Paper Reading Class

Graduate Institute of Systems Biology & Bioinformatics (SyBBi)

系統生物與生物資訊研究所

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Science Building 5

National Central University

SyBBi Paper Reading Class

Graduate Institute of Systems Biology and Bioinformatics
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http://sansan.phy.ncu.edu.tw/~hclee/SB_course/index.htm
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What is Systems Biology?

- Hiroaki **Kitano** (Nature 2002, Science 2002) - Systems biology is an emerging field that enables us to achieve in-depth understanding (of biology) at the system level.

- Marc W. **Kirschner** (Cell 2005) – Systems biology is the study of the behavior of complex biological organization and processes in terms of the molecular constituents.

What is Systems Biology?

- 系統生物是一項以生物分子為基礎探索複雜的生物組織與機制在系統層次行為的新興跨領域學門。他的特徵是用尖端物理/化學原理設計的高通量測量儀器（如基因晶片、雷射測序儀、質譜儀等）取得系統性的生物數據，經過高速及高容量電腦與先進資料庫技術及演算法整理之後，依此根據物理及統計原理衍生對生物系統的假設（或推論），再由該假設推動系統模型的建立與分析。經過模型行為與生物數據之對比，再對模型做適當之修正，或產生新的數據需求。如此反覆回饋，即可望能向以生物分子為基礎對生物系統的宏觀行為取得瞭解漸進。

Brief by HCL to NSC Interdisciplinary Panel, 2006/9/13

A historic perspective

- The “old fashioned” biology era
- The information era (> 1990)
- The systems era (> 2000)

The “old fashioned” biology era

- Rise of molecular biology 1953
- Single element issues – structure and function proteins & genes
- Many, many techniques invented and developed in 2nd half of 2oth century

The information era

- Human genome project (>1990) led to avalanche of data
- Bioinformatics - creation and advancement of algorithms, computational and statistical techniques, management and analysis of biological data.
- Computational biology - hypothesis-driven investigation of a specific biological problem using computers towards discovery and the advancement of biological knowledge.

The systems era

- Rise of high-throughput experimental techniques – micro-array (1995), mass spectrometry of proteins (1987), 2D electrophoresis
- Systems issues: signaling, network, pathway, dynamics
- Integration of biological experiment, bioinformatics and hypothesis driven model analysis towards systems-level understanding

The interdisciplinary nature of systems biology

- The "old fashioned" biology era
  - Biology
  - Biostatistics – biological data ⊕ statistics
- The information era (> 1990)
  - Bioinformatics – biological data ⊕ computer
  - Theoretical/computational biology – biology ⊕ physics/models
- The systems era (> 2000)
  - Systems biology – biology ⊕ data ⊕ computer ⊕ statistics ⊕ physics/models

Marc Kirschner. The meaning of systems biology. *Cell* (2005) 121:503-504

Kirschner is founding chair of the **Dept. of Systems Biology** established by Harvard University in 2004(http://sysbio.med.harvard.edu/).

- The big question to understand in biology is not regulatory linkage but the *nature of biological systems that allows them to be linked together* in many nonlethal and even useful combinations.
- Systems biology is the study of the behavior of complex biological organization and processes in terms of the molecular constituents.

Kirschner: The meaning of systems biology (continued)

- Systems biology is built on
  - Molecular biology in its special concern for information transfer
  - Physiology for its special concern with adaptive states of the cell and organism
  - Evolutionary biology and ecology for the appreciation that all aspects of the organism are products of selection

- Systems biology attempts all of the above through quantitative measurement, modeling, reconstruction, and theory.

H. Kitano. Looking beyond the details. *Current Genetics* (2002) 41:1-10

Kitano is founding director of the **Systems Biology Institute (SBI)** in Tokyo a non-profit private research institution established in 2000 (http://www.sbi.jp/).

- To gain deep systems-level understanding of biology, one needs
  - To know the structure of the system, such as gene/ metabolic/signal transduction networks and physical structures
  - To know the dynamics of such systems
  - Methods to control systems
  - Methods to design and modify systems to generate desired properties.

Kitano: Looking beyond the details.
System structure identification

- Example of system structure (focus of Kitano paper): network of gene regulation, metabolism, and signal transduction.

- A network structure consists of:
  - elements of the network:
    - genes, mRNA, and proteins, (binding site, control sequences, RNAi, NC-RNA, ..)
  - Interaction between elements
  - Associated parameters

Some approaches to understanding interaction between elements

- "Encyclopedia", or maps, of interactions constructed by assembling literature reports of independent experiments
  - **KEGG**: Encyclopedia of Genes and Genomes (Kanehisa and Goto 2000) (http://www.genome.jp/kegg/)
  - **EcoCyc**: Encyclopedia of *Escherichia coli* K-12 Genes and Metabolism (Karp 2001) (http://ecocyc.org/)
  - **BRENDA**: Comprehensive Enzyme Information System (http://www.brenda.uni-koeln.de/)
- Drawback: depends of individual discoveries with varying degrees of reliability and accuracy

Some past approaches to understanding Interaction between elements (cont'd)

