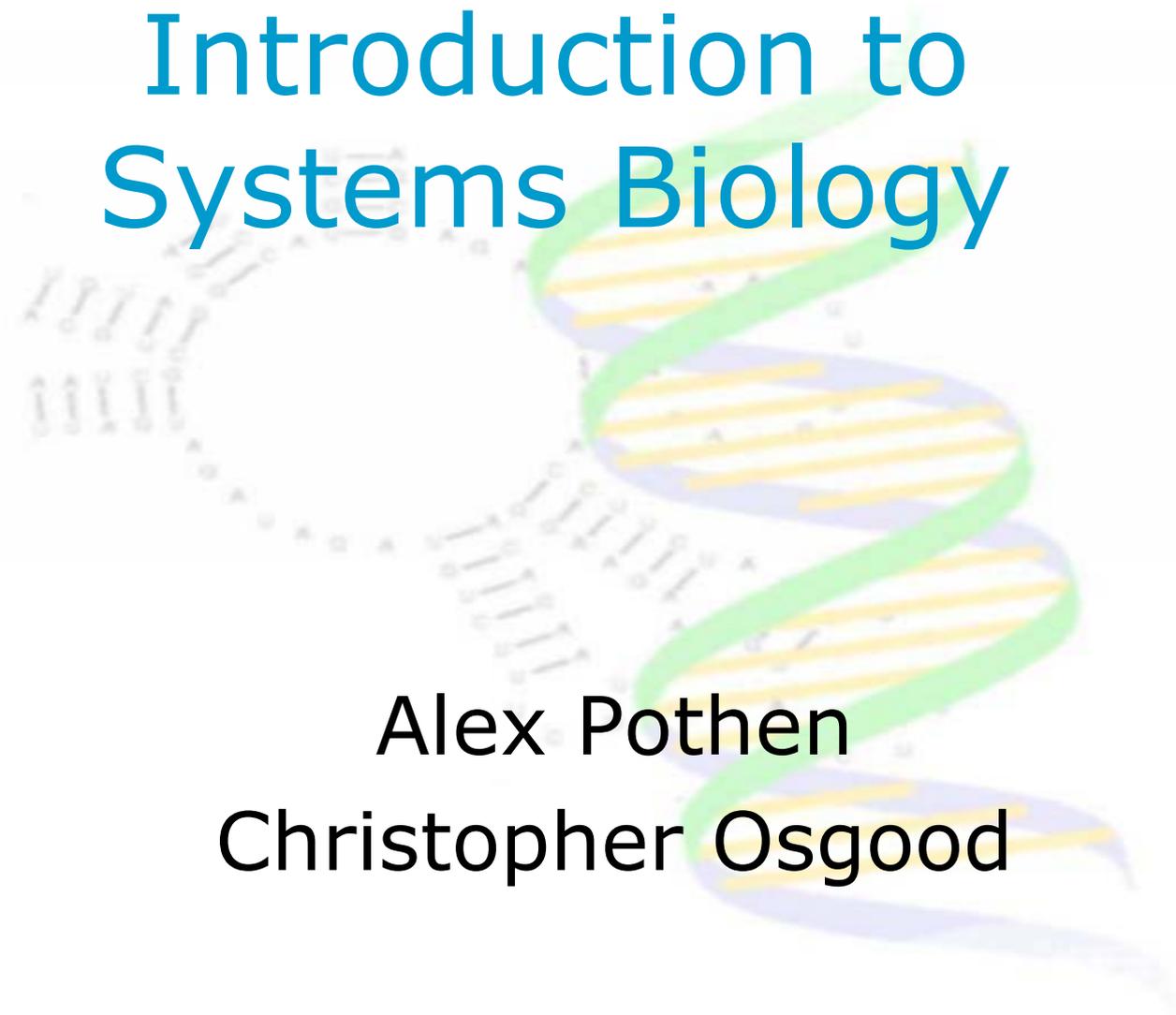


Introduction to Systems Biology



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Topics to be discussed

- Systems Theory
 - Systems Biology
 - Network Biology
 - Network Structure
 - Characterizing Networks
 - Models of Networks
 - Conclusion
- 

What is Systems Theory?

Mathematical Systems Theory is concerned with the description and understanding of systems by the means of mathematics.

- Analysis
- Modeling
- Simulation

...

