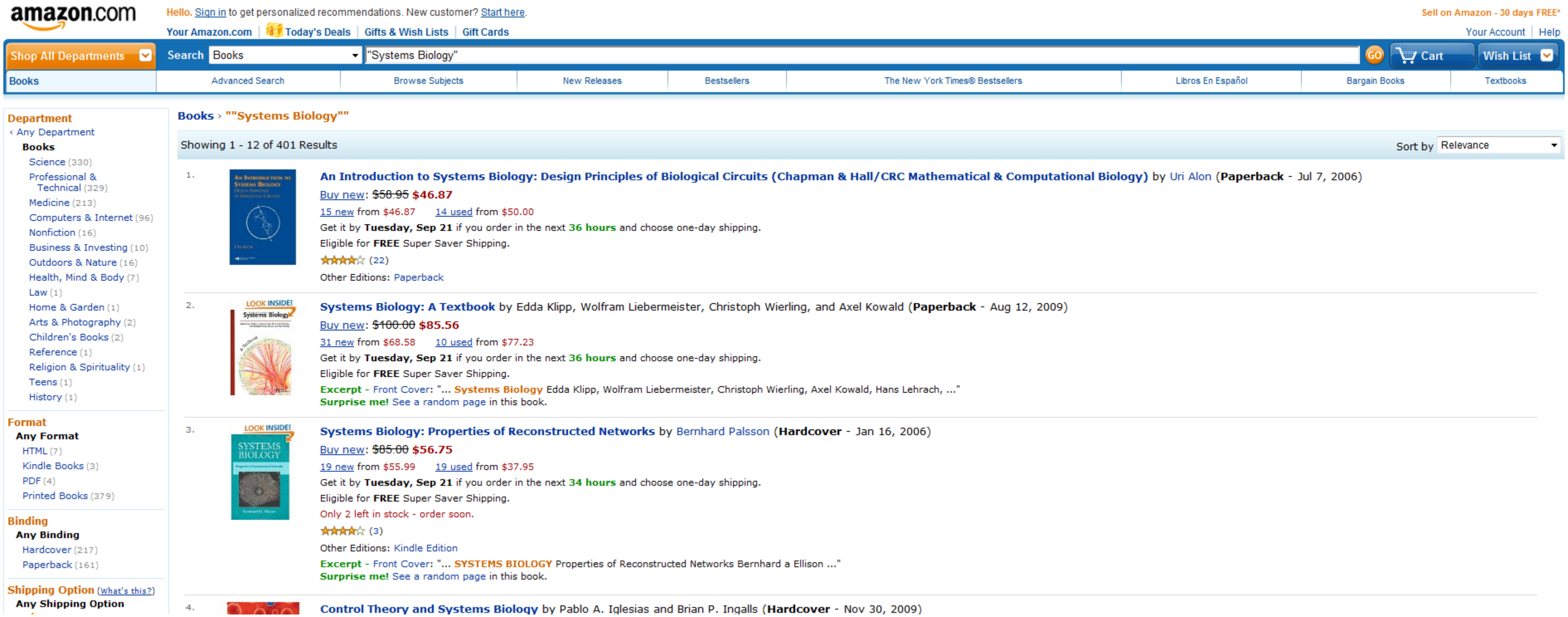

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