시스템 생물학 기초-1

12/08/27,28
주어진 용어에 대해 아는대로 서술하기
- 시스템 생물학
- 컴퓨터생물학
- 생명정보학
시스템 생물학이란?

- **Molecular biology** is the study of biology at a molecular level. The field overlaps with other areas of biology and chemistry, particularly genetics and biochemistry. Molecular biology chiefly concerns itself with understanding the interactions between the various systems of a cell, including the interactions between DNA, RNA and protein biosynthesis as well as learning how these interactions are regulated.

- **Biochemistry** is the study of the chemical processes in living organisms. It deals with the structure and function of cellular components such as proteins, carbohydrates, lipids, nucleic acids and other biomolecules.

- **Genetics** (from Ancient Greek γενετικός genetikos, “genitive” and that from γένεσις genesis, “origin), a discipline of biology, is the science of heredity and variation in living organisms.) The fact that living things inherit traits from their parents has been used since prehistoric times to improve crop plants and animals through selective breeding. However, the modern science of genetics, which seeks to understand the process of inheritance, only began with the work of Gregor Mendel in the mid-nineteenth century. Although he did not know the physical basis for heredity, Mendel observed that organisms inherit traits in a discrete manner—these basic units of inheritance are now called genes.
• **Systems biology** is a biology-based inter-disciplinary study field that focuses on the systematic study of complex interactions in [biological systems](#), thus using a new perspective ([holism](#) instead of [reduction](#)) to study them. Particularly from year 2000 onwards, the term is used widely in the [biosciences](#), and in a variety of contexts. Because the scientific method has been used primarily toward reductionism, one of the goals of systems biology is to discover new emergent properties that may arise from the systemic view used by this discipline in order to understand better the entirety of processes that happen in a biological system.

• Systems ?

• 왜 배워야 되는가 ?

• 무엇을 배워야 되는가 ?
Signal Transduction Pathway
생물 (생명)정보학

• 컴퓨터 시대의 생물학
• Bioinformatics
• 시스템 생물학과의 관계
생명정보학 이란?

- HGP
- DNA 서열 데이터

- 생명정보학: 정보학적 관점과 방법론을 가지고 생물학을 이해 연구하는 학문.
- Computational Biology
Computational Biology

• **Computational biology** is an interdisciplinary field that applies the techniques of **computer science**, **applied mathematics** and **statistics** to address **biological** problems.

1) **Bioinformatics**, which applies **algorithms** and **statistical techniques** to the interpretation, classification and understanding of biological datasets. These typically consist of large numbers of **DNA**, **RNA**, or **protein** sequences. **Sequence alignment** is used to assemble the datasets for analysis. Comparisons of **homologous** sequences, **gene finding**, and prediction of **gene expression** are the most common techniques used on assembled datasets; however, analysis of such datasets have many applications throughout all fields of biology.

2) **Computational biomodeling**, a field within **biocybernetics** concerned with building computational models of biological systems.

3) **Computational genomics**, a field within **genomics** which studies the **genomes** of cells and organisms. High-throughput **genome sequencing** produces lots of data, which requires extensive post-processing (**genome assembly**) and uses **DNA microarray** technologies to perform statistical analyses on the genes expressed in individual cell types. This can help find genes of interests for certain diseases or conditions. This field also studies the **mathematical foundations** of sequencing.

4) **Molecular modeling**, which consists of **modelling** the behaviour of **molecules** of biological importance.

5) **Systems biology**, which uses **systems theory** to model large-scale biological interaction networks (also known as the **interactome**).

6) **Protein structure prediction** and **structural genomics**, which attempt to systematically produce accurate structural models for three-dimensional **protein structures** that have not been determined experimentally.

7) Computational **biochemistry** and **biophysics**, which make extensive use of structural modeling and simulation methods such as **molecular dynamics** and **Monte Carlo method**-inspired **Boltzmann sampling** methods in an attempt to elucidate the **kinetics** and **thermodynamics** of protein functions.
전산학-생물학

• 컴퓨터가 어떻게 도움이 되었는가?
생물학의 정보란?