Dynamic Systems

- Definition

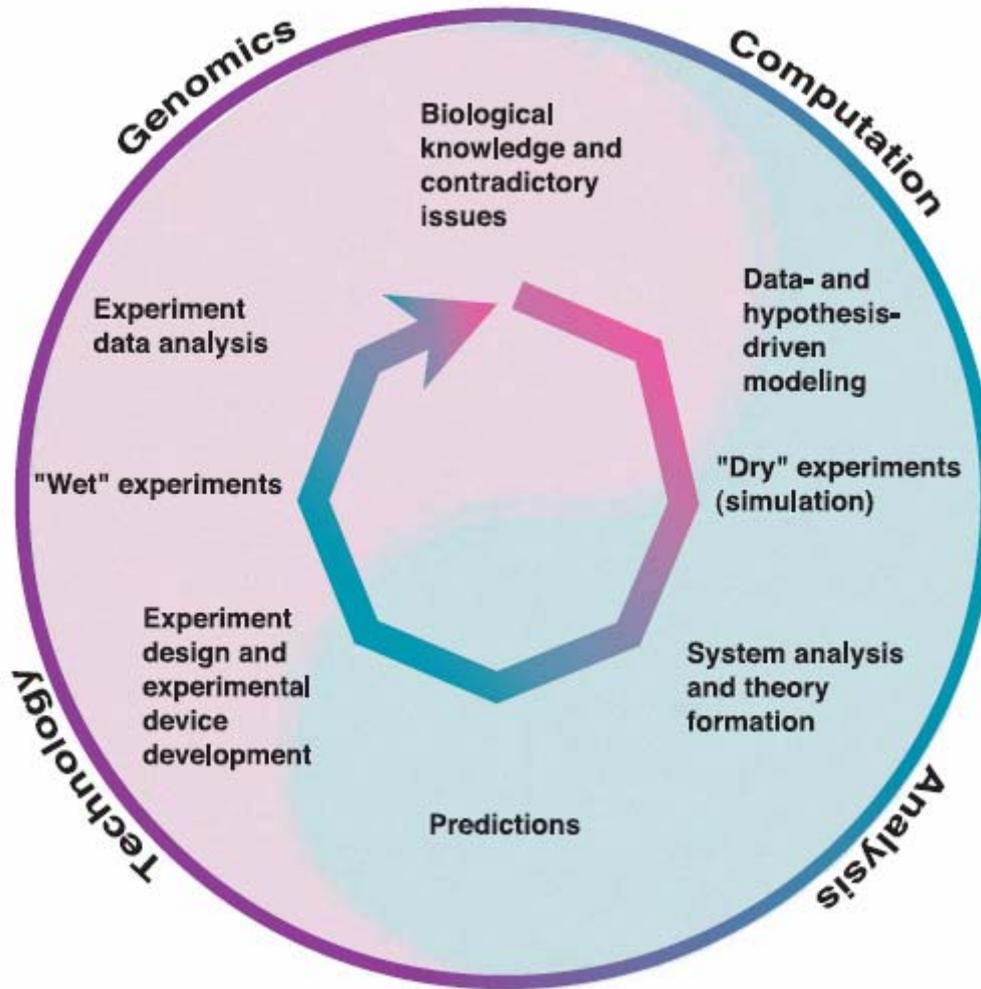
A *system* is an object in which variables of different kinds interact and produce observable signals.

In a *dynamic* system the current output value depends not only on the current input value but also on its earlier values.

What is Systems Biology?

- „Aims at systems-level understanding [which] requires a set of principles and methodologies that links the behaviors of molecules to systems characteristics and functions“
(*H. Kitano, ICSB 2000*)
- Question is, what do we mean by **biological systems**?
- By **"system"**, we mean a bunch of parts that are connected to one another and work together.
- Current primary focus is the **cell** but the perspective needs to be extended to tissues, organs, organisms, populations, ecosystems,..

