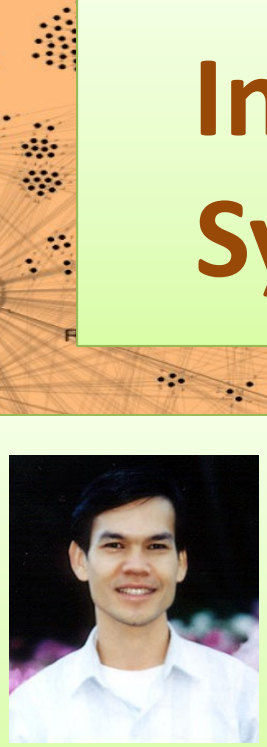
Introduction to System biology



Wises Namwat, Ph.D.

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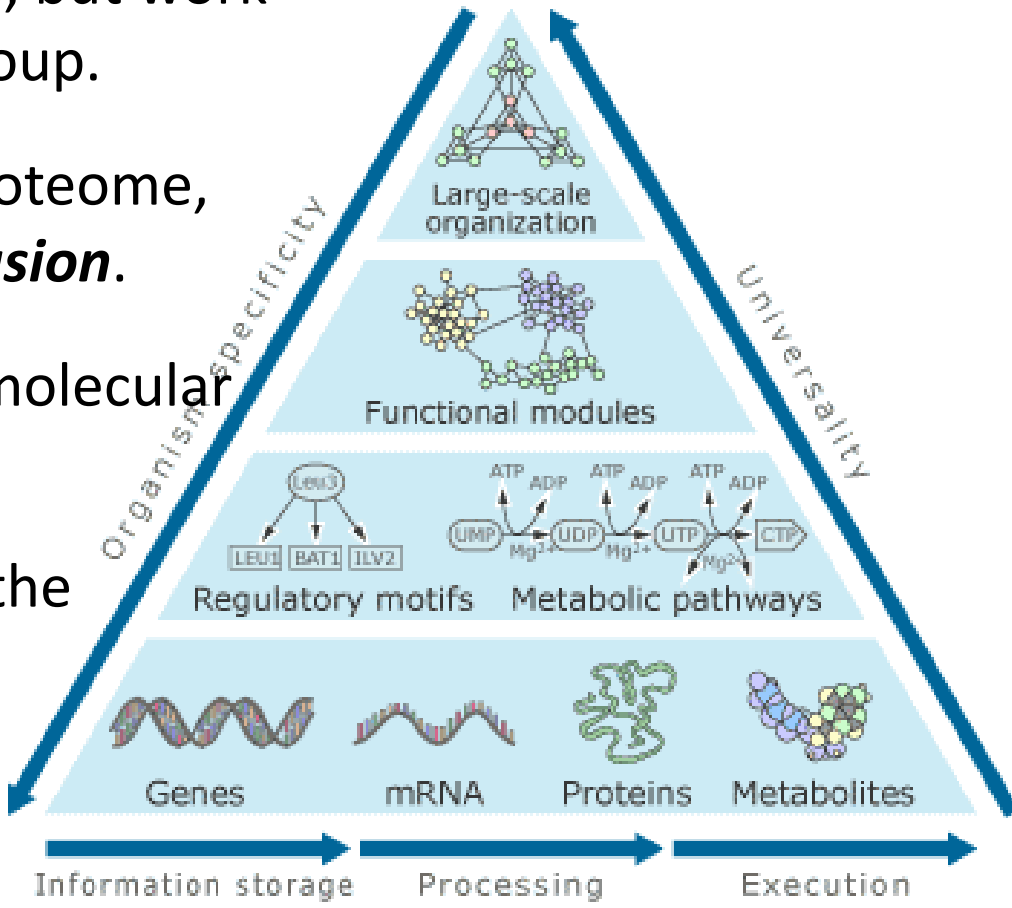
Outline of the Lectures

1. **Introduction** to Systems Biology
   - Basic Principles
2. **Modeling** of biochemical reactions
   - Deterministic Models
   - Stochastic Models
3. Biological **Networks**
   - Types, Goal, Graph of biological networks
4. **Application** of Biological Systems

What is a system biology?

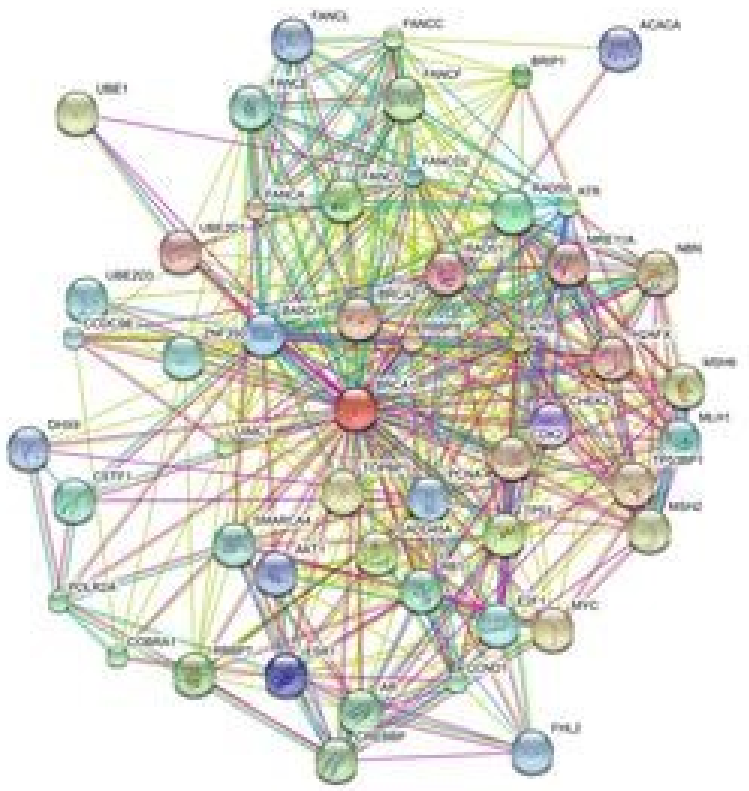
Why system biology?

- **No single gene works alone**, but work as a group, and between group.
- Genome, Transcriptome, proteome, ect. ***require systemic conclusion***.
- **to increase knowledge** in (molecular and cell) biology
- **Prediction** the response of the system



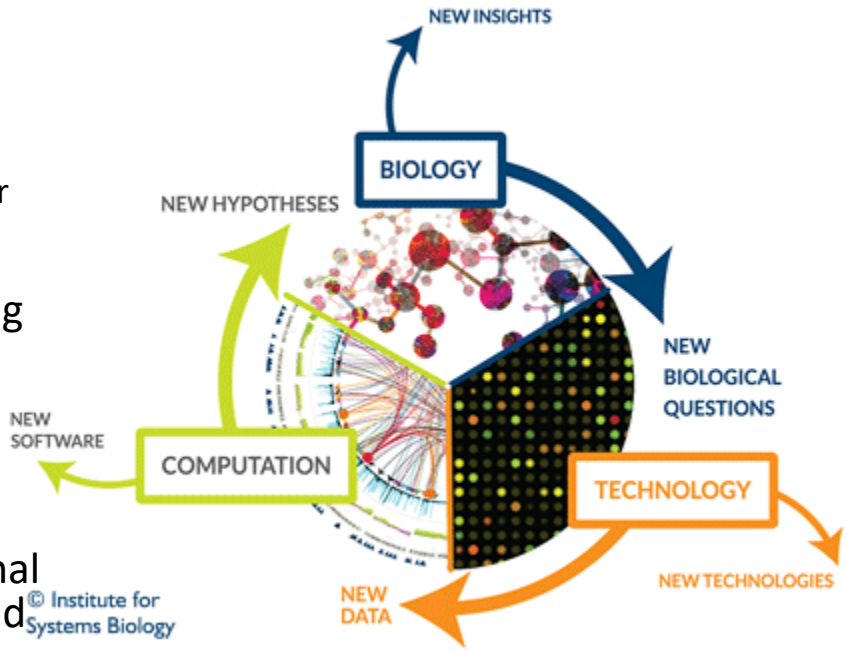
What is system biology?

- a **whole-istic approach** to understanding biology
- to **understand biological systems** as a system or in simpler words
- Present basic **structure and dynamics properties** of model
- underpinning **inter- and intra-cellular dynamical** networks
- **cellular and organismal function**, rather than the characteristics of isolated parts of a cell or organism.



Definition of system biology

- Complex network of biologically relevant entities.
  - But consider in many scales: Whole body, organ, system, cell, organelle, ecosystem
  - Time scale e.g. period of response to adrenaline or year(s)
- the computational and mathematical modeling of complex biological systems.
- the integration of experimental and computational research
- monitoring the gene, protein, and informational pathway responses; integrating these data; and ultimately, formulating mathematical models that describe the structure of the system and its response to individual perturbations.
- also known as Systeomics



Institute for Systems Biology

SBI The Systems Biology Institute AUSTRALIA

System biology workflow

Data

- Bottom up, from individual exp.
- Top down, from high through put exp.