- 서열
- 발현 profile
- 발현 정도
- 정성적/정량적인 정보

- 정보의 질적/양적 증가: 폭발적인
생명정보학자에게 필요한 기술

- 분자 생물학에 깊은 이해
- 분자 생물학 패키지에 대한 이해
- 리눅스나 유닉스 환경에 익숙
- 컴퓨터 언어프로그래밍에 익숙

- 그럼 지금 무엇을 준비 해야 되는가?
시스템 미생물학

- 시스템 미생물학이란 무엇인가?
- 컴퓨터를 이용한 대사 회로 분석 및 모델링 기술

- 시스템 생명공학
시스템 생물학과 그 응용

• 균주 개량 연구
  - 유전체 염기 서열 분석 통해
  - 전사체 분석
  - In Silico 모델 이용한
시스템 생명공학

미생물에 화학제품 공장을 지을 수 있을까요?
시스템 생명공학

석유화학산업시대에서 산업생명공학시대로의 전환

산업생명공학(Biorefinery)의 장점 및 중요성

- 지속가능
- 환경친화적
- 비용절감
대사 공학

- 대사공학: 대사회로의 증폭・억제・조절・신규도입 등에 의해 균주의 대사특성을 우리가 원하는 방향으로 바꾸는 일련의 기술

대사 회로란?

생물이 생명을 유지하기 위해 영양분을 외계로부터 섭취하여 필요한 구성물질로 바꾸고, 이 때 생긴 부산물을 체외로 배출하는 과정에서 나타나는 화학변화를 총칭한 것이다.
시스템 생명공학이란 무엇인가?

• 미생물을 다차원에서 분석함으로써
• 원하는 형질로 전환시키는 기술
Central dogma (유전 정보의 흐름을 나타내는 분자 생물학의 기본 원리)

전사는 DNA의 유전정보를 RNA로 바꾸는 과정이다

유전정보가 해독되어 단백질 생산

단백질
오믹스 (omics)

생명체의 구성성분들의 총합 (X-ome) 및 이를 연구하는 학문

기존의 방법

새로운 방법

RXR
BRCA
actin
ras
Wnt
유전체 (Genome)

생명체에 담긴 유전정보 전체를 의미한다.
단백체 (Proteome)
전사체 (Transcriptome)
대사체 (Metabolome)

Experiment → in situ high throughput analysis → Metabolome profiles

Fluxome profiles → Characterization
흐름체 (Fluxome)
미생물을 다자원에서 분석할 수 있게 됨
이 많은 실험을 언제 다 하지?

컴퓨터로 미리 실험을 해본다

Combinatorial gene knockout

\[ \binom{1000}{2} = 499,500 \]
\[ \binom{1000}{3} = 166,167,000 \]
\[ \binom{1000}{4} = 41,417,124,750 \]

***
미생물 실험도 컴퓨터 게임처럼?
미생물을 원하는 형질로 전환시키는
우수 균주

형질 전환

실험 데이터

Feedback

컴퓨터를 이용한 분석 및 예측
시스템 생명공학... 대사공학... 시스템 대사공학...
미생물의 응용 분야
바이오 연료

바이오 플라스틱

화학구조식
의약품
환경정화 작용

난 더러운 게 좋아!

Mmmm, good!
미생물 농약
발효식품
Medical care

Food & animal feed

Health care

Amino acid

Sports

Beauty care

Val, Leu, Ile: effective in hepatic failure
Glu: antulcer drug
Arg: immune-enhancing effect

Val, Leu, Ile: Muscle building, increase of stamina, recovery from fatigue

The skin moisturizing effect
Collagen composition
Care of damaged cuticles
Efficient burning of body fat

20 kinds of amino acids that make up proteins

Essential amino acids
Valine, Lysine, Histidine, Leucine, Methionine, Tryptophan, Threonine, Phenylalanine, Isoleucine

Glutamic Acid, Glutamine, Tyrosine, Glutamate, Alanine, Proline, Cysteine, Aspartic Acid, Asparagine, Arginine
"세계 최고 효율 아미노산 생산기술 개발"

KAIST 이상엽 교수팀, 미국PNAS 온라인판에 게재 
생물공학 관련 산업발전에 크게 기여할 듯

말년 아미노산의 하나인 '발린(L-valine)'을 세계에서 가장 효율적으로 생산할 수 있는 기술이 국내 연구진에 의해 개발됐다.