Systems Biology Research Cycle Vision

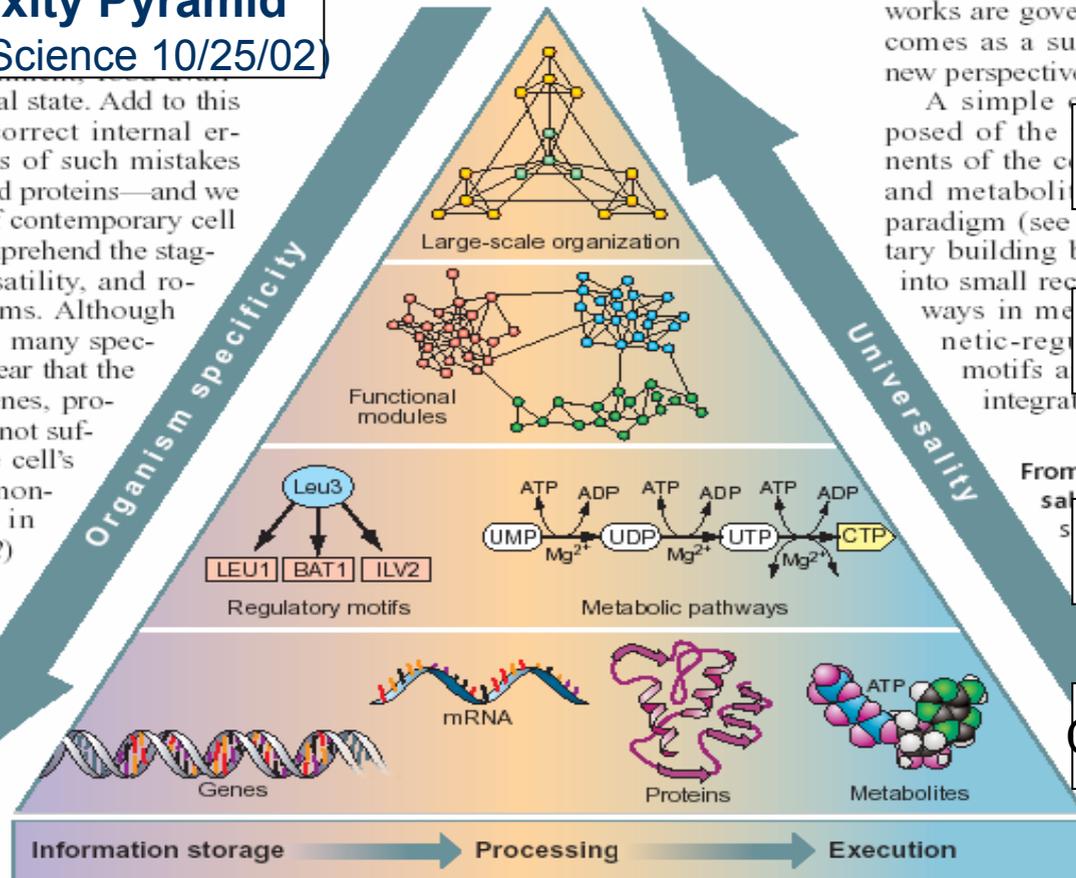


A systems biology view...

Life's Complexity Pyramid (Oltvai-Barabasi, Science 10/25/02)

ability, and developmental state. Add to this an amazing ability to correct internal errors—battling the effects of such mistakes as mutations or misfolded proteins—and we arrive at a major issue of contemporary cell biology: our need to comprehend the staggering complexity, versatility, and robustness of living systems. Although molecular biology offers many spectacular successes, it is clear that the detailed inventory of genes, proteins, and metabolites is not sufficient to understand the cell's complexity (1). As demonstrated by two papers in this issue—Lee *et al.* (2) on page 799 and Milo *et al.* (3) on page 824—viewing the cell as a network of genes and proteins offers a viable strategy for addressing the complexity of living systems.

According to the basic dogma of molec-



finding that the structures of t works are governed by the same comes as a surprise, however, a new perspective on cellular organ

A simple complexity pyramid posed of the elements of the c and metabolic

paradigm (see the figure). These tary building blocks organize th into small recurrent patterns, ca ways in me netic-reg motifs a integrated to form functi