Model

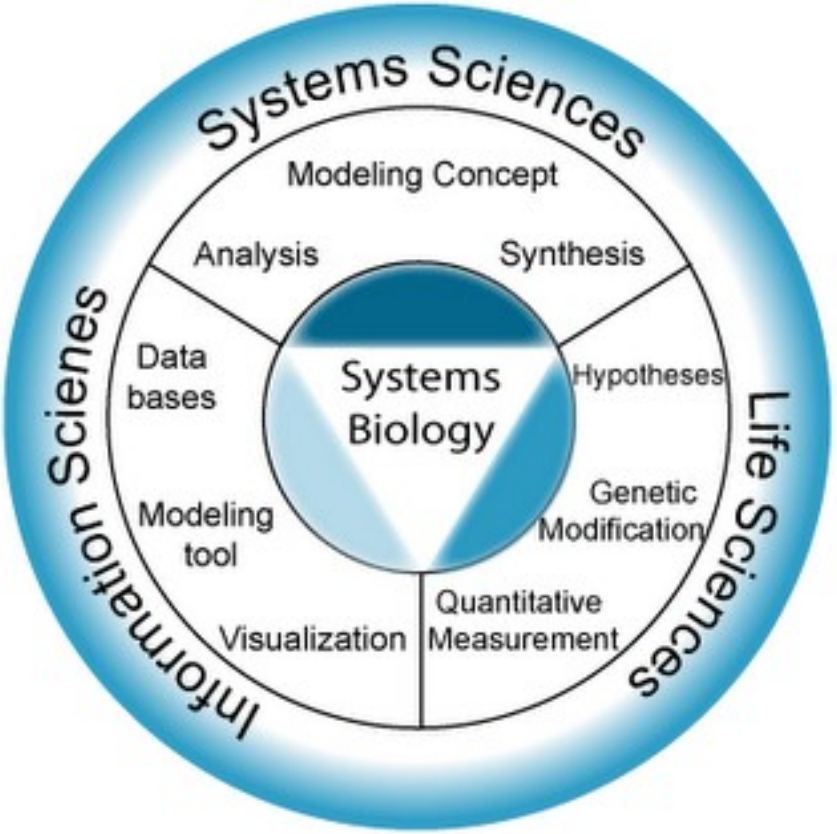
- Dynamic linkage or relationship
- Time course, concentration dependence

Network

- Combined models
- Cell or organ or organism

Main Related Disciplines

- (molecular) Biology
- Biotechnology
- Mathematics and Statistics
- Physics and Chemistry
- Information Science
- Engineering (Biomedical, Chemica Computer, Systems & Control, Electronic)
- …

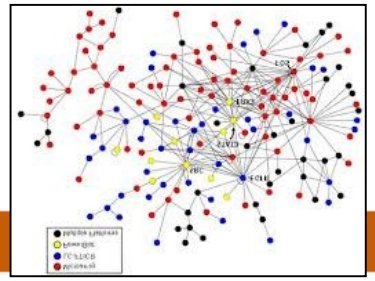


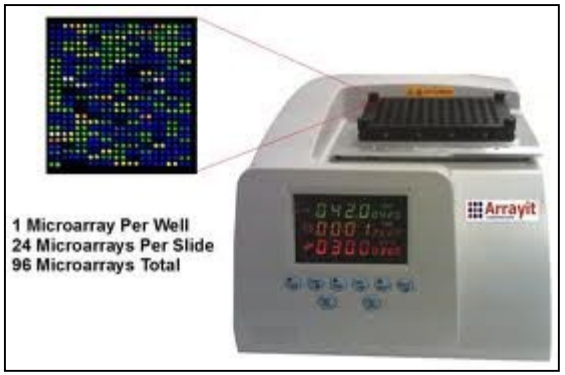
Two approaches to gain **data**

1. **Bottom-up** (integrating independent experimental data into a conclusive representation of a network), or

2. **Top-down approaches** (uses high-throughput data from DNA micro-array and other new measurement technologies).

- Then, integrating computational and theoretical methods with experimental efforts





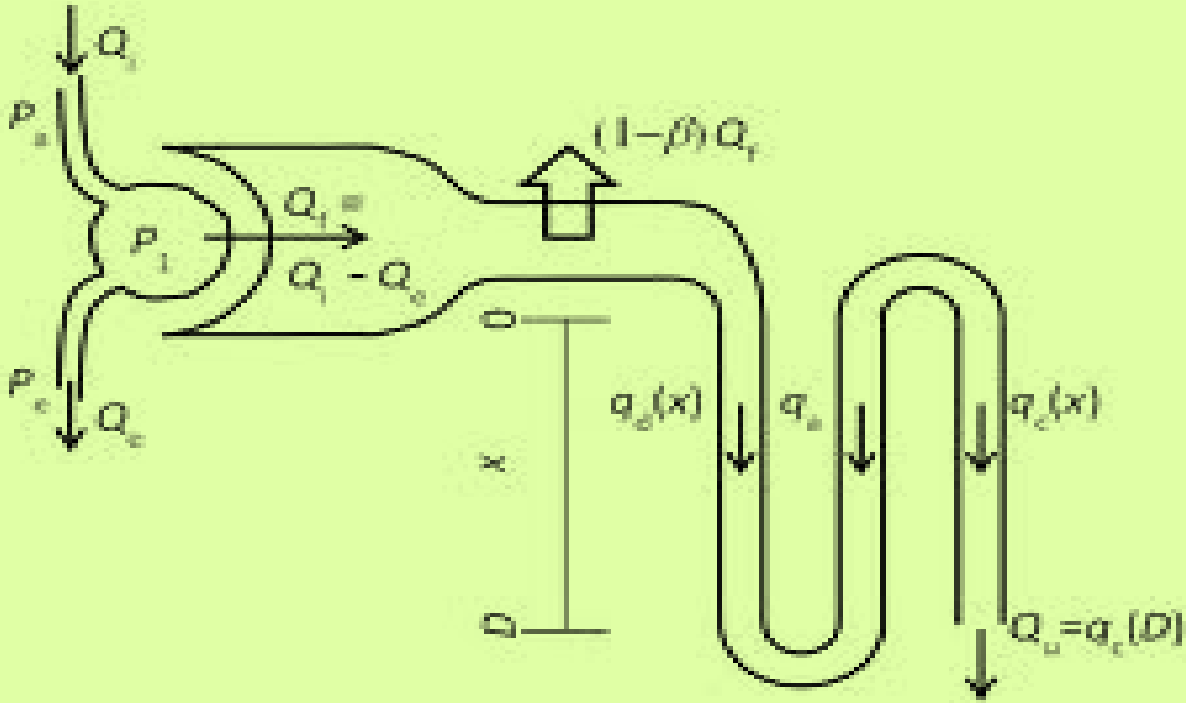
Foundations of system biology

- New experimental **techniques** in genomics and proteomics
- Classical mathematical **modeling** of biological processes
- **Computer** power for simulation of complex systems
  - Storage and retrieval capability in large databases and data mining techniques
  - Internet as the medium for the widespread availability from multiple sources of knowledge

Goals of system biology

1. **Models** to reveal mechanisms causing alternated phenotypes and invent novel therapies and drugs
2. **Predictive tools** to design cells with desired properties cheaply and reliably (Health, biotechnology, industry, agriculture)
3. **Individualized and predictive medicine**
4. **GMOs** e.g.: biodegradable bacteria, biosynthetic fuel bacteria

Model



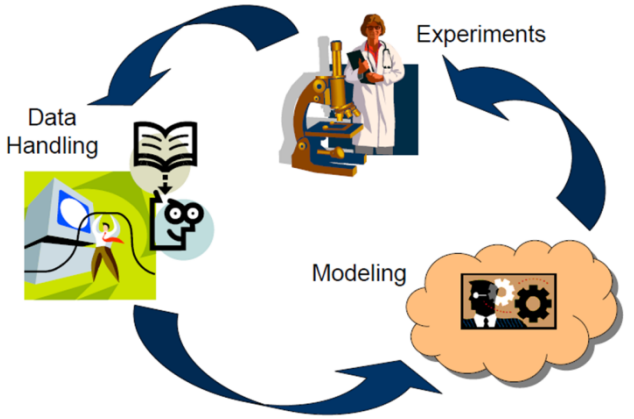
The mathematical model of renal blood flow, glomerular filtration

What is a Model?

- It depends on whom you ask…
  - Geneticist: the mouse model of certain study
  - Chemist: a reaction model, described by dots (for metabolites) and arrows (for reactions)
- **Abstract representation of objects** (enzyme, protein, gene) or processes (reaction, regulation) that explains features of these objects or processes (basic structure and dynamic properties)

Model Development

1. **Formulation** of the problem
2. Available **knowledge**
3. Selection of **model structure**
4. **Robustness/Sensitivity** analysis
   - Test the dependence of the system behavior on changes of the parameters
5. Experimental tests
6. Assessment of the agreement and divergences between experimental results and model behavior
7. Iterative refinement of the hypotheses (and of the model)