한국경제 2007년4월25일 수요일

아미노산 20% 중산 '파워균주' 개발

이상엽 KAIST 교수

국내 연구진이 인체내에 괴수 아미노산의 하나인 발린(L-valine)을 기준 금량보다 20% 이상 더 생산할 수 있는 균주를 개발했다.

이상엽 한국과학기술원(KAIST) 교수(사진)는 시행성을 둘러싼 생물학적 기술을 이용해 세계 최고 수준(10g/L)의 발린 생산 균주 개발에 성공했다고 25일 밝혔다.

FACULTY OF 1000 BIOLOGY
MAJOR ADVANCES. EXPERT OPINIONS.

Faculty Comments

Faculty Member: Ethel John Davis

In this work, the authors describe a general methodology for generating an organism suited for industrial application. What was done here was to take a target strain, which included genes, to direct the synthesis of the L-valine gene. This strain is of interest in the industrial setting, but, more importantly, the authors have described a general paradigm for altering the yield of small molecules.
바이오 부탄올 생산기반 마련
시스템 생물학/맞춤형 예방의학

참고 자료: 황대희 /김종민
시스템 생물학/맞춤형 예방의학

그림 3. single cell로부터 다양한 측정을 하기 위한 lab-on-a-chip 기구의 모식도 (Wasten and Hood, 2004에서 인용, copyright@Journal of Proteome Research). 자세한 설명은 참고 논문 참조.
Prions cause transmissible neurodegenerative diseases and replicate by conformational conversion of normal benign forms of prion protein (PrP\textsuperscript{C}) to disease-causing PrP\textsuperscript{Sc} isoforms. A systems approach to disease postulates that disease arises from perturbation of biological networks in the relevant organ. We tracked global gene expression in the brains of eight distinct mouse strain–prion strain combinations throughout the progression of the disease to capture the effects of prion strain, host genetics, and PrP concentration on disease incubation time. Subtractive analyses exploiting various aspects of prion biology and infection identified a core of 333 differentially expressed genes (DEGs) that appeared central to prion disease. DEGs were mapped into functional pathways and networks reflecting defined neuropathological events and PrP\textsuperscript{Sc} replication and accumulation, enabling the identification of novel modules and modules that may be involved in genetic effects on incubation time and in prion strain specificity. Our systems analysis provides a comprehensive basis for developing models for prion replication and disease, and suggests some possible therapeutic approaches.

*Molecular Systems Biology* 24 March 2009; doi:10.1038/msb.2009.10

*Subject Categories*: neuroscience; molecular biology of disease

*Keywords*: microarray; network analysis; neurodegenerative disease; prion
A systems approach to prion disease

Figure 1  Strategies for identification of 333 core differentially expressed genes (DEGs) and their functional analysis in mouse prion diseases. Two prion strains (RML and 301V) were used for inoculating mice from six different genetic backgrounds (B6, B6.1, FVB, Tg4053, Prnp0/+, and Prnp0/0) to generate eight prion–mouse combinations. From the list of 7400 DEGs identified from at least one of the five combinations with normal levels of prion protein (1X), 333 DEGs shared by all five were selected through novel statistical methods to represent perturbed networks essential to prion pathophysiology. Venn diagram shows the overlap of the 333 DEGs with DEGs from Tg4053-RML (mice expressing eight times of normal prion protein levels) and from 0/+-RML (mice expressing one-half of normal prion protein levels). Among 333 DEGs, 161 genes were mapped to networks through protein–protein interaction network or metabolic pathways. Also, by comparison of 333 DEGs with previous prion microarray studies, we identified 178 DEGs that have not been reported in connection with prion disease.
Visualizing molecular interaction networks
Visualizing molecular interaction networks

• Cytoscape  http://www.cytoscape.org/
• BioLayout  http://www.biolayout.org/
• Osprey  http://biodata.mshri.on.ca/osprey/servlet/Index
• VisANT  http://visant.bu.edu/
The spread of viruses in scale-free networks is aided by hubs--once a hub gets a virus, it can pass it on to a very large number of nodes.
Protein-Protein Interaction

Protein-protein interaction in *Saccharomyces cerevisiae*
Human protein network of PKB
A Random network

Ab

B Scale-free network

Bb

C Hierarchical network

Ca

Ac

Bc

Cc
What do we get an information from protein network?