System

Functional Modules

From the particular to the general

Building Blocks

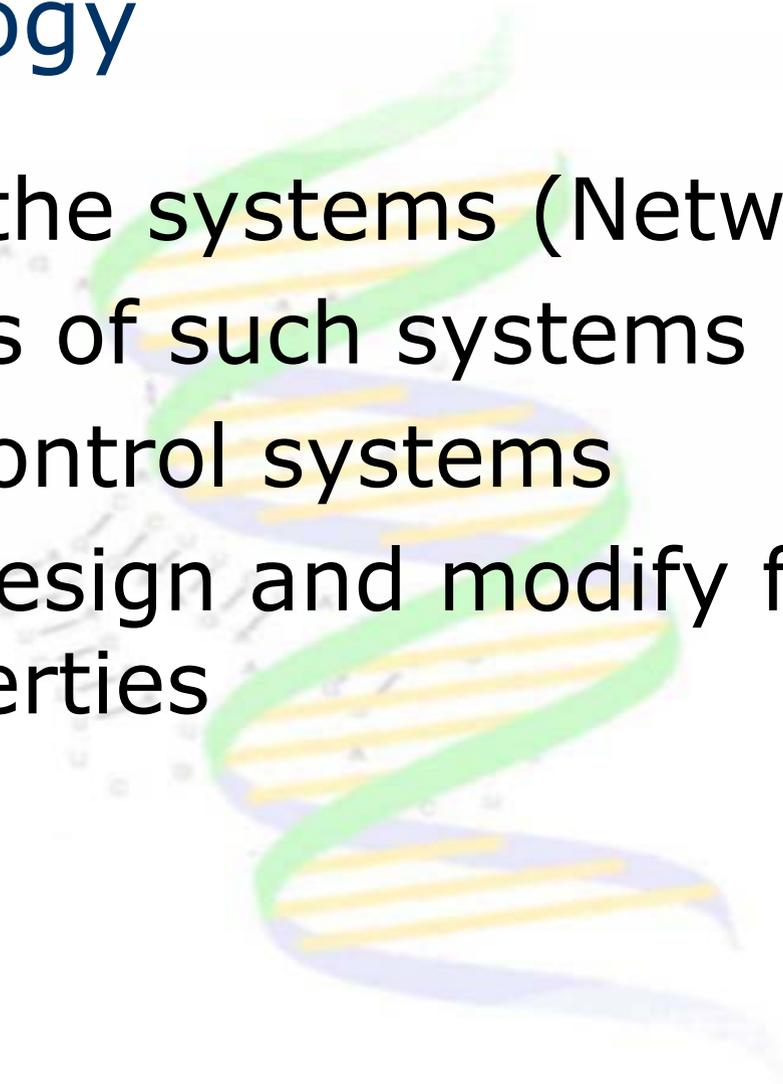
scriptome, proteome, metabolome
There is rem

Components

level into of cellular organ be achieved whe the cell as a complex network in

Network Biology

- Structure of the systems (Network)
- The dynamics of such systems
- Methods of control systems
- Methods to design and modify for desired properties



Network Structure

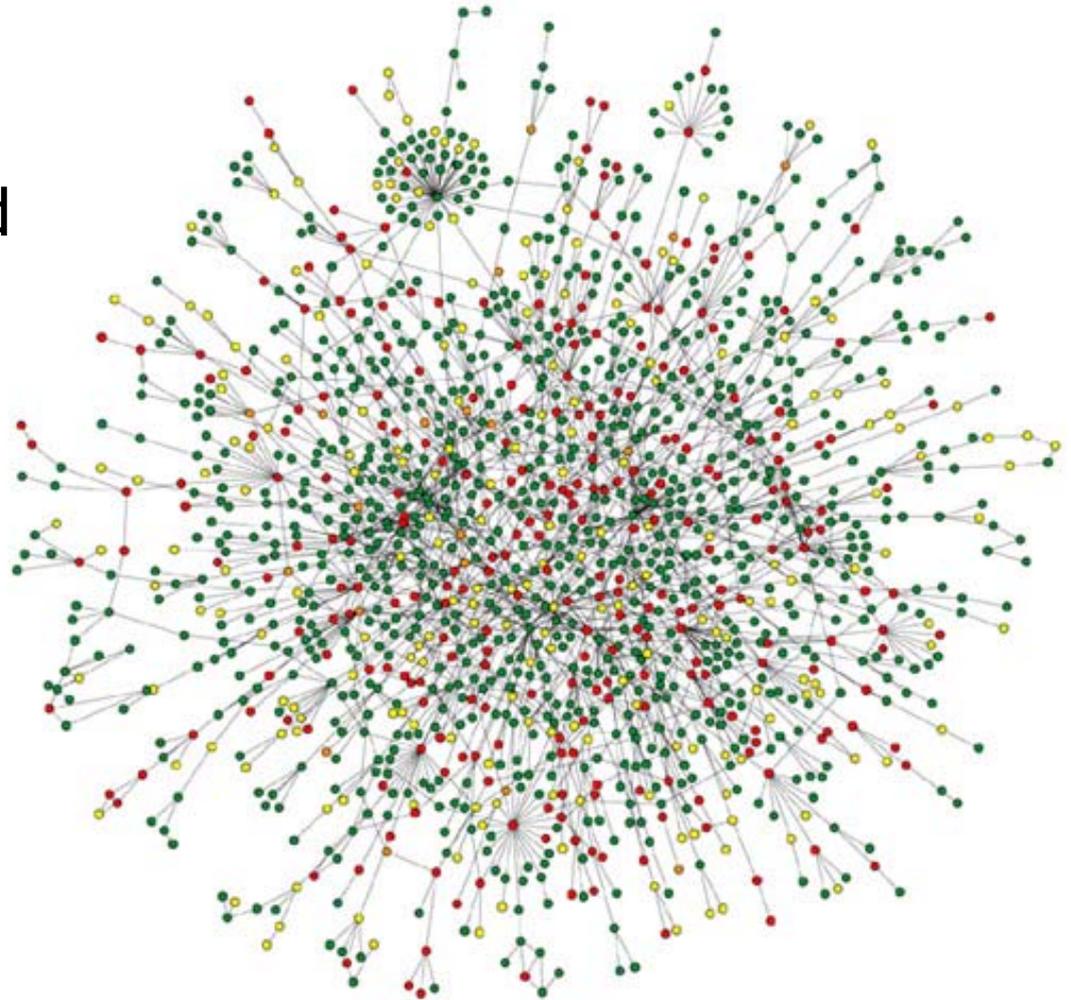
- Bottom-up approach
 - tries to construct a gene regulatory network based on the compilation of independent experimental data
 - This approach is particularly suitable for the end-game scenario where most of the pieces are known and one is trying to find the last few pieces