Model Organisms

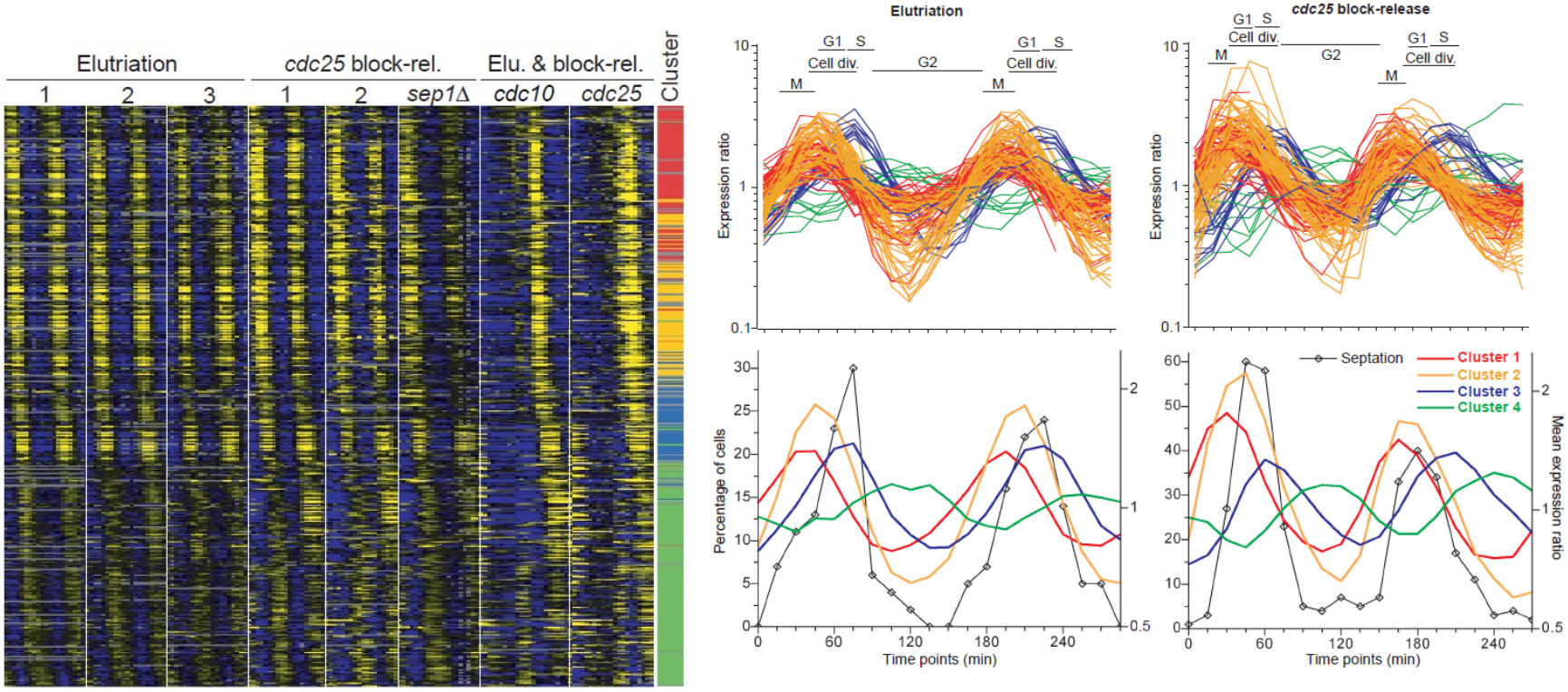
Organism	*Number of chromosomes (haploid genome)*	*Genome size (base pairs; genes)*
Mycoplasma genitalium (prokaryote)	1 circular chromosome	$580 \cdot 10^3$ bp; 480 genes
Escherichia coli (prokaryote)	1 circular chromosome	$4.6 \cdot 10^6$ bp; 4,290 genes
Saccharomyces cerevisiae (budding yeast; eukaryote)	16 chromosomes	$12.5 \cdot 10^6$ bp; 6,186 genes
Arabidopsis thaliana (flowering plant; eukaryote)	5 chromosomes	$100 \cdot 10^6$ bp; ~25,000 genes
Drosophila melanogaster (fruit fly, eukaryote)	4 chromosomes	$180 \cdot 10^6$ bp; ~14,000 genes
Mus musculus (mouse, eukaryote)	20 chromosomes	$2.5 \cdot 10^9$ bp; ~30,000 genes
Homo sapiens (human, eukaryote)	23 chromosomes	$2.9 \cdot 10^9$; ~30,000 genes

Getting Experimental Data

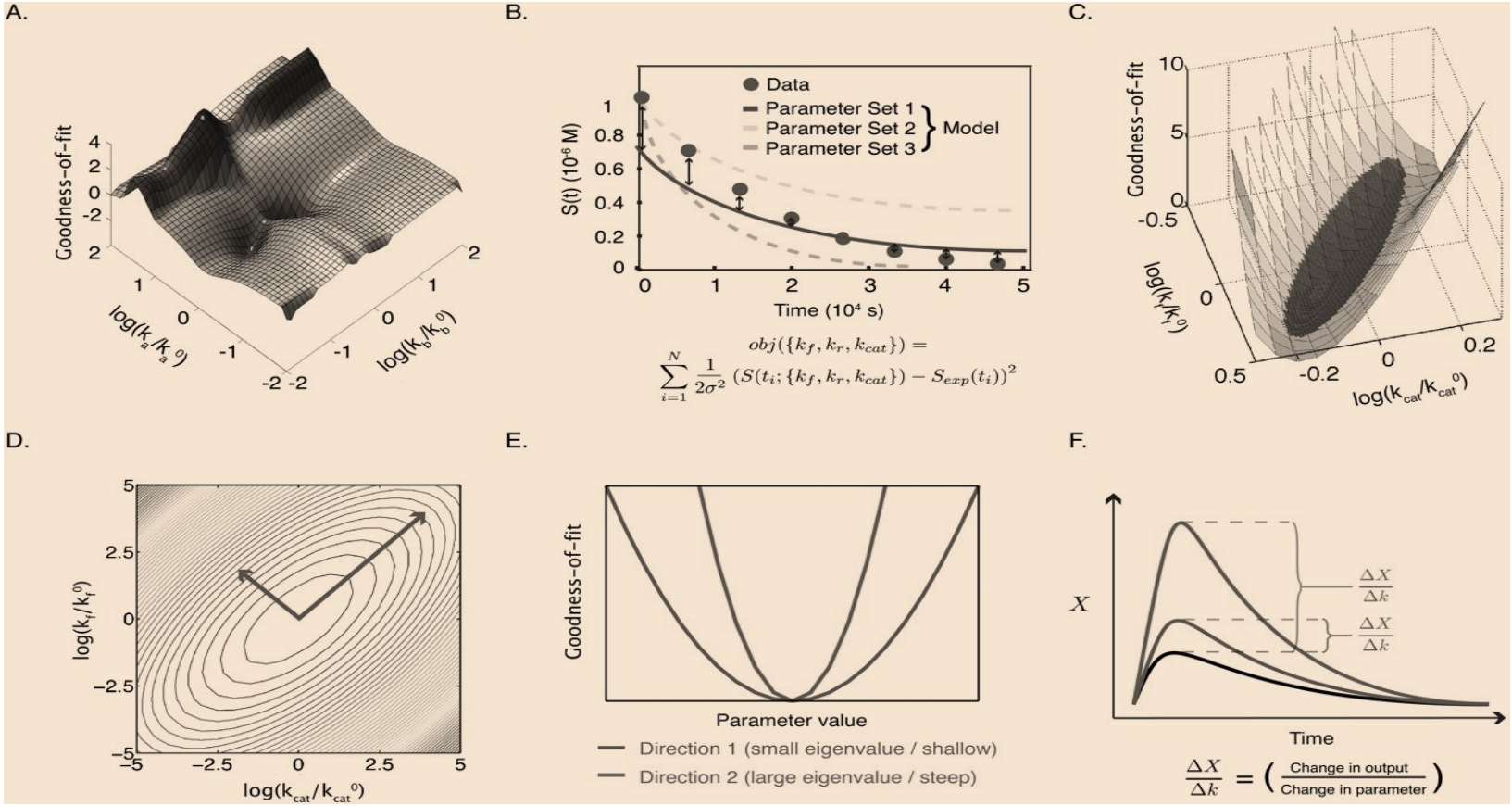
- How to get quantitative data out of experiments designed to give qualitative answers
- Gel Electrophoresis
- Hybridization and Blotting
- Yeast Two-Hybrid (Y2H)
- Probes Hybridization
- Mass Spectrometry
- RNA Interference (RNAi)
- DNA Microarrays, Protein Microarrays, Proteomics (Topdown)

Time-Course Experimental Data

- Microarrays enable to derive time-course experimental data, with a desired sampling time