Protein network in *S. cerevisiae*

1548 proteins and 2700 links

Functional Connection

Blue: membrane fusion
Gray: chromatin structure
Green: cell structure
Yellow: lipid metabolism
Red: cytokinesis
Biological Networks and Complex Systems

Complexity

Network

Scale-free network & Hierarchical network

Kinome

Metabolism

Cell Cycle

Signaling

Whole

UNCOVERING ORDER HIDDEN WITHIN COMPLEX SYSTEMS
가상세포

Cyber Cells

가장 단순한 생(生) 세포일지라도 수퍼컴퓨터가 완벽한 모델을 재현해 낼 수 없음을 만큼 그 행동양식은 매우 복잡하다. 그러나 그 불완전한 모델조차 생물학의 기초를 뒤쫓을 만큼 위력이 있다. (W.Wayt Gibbs)
대장균을 감염시키는 T7 박테리오파지에 의해 시작된 유전자 공격은 세밀한 컴퓨터 시뮬레이션을 이용하는데 연구되었음

인간세포 중 최초로 컴퓨터에 의해 모델링 된 적혈구 세포
인간 지능 세포 프로젝트

Genetic Circuits Research group (UCSD)
인체에 질병을 유발하는 대장균, influenzae, 헬리코박터 파이로리 등 박테리아의 genome을 기반으로한 모델

E-cell (Keio Univ. Japan)
생물정보공학실험실에서 만든 수학상의 세균으로 mycoplasma genitalium의 유전자를 기반으로 구축

Virtual cell (UConn)
세포시뮬레이션 패키지

M- cell (Salk Institute & Pittsburgh Supercomputer Center)
신경세포와 근육세포 사이의 시냅스에 대한 시뮬레이션

In silico Cell (Physiome Sciences, Princeton)
프로그램어 언어인 CellML 개발: 세포모델을 공유하고 결합할 수 있는 공통어

Microbial Cell project (미국 에너지성이 지원하는 연구 프로그램)
분자수준의 단세포 유기체를 분석, 생화학적 모델을 개발
Metabolic flux analysis (MFA)
Definition of Metabolite Balancing model
Classification of the defined model according to Determinacy and Redundancy
Determination of balanceable rates, consistency check, gross error detection and data reconciliation in redundant system
Determination of calculable rates
Flux balance analysis
Register multiple objective function candidates
Choose maximizing or minimizing a linear objective function
Initial conditions for constraints
  reversible reaction: \(-\infty < r < \infty\)
  irreversible reaction: \(0 < r < \infty\)
  uptake metabolite: \(-\infty < m < 0\)
  secretion metabolite: \(0 < m < \infty\)
  unknown metabolite: \(-\infty < m < \infty\)
  intermediate metabolite: \(m = 0\)
Calculation of flux distributions by matrix operation or linear programming
MFAML로 표현한 대장균 가상세포의 예
Minimal Cell technology
（최소세포）

http://www.tigr.org/minimal

하나의 살아있는 세포를 구성하는데 반드시 필요한 유전자의 최소 숫자는 얼마 일까? 현재 많은 유전체 사업이 완료되어 있기 때문에, 우선 이들을 비교하여 최소 유전자수를 알아볼 수 있을 것이다. 반드시 필요한 유전자는 모든 유전체에서 공통적으로 존재할 것이기 때문이다.
Global Transposon Mutagenesis and a Minimal Mycoplasma Genome

Clyde A. Hutchison III, Scott N. Peterson, Steven R. Gill, Robin T. Cline, Owen White, Claire M. Fraser, Hamilton O. Smith, J. Craig Venter

Mycoplasma genitalium with 517 genes has the smallest gene complement of any independently replicating cell so far identified. Global transposon mutagenesis was used to identify nonessential genes in an effort to learn whether the naturally occurring gene complement is a true minimal genome under laboratory growth conditions. The positions of 2209 transposon insertions in the completely sequenced genomes of M. genitalium and its close relative M. pneumoniae were determined by sequencing across the junction of the transposon and the genomic DNA. These junctions defined 1354 distinct sites of insertion that were not lethal. The analysis suggests that 265 to 350 of the 480 protein-coding genes of M. genitalium are essential under laboratory growth conditions, including about 100 genes of unknown function.