- Modeling and simulation of biological systems based on literature reports of independent experiments
  - lambda phage decision circuit
  - early embryogenesis and morphogenesis of *Drosophila*
  - cell cycle/cellular aging
  - circadian rhythms
  - (IP3 receptor-based) calcium oscillation
  - bacterial chemotaxis (趨化性)
  - many others

Pro and *con* for modeling and simulation

- *Pro*
  - resolves conflicts in hypotheses
  - finds hypothesis to explain counterintuitive and contradictory data
  - provides conceptual understanding (added by hcl)
- *Con*
  - depends on fragmented data with varying degrees of reliability and accuracy
  - too many factors left unknown
- Usefulness and impact will increase with availability of high-precision data

High-throughput biology

- Microarray
  - clustering of expression profiles
  - gene-disruption data
- (protein–protein interaction) yeast two-hybrid data
- Many high-throughput experimental methods and equipments developed since Kitano's 2002 paper
  - Mass spectrometry
  - Protein microarray

Kitano: Looking beyond the details.
System behavior analysis

- (Steady state) Flux balance analysis
  - use only the structure of the network
  - provide theoretical upper-bound, lower-bound, and optimal operation points of the circuit in steady-state condition
  - papers by JS Edward, BO Palsson
- (Dynamical) Bifurcation analysis
  - reveals system level characteristics
  - provides insights for medical treatments
  - papers by J Tyson and B Novak

Kitano: Looking beyond the details.
System control

- One of the most important areas in systems biology; research not yet taken off
- Method to control the state of biological systems:
  - controlled environmental stimuli
  - chemical injection
  - drug absorption
  - physical intervention
- Some key questions:
  - How can we transform malfunctioning cells into healthy cells?
  - How can we control cancer cells, to turn them into normal cells or cause apoptosis?
  - Can we control the differentiation of a specific cell into a stem cell and control its subsequent differentiation into the desired cell type?
- Literature search for development after 2002

Kitano: Looking beyond the details.
System design

- No meaningful results as yet
- Some futuristic applications
  - Design and grow organs from the tissue of the patient him/herself
  - Use biological materials for robotics or computation
  - Revolutionize industrial systems by using materials that have self-repair and self-sustaining capabilities

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Kitano: Looking beyond the details.
Measurement issues

- Computational efforts alone will never solve the (systems biology) problem
- The popular notion: ‘‘biological science will turn into information science’’ will never realize
- Comprehensiveness of the measurement is a critical issue
  - Factor comprehensiveness – Eg., no. of proteins and genes involved in a system
  - Time comprehensiveness
  - Item comprehensiveness – Eg., gene expression, protein concentration, localization
- Automated and computerized measurement is crucial

Papers to study and report (cont'd)

- **General**
  - The evolution of molecular biology into systems biology. Westerhoff et al. Nature Biotech. 2004, 22:1249-1252.
- **Data base & software**
  - Kyoto encyclopedia of genes and genomes (KEGG). Kanehisa & Goto, Nucl. Acids Res. (2000) 28:27–30.
  - Systems biology mark-up language (SBML). Hucka et al. Bioinformatics 2003, 4:524–531
- **Measurement and instrument**
  - Exploring the new world of the genome with DNA microarrays.
  - Brown & Botstein, Nat. Gen. supplement. 1999, 21:33-37.
  - Mass Spectometry. R Aebersold & M Mann. Nature 2003, 422:199-207.
  - Micro-fluidic systems. Anderson et al. 2000; Ikuta et al. 2001
  - Cell lineage of C. elegans. Onami et al. 2001
- **Systems Biology experiment and theoretical**
  - Yeast cycle. Chen et al. Mol. Biology of the Cell 2000, 11:369–391.
  - A genomic code for nucleosome positioning. Eran Segal1 et al. Nature online 16 June 2006.

Papers to study and report

- **Systems Biology experiment and theoretical** (cont'd)
  - A Protein Interaction Map of Drosophila melanogaster. Giot et al. Sienceexpress 6 November 2003 pp 1-19
  - A first-draft human protein-interaction map. Lehner & Fraser. Gen Biology 5:R93 pp1-9. http://genomebiology.com/2004/5/9/R63
  - A Genomic Regulatory Network for Development , E. Davidson et al. Science, 0036-8075, March 1, 2002, Vol. 295

- **Modeling and simulation**
  - Circuit simulation of genetic network. McAdams & Shapiro. Science 1995, 269:650–656.
  - Dynamics of the p53-Mdm2 feedback loop in individual cells. Lahav et al. Nat Gen 2004, 36:147-150.
  - (Bacterial chemotaxis) Robustness in simple biochemical networks. Barkai & Leibler. Nature 1997, 387:913–917
  - Network Motifs: Simple Building Blocks of Complex Networks. Milo et al. Science 2002, 298:824-827.
  - Network biology. Barabasi & Oltvai. Nature Rev. 2004, 5:101-114.
  - Advances in flux balance analysis. Kauffman et al. Curr. Op. Biotech. 2003, 14:491–496
  - Sniffers, buzzers, toggles and blinkers: dynamics of regulatory and signaling pathways in the cell. Tyson et al. Curr. Op. Cell Bio. 2003, 15:221–231

Website for this course

http://sansan.phy.ncu.edu.tw/~hclee/SB_course/index.htm

Happy reading!