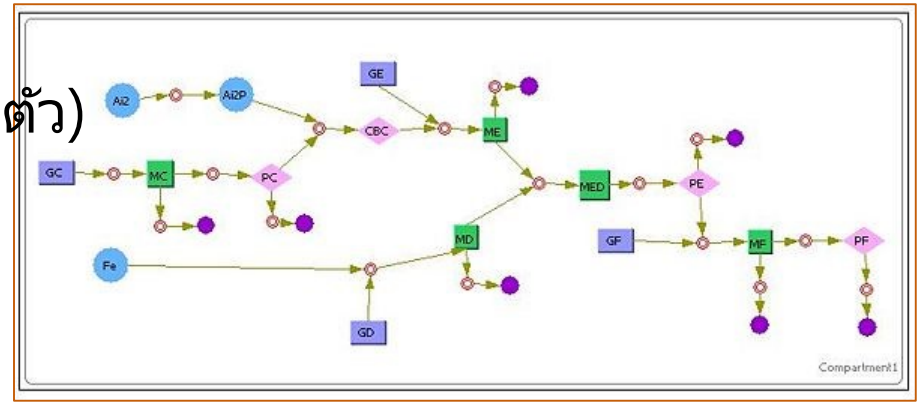
Modeling biochemical reactions

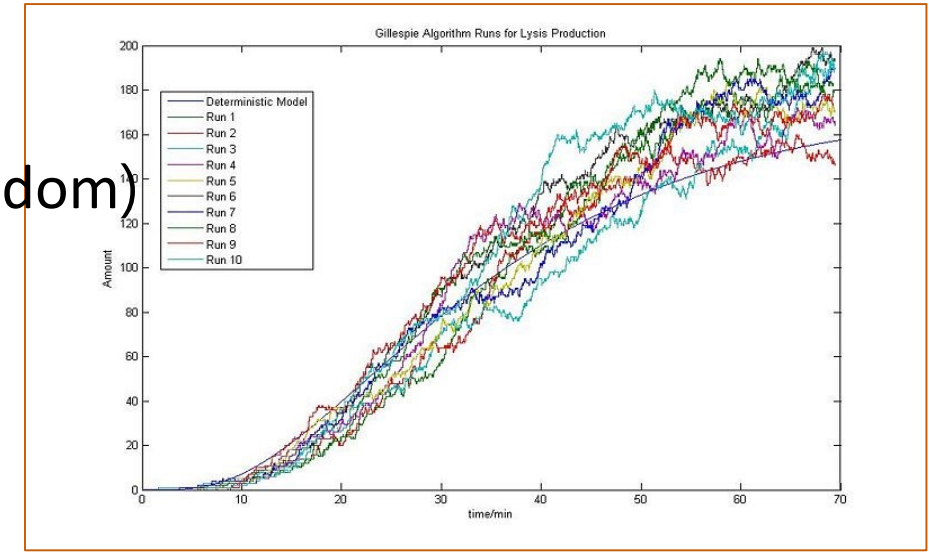


Chen W W et al. Genes Dev. 2010;24:1861-1875

Modeling of biochemical reactions

1. Deterministic models (แบบตายตัว)
   - Michaelis–Menten model
   - Regulation of enzymatic reactions
   - The Quasi–Steady–State Approximation
   - Allosteric reaction
2. Stochastic models (แบบสุ่ม random)





Michaelis-Menten Model

- The basic model of enzymatic reaction was proposed by Michaelis and Menten in 1913

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} SE \xrightarrow{k_2} P + E$$

L. Michaelis (1875-1949)

- The law of mass action (LMA) states that the reaction rate is proportional to the product of the concentrations of the reactants

$$A + B \xrightarrow{k} C \quad \Rightarrow \quad \frac{d[C]}{dt} = k[A][B]$$

$$mA + nB \xrightarrow{k} C \quad \Rightarrow \quad \frac{d[C]}{dt} = k[A]^m[B]^n$$

M. Menten (1879-1960)

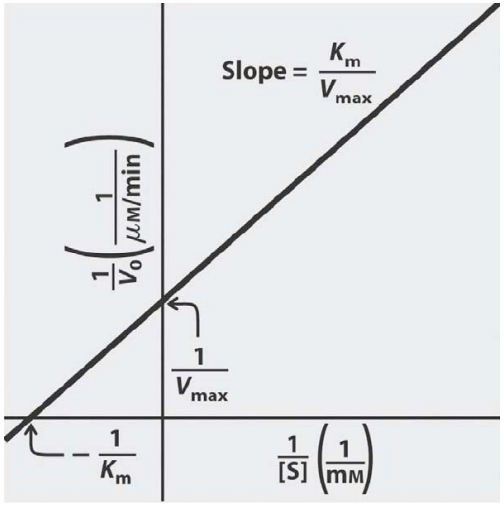
Regulation of Enzymatic Reactions

Lineweaver–Burk Plot

- The L–B plot (or double reciprocal) is a common tool in biochemistry analysis of enzyme kinetics
- It is easily derived by inverting the equation of S in the M–M model
- It is very useful because it enables linear regression of experimental data

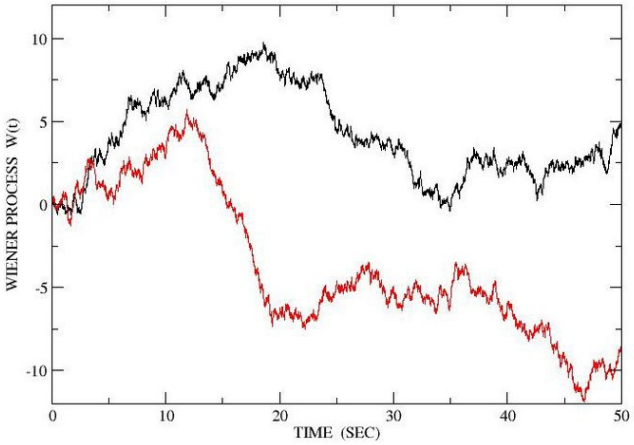
$$\frac{1}{V_0} = \frac{K_m + [S]}{V_{max}[S]}$$

$$\frac{1}{V_0} = \frac{K_m}{V_{max}[S]} + \frac{1}{V_{max}}$$



Stochastic models

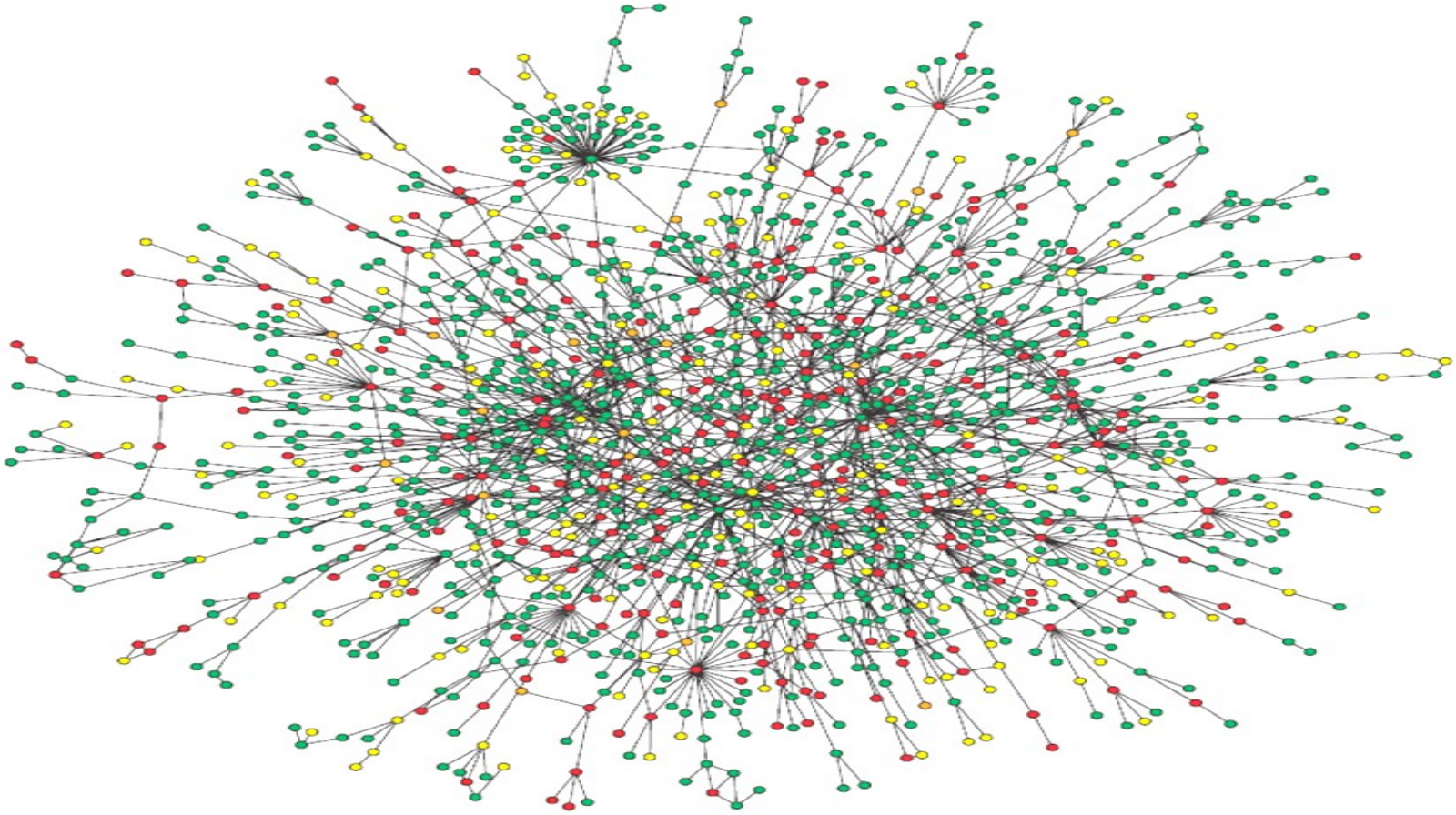
- The models considered so far are deterministic, i.e. given the initial conditions (the state at t_0) *and the exogenous signals perturbing the model,* the response is univocally determined
- A stochastic model, on the contrary, involves random variables, therefore its behavior cannot be predicted *a priori, although it can be statistically* characterized
- The figure shows two realization of the same stochastic process, starting from the same initial condition



Biological Systems are Stochastic

- Every molecular reaction can be described only in terms of its **probability** of occurrence
- Diffusion of molecules is a realization of a random walk process (**Brownian motion**)
- So, why deterministic model are so widespread?
  - A **large number of molecules,** therefore the average effect is well described through deterministic equations
- When is it necessary to use stochastic models/simulations?
  - When the mechanism to be described is based on the interaction of few molecules, or we want to simulate the functioning of a little pool of cells

Biological Networks



Outline

- Type of biological networks
- Goal
- Graph
- metabolic networks
- gene regulatory networks