Network Structure

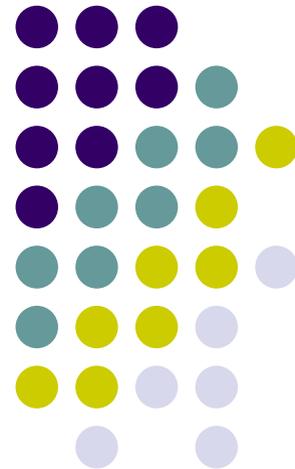
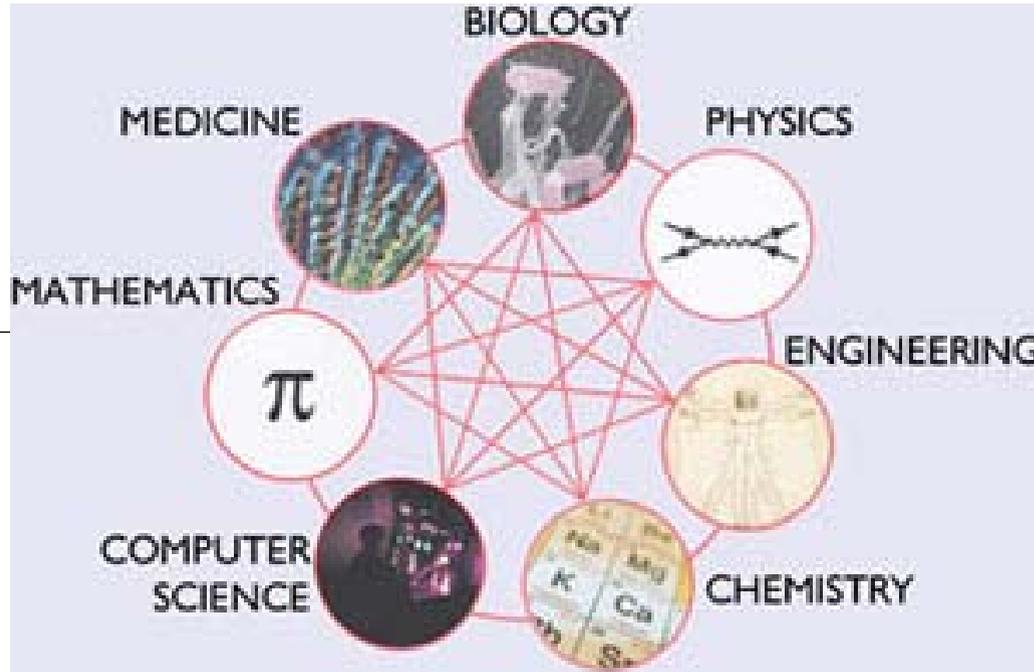
- Top-down approach tries to make use of high-throughput data using DNA microarray and other new measurement technologies
- Most of the methods developed in the past translate expression data into binary values, so that the computing cost can be reduced. However, such methods seriously suffer from information loss in the binary translation process and cannot obtain the accurate network structure.