Mycoplasma genitalium 에는 517개의 유전자가 있는데, Haemophilus influenzae의 1703개의 유전자와 비교해 볼 때 240개의 상동 유전자가 있고, 22개의 non-orthologous 유전자가 치환되어 있으며, 6개의 유전자는 기능적으로 중복되었거나, 기생과 관련되어 있다. 따라서 아래와 같이 계산하면,
240 homologues to H. influenzae genes
+23 non-orthologous displacements
-6 (functional redundancy, parasite-specific)
현재 세포를 유지하는데 필수적인 최소 유전자는 257개로 추측된다.
따라서, Mycoplasma genitalium 에는 517개의 유전자 (단백질 coding 유전자는 480) 중에서 반드시 필요한 필수유전자는 265 – 350 개로 추산 (100개는 기능이 밝혀져 있지 않음)
In the spring of 1996, initially called the 'Mycoplasma project', had started in Laboratory for Bioinformatics, Keio University SFC (Shonan-Fujisawa campus).

1. the project to focus on the kinetic dynamics of metabolic pathways and the control of enzyme productions through the expressions of genes
2. development of a generic software system based on object-orientation in C++ language. The software was initially named ECL (Electronic Cell Laboratory), and was later given the current name 'E-Cell System', or 'Electronic Cell System

In August and September of 1997, the software had been used in a collaborative project between Keio and TIGR (The Institute for Genomic Research), which aimed at in silico reconstruction of a virtual hypothetical cell with 127 genes based on Mycoplasma genitalium, which can self-sustain by producing energy from glucose with enzymes created from those genes.

E-Cell 3, initially started its development on Bioinformatics.org and later moved to Sourceforge.net in early 2003, is a complete reconstruction of E-Cell 1. E-Cell 3 can be viewed as an object-oriented computation platform on which any types of simulation algorithms can be used in any combination.
<table>
<thead>
<tr>
<th>Gene type</th>
<th>Mycoplasma genitalium</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycolysis</td>
<td>9</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Lactate fermentation</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Phospholipid biosynthesis</td>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Phosphotransferase system</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Glycerol uptake</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>RNA polymerase</td>
<td>6</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Amino acid metabolism</td>
<td>2</td>
<td>0</td>
<td>2</td>
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<tr>
<td>Ribosomal L subunit</td>
<td>30</td>
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<tr>
<td>Ribosomal S subunit</td>
<td>19</td>
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<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Elongation factor</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Protein coding genes</td>
<td>98</td>
<td>7</td>
<td>105</td>
</tr>
<tr>
<td>RNA coding genes</td>
<td>22</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>120</strong></td>
<td><strong>7</strong></td>
<td><strong>127</strong></td>
</tr>
</tbody>
</table>

The column labeled ‘M. genitalium’ represents the number of genes taken from the genome of Mycoplasma genitalium. The column labelled ‘Other’ represents the number of genes that are not found in the gene list of M. genitalium and thus have been taken from other organisms, such as Escherichia coli. The 127 genes include 22 RNA coding genes.
M. genitalium

Only 480 genes
Construction of "Virtual Cell"

- It has:
  - 127 genes
  - 4268 molecular species
  - 495 reactions

- It performs:
  - glycolysis
  - lipid synthesis
  - transcription, translation and degradation
E-Cell의 모델 세포를 이용하여 세포 대사경로의 특성을 실험한 일례로서, 세포를 둘러싼 외부 환경에서 에너지원이 되는 당(glucose)을 제거할 때, 세포질 내의 에너지 운반체인 ATP 분자의 수의 변화를 보인 것이다. 그림에서 x축은 경과된 시간을 나타내고, y축은 세포질 내의 ATP 분자의 개수를 나타낸다. 그림에서 나타난 것과 같이 세포가 가사(starvation)하기 직전에 ATP의 양이 일시적으로 증가하는 것은 흥미로운 결과이다. 이와 같은 결과는 일정 양의 ATP가 해당작용(glycolysis) 경로(pathway)에서 충분한 양의 ATP를 생성하기 위해 사용된다는 사실로부터 설명될 수 있다. 이것은 ATP 생성 중간물질이 완전히 소모되기 직전에 해당작용의 원료가 되는 당이 없으면 해당작용을 위한 ATP 소모가 없어지기 때문에 순간적으로 ATP의 총량이 순간적으로 증가하는 것이다. 이와 같은 실험은 E-Cell과 같은 가상 모델 시뮬레이션을 통해서 용이하게 수행될 수 있다.
E-Cell 사용자 인터페이스
Virtual Cell

http://www.nrcam.uchc.edu/index.html
The software is composed of three main components:

- Modeling Framework
- Mathematics Framework
- WWW Interface-Biological Oriented Interface with Integrated Math Editor

1. The modeling framework represents the physiological models of the Virtual Cell and allows for persistence and database support.