Types of Biological Network

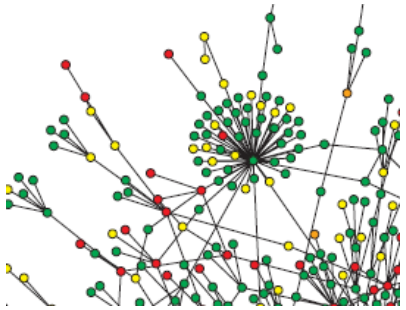
- distinguished at the molecular level
  - Gene regulatory
  - Metabolic
  - Signal transduction
  - Protein–protein interaction
- different description levels, e.g.
  - Immunological
  - Ecological
- Here we will focus exclusively on molecular processes that take place within the cell

Goals of network

- A major challenge to construct network of the complex macromolecular interactions at the gene, metabolite and protein levels
  - reasonable
  - accuracy
- Once identified, the network model can be used to
  - simulate the process it represents
  - predict the features of its dynamical behavior
  - extrapolate cellular phenotypes

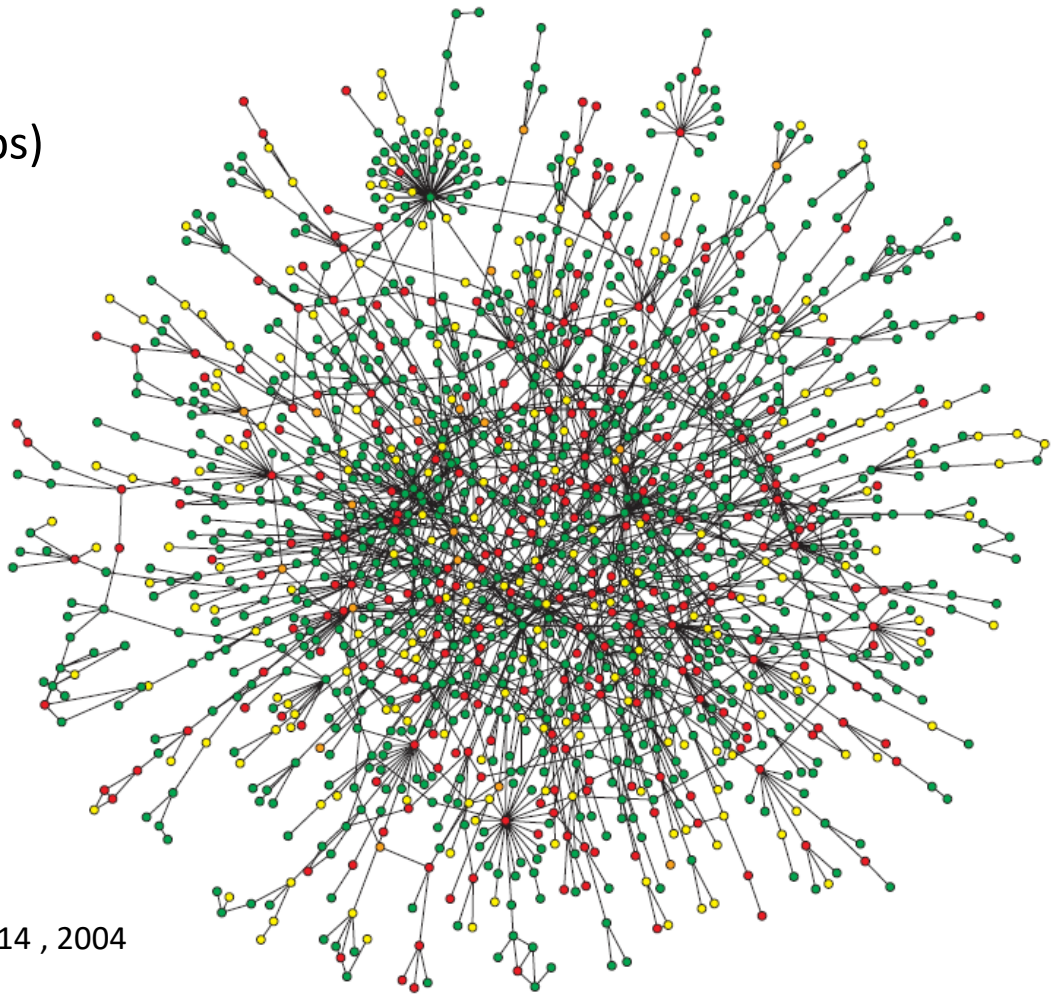
Graphs of Biological Networks

- Depending on the kind of biological network, the edges and nodes of the graph have different meaning
- Metabolic network
  - nodes: metabolic product, edge: a reaction transforming A into B
- Transcriptional regulation network (protein–DNA)
  - nodes: genes and proteins, edge: a TF regulates a gene
- Protein – protein network
  - nodes: proteins, edge: interaction between proteins
- Gene regulatory networks (functional association network)
  - nodes: genes, edge: expressions of A and B are correlated



P–P Interaction Network in Yeast

- This network is based on yeast two–hybrid experiments
- Few highly connected nodes (hubs) hold the network together
- The color of a node indicates the phenotypic effect deriving from removing the corresponding protein
  - red: lethal
  - green: non–lethal
  - orange: slow growth
  - yellow: unknown



Barabasi et al, Nature Review Genetics 101(5), 101–114 , 2004

Metabolic model

Metabolic reactions can be divided in two categories

- Catabolic reactions: breakdown of complex compounds to get energy and building blocks
- Anabolic reactions: assembling of the compounds used by the cellular mechanisms

Metabolic Network in Yeast

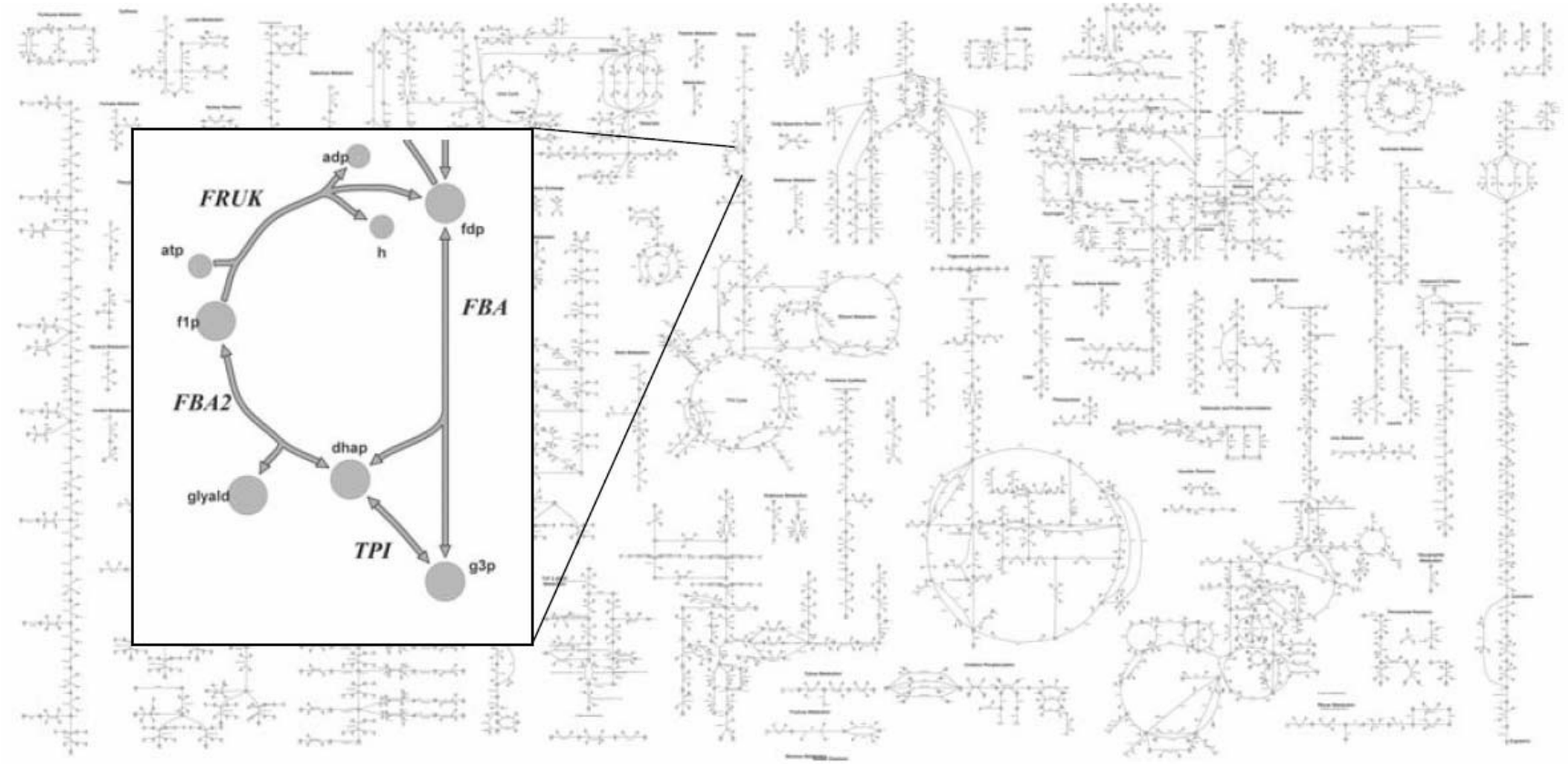
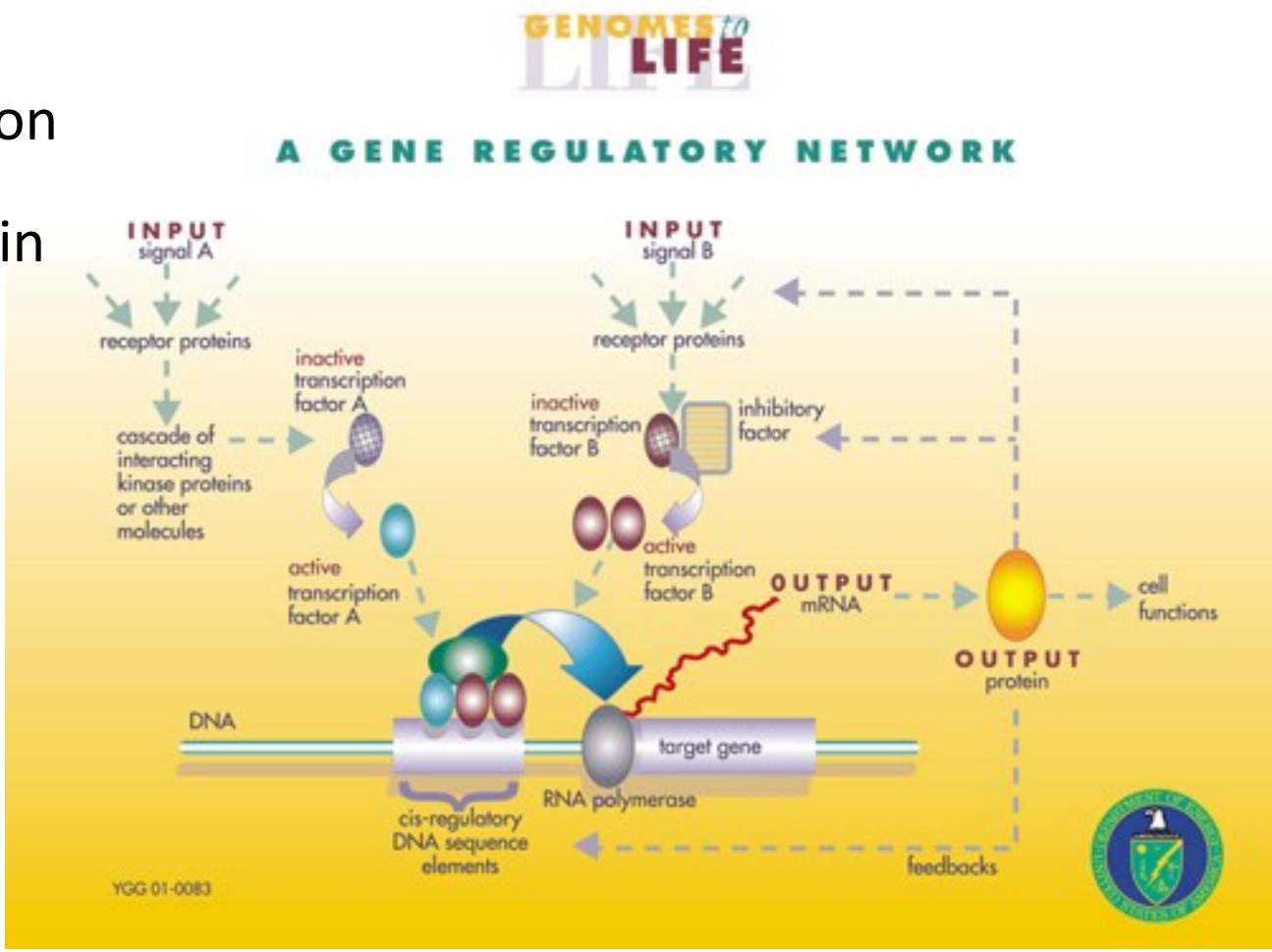