Protein interaction network

Yeast map of protein-protein interactions based on yeast two-hybrid method

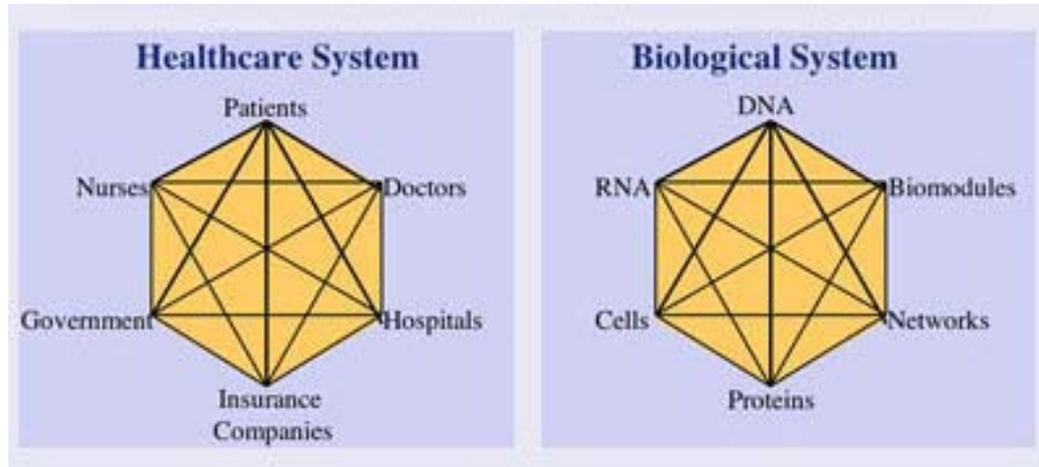


Biology



The mission of the Institute for Systems Biology is two-fold: revolutionizing biology through a systems approach; and predictive, preventive and personalized medicine.

What exactly is Systems Biology?



- What is required to understand our medical healthcare system? The healthcare system has individual groups: patients, physicians, nurses, hospitals, insurance companies, government insurance, etc. To understand the whole healthcare system, the relationships of the elements (e.g. individual patients, physicians, nurses, etc.) within a group must be ascertained with respect to one another and the elements in other groups. This information must be integrated together to obtain a view of how the system works.
- So it is with systems biology—the types of biological information (DNA, RNA, protein, protein interactions, biomodules, cells, tissues, etc.) also have their individual elements (e.g. specific genes or proteins) and the relationships of these with respect to one another and the elements of other types of biological information must be determined and, once again, all of this information integrated to obtain a view (model) of the system as a whole.
- Hence the importance of high-throughput facilities with global capacities (e.g., measure all genes or all proteins) and a strong computational infrastructure, as well as the need to invent new global tools for acquiring differing types of biological information and to develop the computational tools to integrate and model this information



- Cross-disciplinary science created many of the global tools necessary for systems biology (e.g., DNA sequencer, oligonucleotide or DNA arrays, the many strategies and tools of proteomics, etc.).
- The Internet provided us with the means for instant global communication and the ability to store and transmit large amounts of data.
- **The Human Genome Project** changed how biologists view and practice biology.

Specifically:



Discovery science introduced the possibility of global informational analyses.

A genetics parts list of all human genes and their control region sequences emerged.

The idea that biology is an informational science with three major types of information emerged: the digital or one-dimensional structure of DNA and gene, the three-dimensional structures of proteins, the molecular machines of life; and biological systems with their emergent behaviors.

Tools for high-throughput quantitative measurements of biological information were developed (e.g., DNA sequencer, DNA arrays, proteomics, etc.).

Computer science, mathematics, and statistics were employed to handle, store, analyze, integrate, model and disseminate biological information.

Model organisms (yeast, worm, fly, and mouse) were used as Rosetta Stones for deciphering complex biological systems in humans. This is possible because all of life arose from a common ancestor and the basic mechanisms for life's most fundamental processes; metabolism, information storage, and expression etc., are shared by all living organisms.

We will soon be able to decipher the logic of life from a genome. We can then compare how this logic has changed in living organisms through comparative genomics. Comparative genomics will be one of the keys to deciphering human biological complexity.