2. The mathematics framework transparently solves an important class of mathematical problems encountered in the cellular modeling.

3. The WWW accessible graphical user interface provides access to the technology mentioned above. The user interface has been developed using Java 2 Applets.
Modeling process
대사공학과 Cyber Cell

http://mbel.kaist.ac.kr/mfaml/
Metabolic Engineering
Systems Biotechnology
NanoBiotechnology

**X-omics:** Genome, transcriptome, proteome, metabolome & fluxome

**In silico:** Genome-scale model, modeling & simulation of cell

**NanoBiotech:** Platform tech. for biochips & biosensors
Metabolic Flux Analysis

Transportation flux

Metabolic reactions

Stochiometric matrix (constraints)

Objective function

Optimization

Graphical visualization

Analysis

Input

Experimental parameters

Output
실제세포

가상세포

컴퓨터를 이용한 모델링

산업에 응용

공학적 응용

산업적 응용

기능 및 구조 분석

실험결과 이해

대사 경로
Techniques associated with systems biology

• According to the interpretation of System Biology as the ability to obtain, integrate and analyze complex data from multiple experimental sources using interdisciplinary tools, some typical technology platforms are:

  • **Transcriptomics**: whole cell or tissue gene expression measurements by DNA microarrays or serial analysis of gene expression
  • **Proteomics**: complete identification of proteins and protein expression patterns of a cell or tissue through two-dimensional gel electrophoresis and mass spectrometry or multi-dimensional protein identification techniques (advanced HPLC systems coupled with mass spectrometry). Sub disciplines include phosphoproteomics, glycoproteomics and other methods to detect chemically modified proteins.
  • **Metabolomics**: identification and measurement of all small-molecules metabolites within a cell or tissue
  • **Glycomics**: identification of the entirety of all carbohydrates in a cell or tissue.

In addition to the identification and quantification of the above given molecules further techniques analyze the dynamics and interactions within a cell. This includes:

  • **Interactomics** which is used mostly in the context of protein-protein interaction but in theory encompasses interactions between all molecules within a cell
  • **Fluxomics**, which deals with the dynamic changes of molecules within a cell over time
  • **Biomics**: systems analysis of the biome.
Techniques associated with systems biology

• The investigations are frequently combined with large scale perturbation methods, including gene-based (RNAi, mis-expression of wild type and mutant genes) and chemical approaches using small molecule libraries. Robots and automated sensors enable such large-scale experimentation and data acquisition. These technologies are still emerging and many face problems that the larger the quantity of data produced, the lower the quality. A wide variety of quantitative scientists (computational biologists, statisticians, mathematicians, computer scientists, engineers, and physicists) are working to improve the quality of these approaches and to create, refine, and retest the models to accurately reflect observations.

• The investigations of a single level of biological organization (such as those listed above) are usually referred to as Systematic Systems Biology. Other areas of Systems Biology includes Integrative Systems Biology, which seeks to integrate different types of information to advance the understanding the biological whole, and Dynamic Systems Biology, which aims to uncover how the biological whole changes over time (during evolution, for example, the onset of disease or in response to a perturbation). Functional Genomics may also be considered a sub-field of Systems Biology.
Techniques associated with systems biology

- The systems biology approach often involves the development of mechanistic models, such as the reconstruction of dynamic systems from the quantitative properties of their elementary building blocks. For instance, a cellular network can be modelled mathematically using methods coming from chemical kinetics and control theory. Due to the large number of parameters, variables and constraints in cellular networks, numerical and computational techniques are often used. Other aspects of computer science and informatics are also used in systems biology. These include new forms of computational model, such as the use of process calculi to model biological processes, the integration of information from the literature, using techniques of information extraction and text mining, the development of online databases and repositories for sharing data and models (such as BioModels Database), approaches to database integration and software interoperability via loose coupling of software, websites and databases and the development of syntactically and semantically sound ways of representing biological models, such as the Systems Biology Markup Language.