Figure 3.4: Graphical depiction of metabolic reaction networks. This map represents the metabolic network in yeast. Courtesy of Natalie Duarte; see http://systemsbiology.ucsd.edu for more details.

Palsson, *Systems Biology: Properties of Reconstructed Networks, 2006*

Gene regulation

- Signal/ ligand
- Signal transduction
- Regulatory protein
- Operator
- Expression of target gene

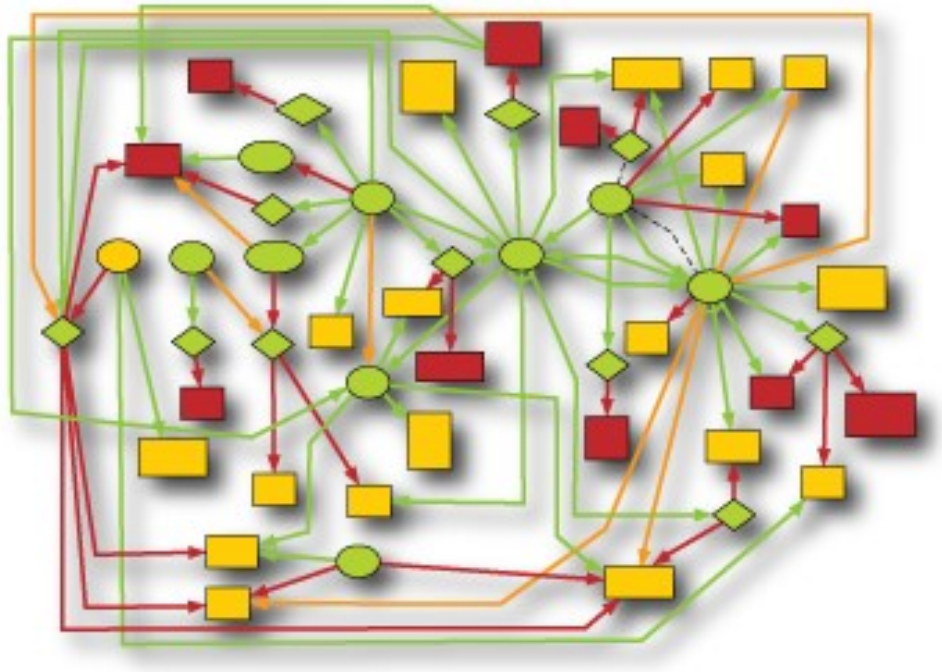


Gene regulatory networks

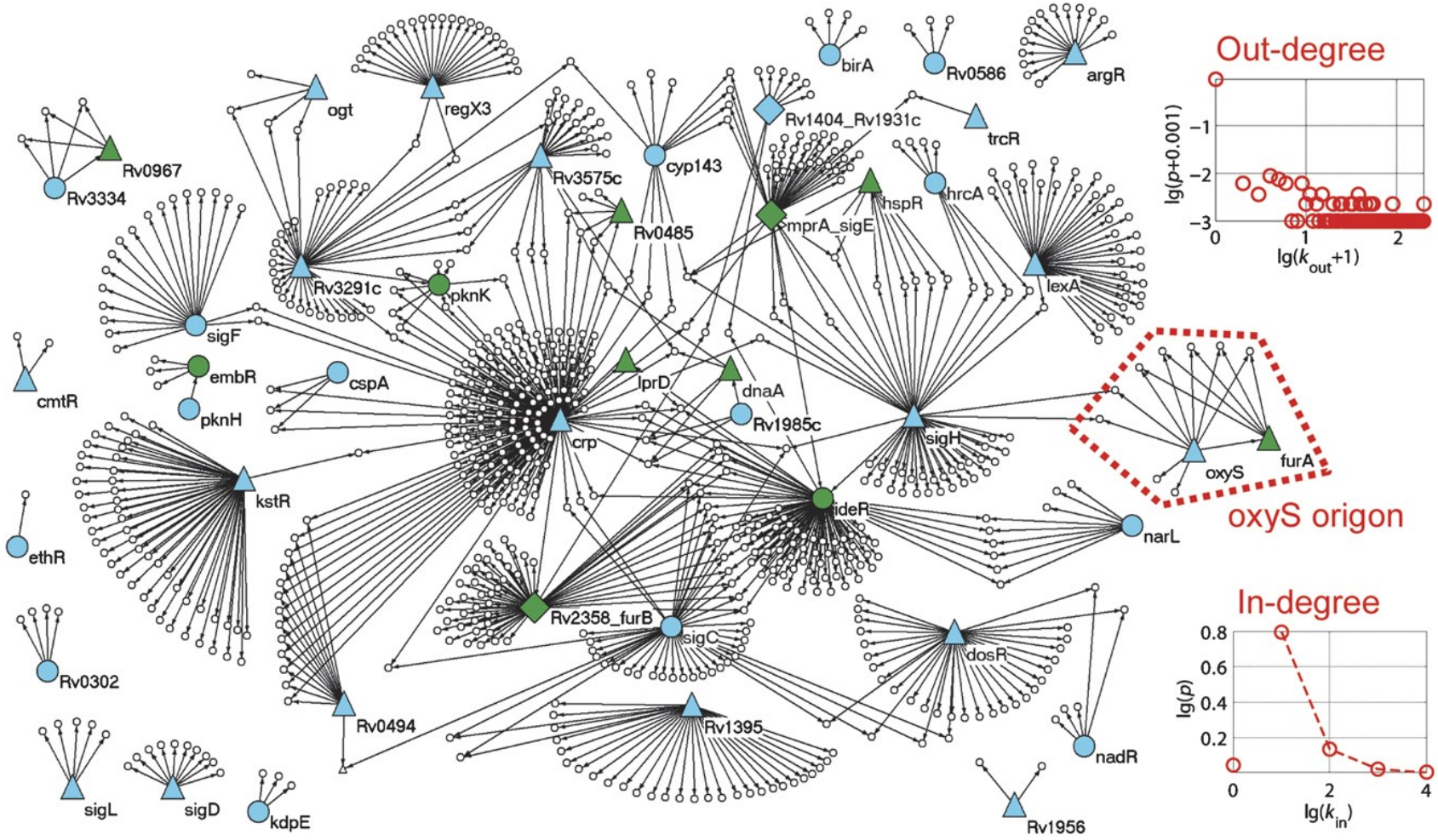
- Proteins and ligands bind to specific promoter(s) of the gene(s)
- The gene(s) may encode enzyme of a cascade regulator (signal transduction pathway
- Regulation in many level:
  - Transcription: initial, extension, termination
  - Translation: microRNA, ribosome binding ability
  - protein modification: glycosilation
- involve interactions between DNA, RNA, proteins and other molecules
- the edges of the corresponding graph do not represent chemical interactions, but functional influences of one gene on the other