生物圈



生態體系

ECOSYSTEM LEVEL
Rain forest

社區

COMMUNITY LEVEL
All organisms in rain forest

族群

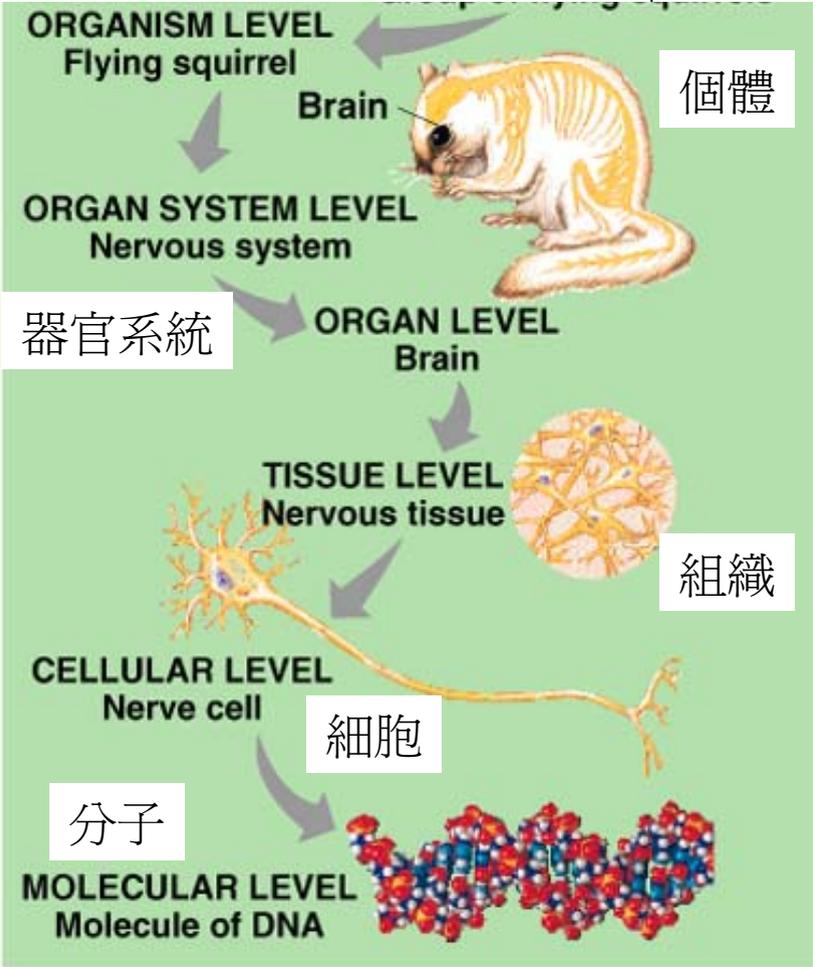
POPULATION LEVEL
Group of flying squirrels