Regulatory genomics

- very similar genomes, but due to variations in the gene regulation cause different phenotype.
- discovering cis-regulatory elements or DNA motifs in large genomes cause complex network



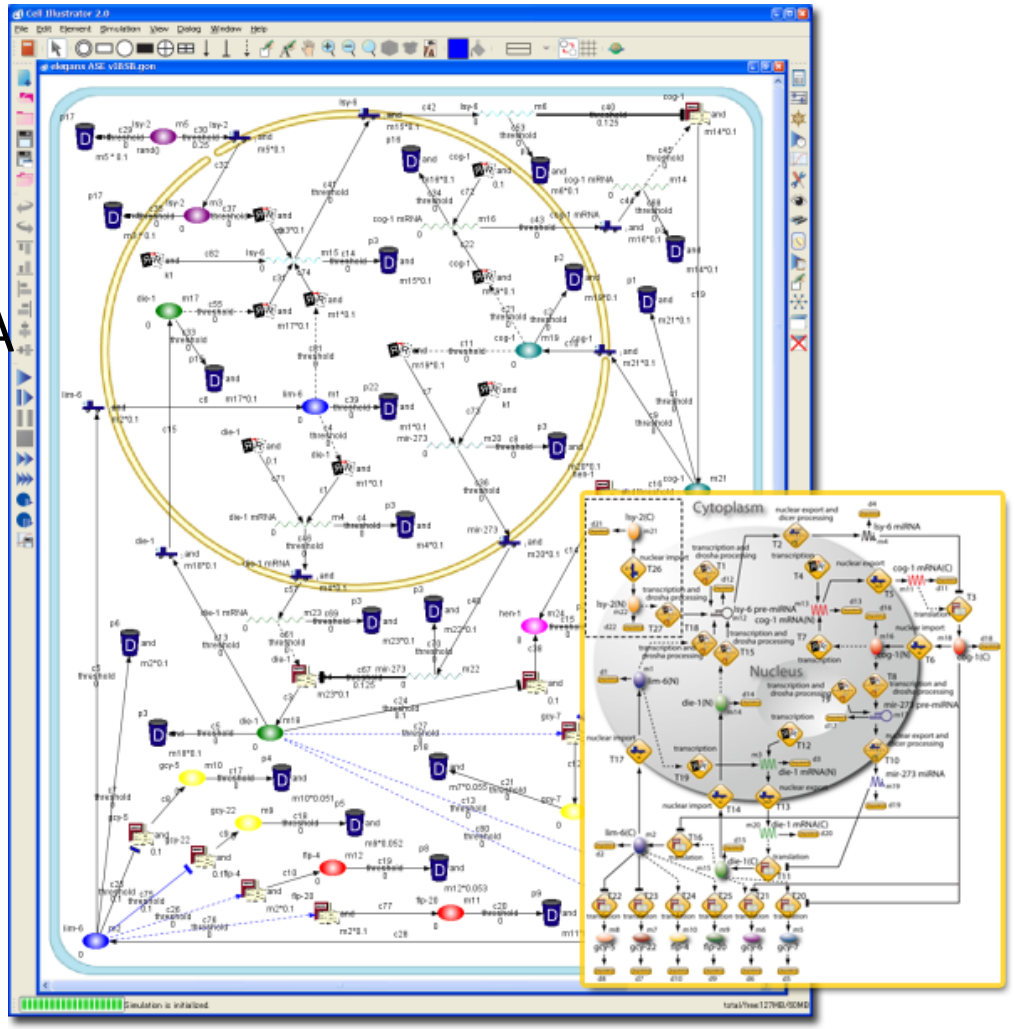
M. tuberculosis **gene regulatory network** during growth arrest



Gábor Balázsi, Allison P Heath, Lanbo Shi & Maria L Gennaro

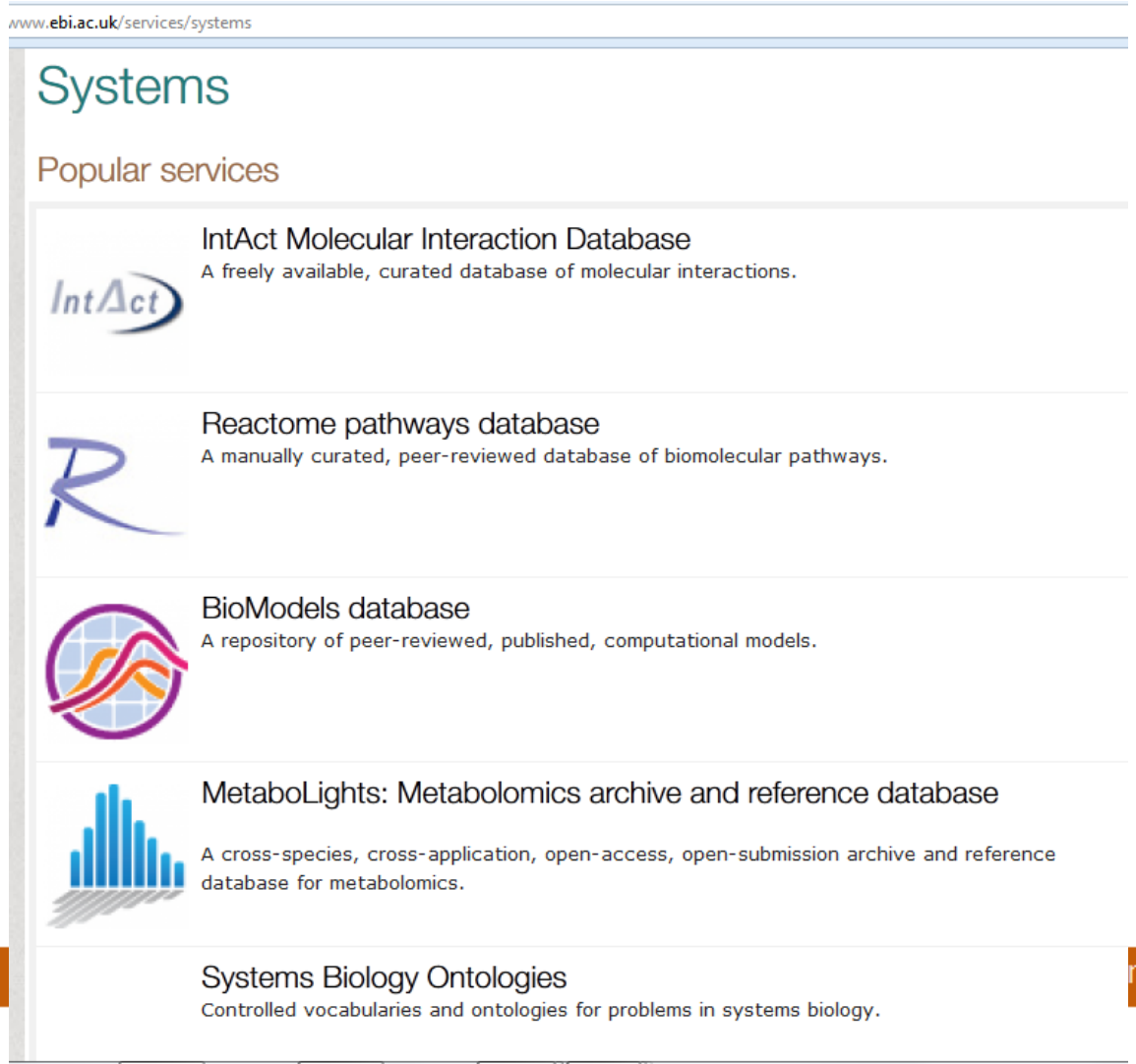
MicroRNA in **gene regulatory networks**

- 70 mer short RNA transcribed from genome in nuclease
- 20-24 mer of mature miRNA
- Suppress translation of target gene