ORGANISM LEVEL
Flying squirrel

個體

Brain

ORGAN SYSTEM LEVEL
Nervous system



原子

The Science of Life



Biosphere 生物圈

Ecosystem 生態系

Community 聚落

Population 族群

Organism 個體

System 系統

Organ 器官

Tissue 組織

Cell 細胞

Cell 細胞

Organelle 胞器

Supramolecule 超巨分子

Macromolecule 巨分子

Molecule 分子

Atom 原子

Cell: The unit of life
DNA: The molecule of life
Proteins: The machines of life

Nucleic Acids
(核酸):
DNA
RNA

Protein
蛋白質

Saccharide
醣類

Lipid
脂類

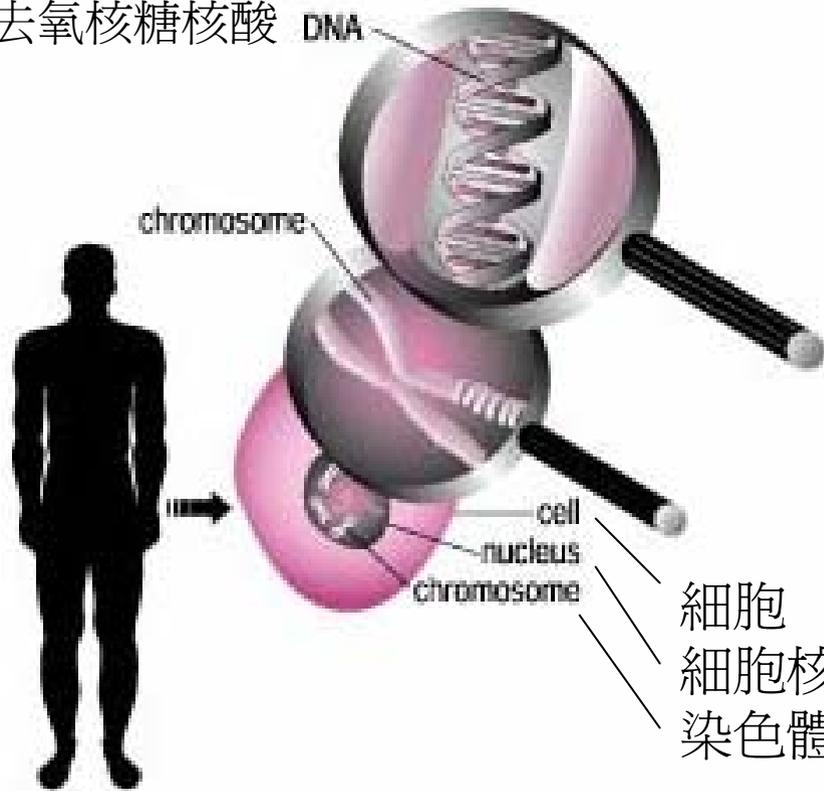
個體 - 細胞 - 胞器 - 分子

Organism - Cell - Organelle - Molecules



Deoxyribonucleic Acid =

去氧核糖核酸 DNA



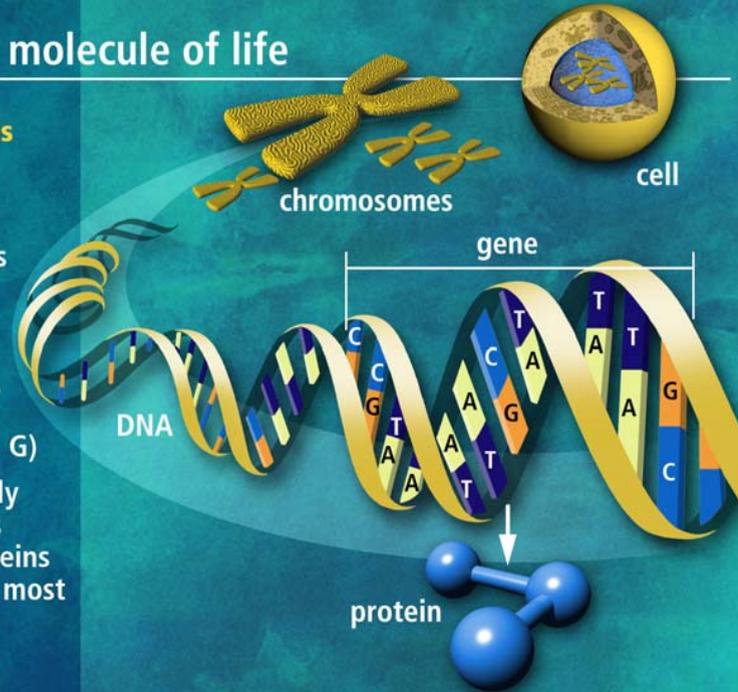
DNA the molecule of life

Trillions of cells

Each cell:

- 46 human chromosomes
- 2 meters of DNA
- 3 billion DNA subunits (the bases: A, T, C, G)
- Approximately 30,000 genes code for proteins that perform most life functions

Y-GG 01-0085



人體由上兆個細胞組成
每個細胞具有：
46 條染色體
2 米長的DNA
30 億個鹼基 (A, T, G, C)
3~4萬個基因



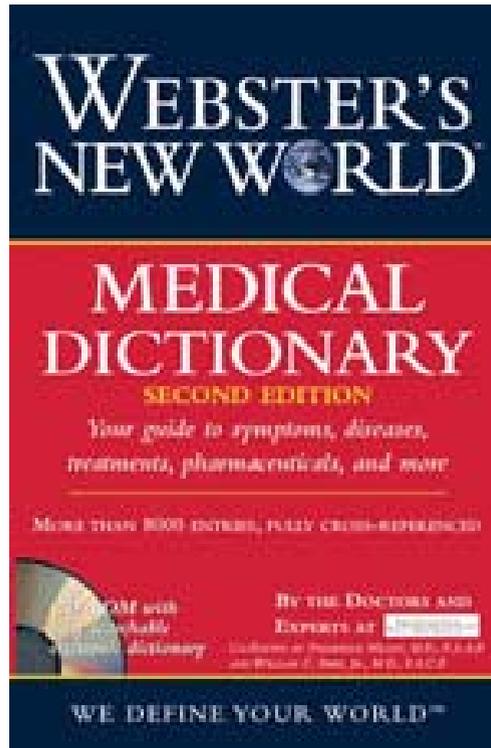
The Human Genome Project (HGP) began in 1990 as an effort by researchers from around the world to map and sequence the human genome - the totality of human DNA - as well as the genomes of important experimental organisms, like yeast, the nematode worm, and mouse. In 2000, the collaborators in the HGP announced the completion of a draft revealing 90% of the human sequence and in February 2001, the initial analysis of the human genome sequence was published in the scientific literature.

<http://www.genome.gov/Pages/EducationKit/>

<http://www.genome.gov/Pages/EducationKit/>



<http://www.ncbi.nlm.nih.gov/genome/guide/human/>
<http://www.ncbi.nlm.nih.gov/genome/guide/human/>



<http://www.medterms.com/script/main/hp.asp>