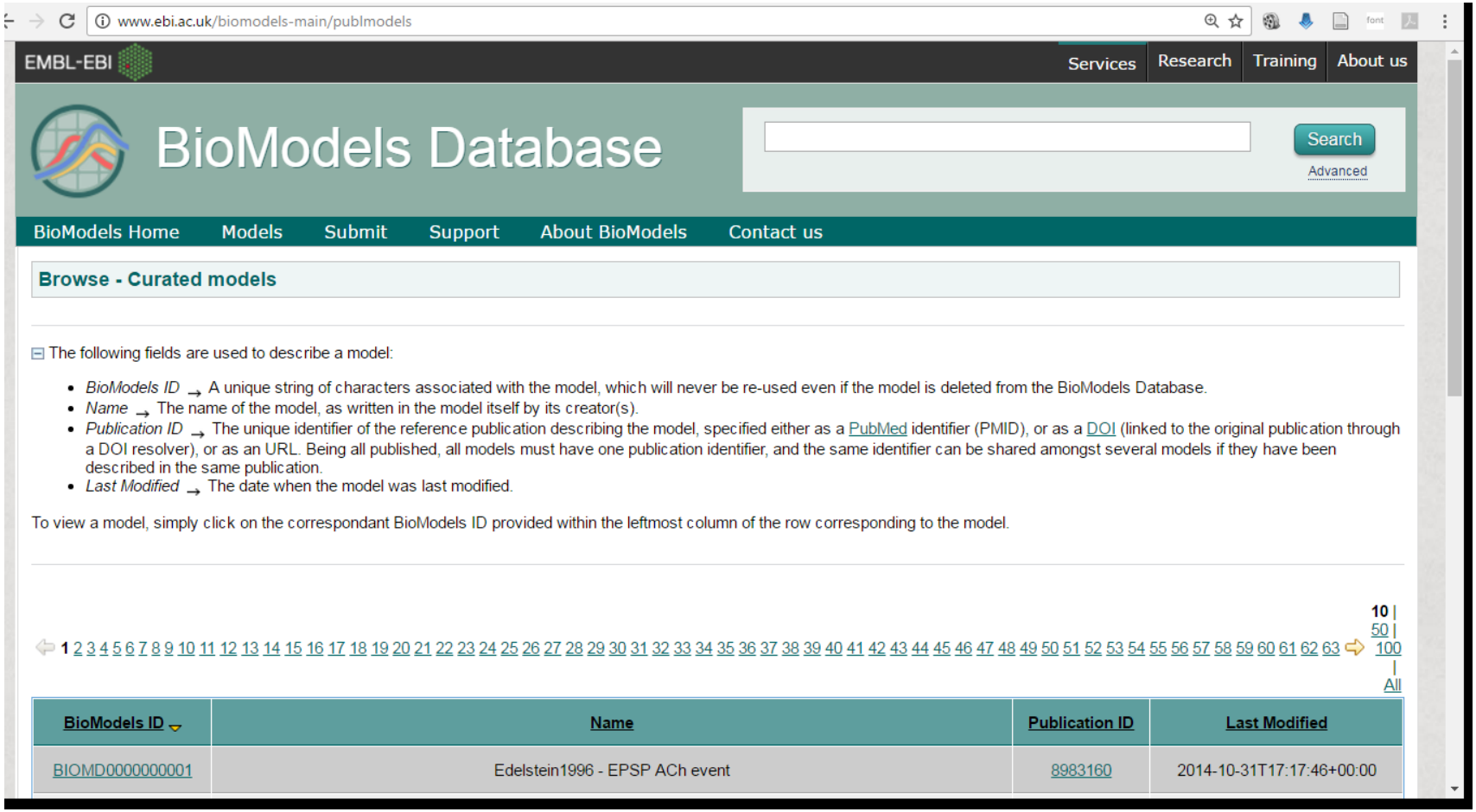
Model available

- http://www.ebi.ac.uk/services/systems



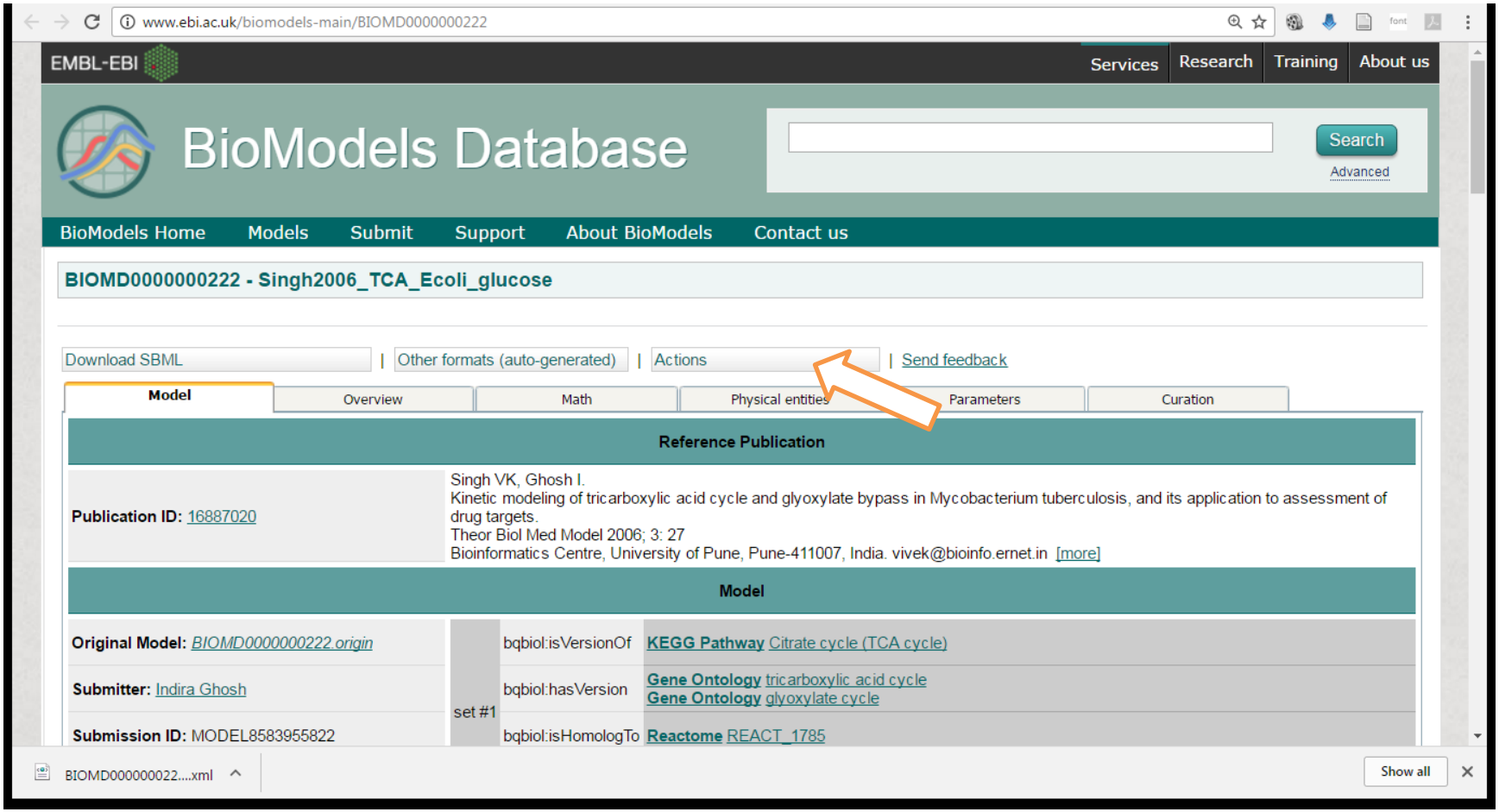
BioModel database

- http://www.ebi.ac.uk/biomodels-main/publmodels

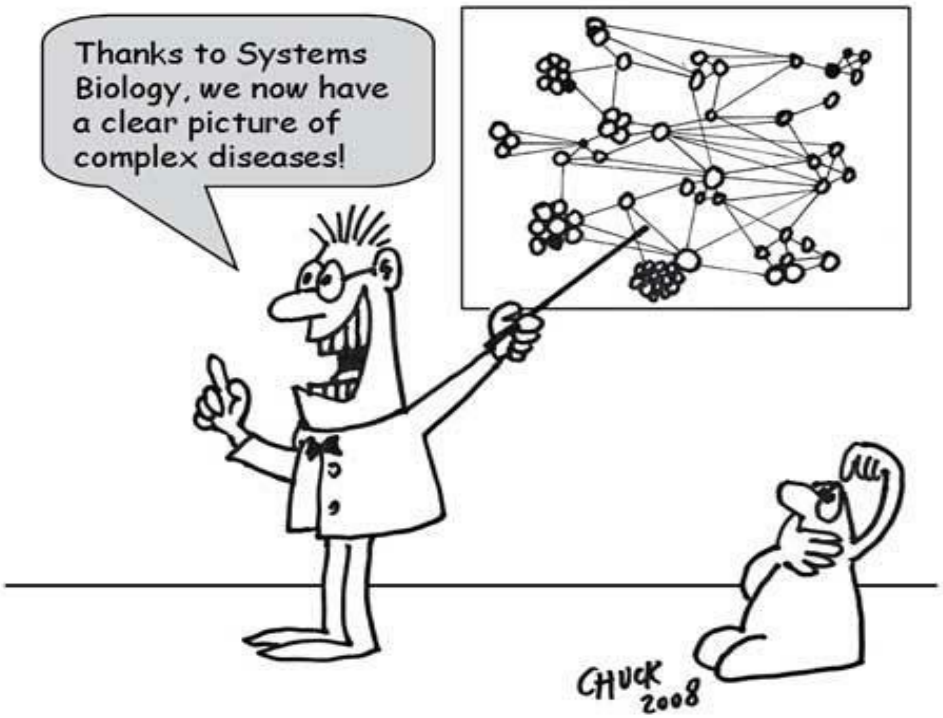


BIOMD0000000222 - Singh2006_TCA_Ecoli_glucose

- http://www.ebi.ac.uk/biomodels-main/BIOMD0000000222

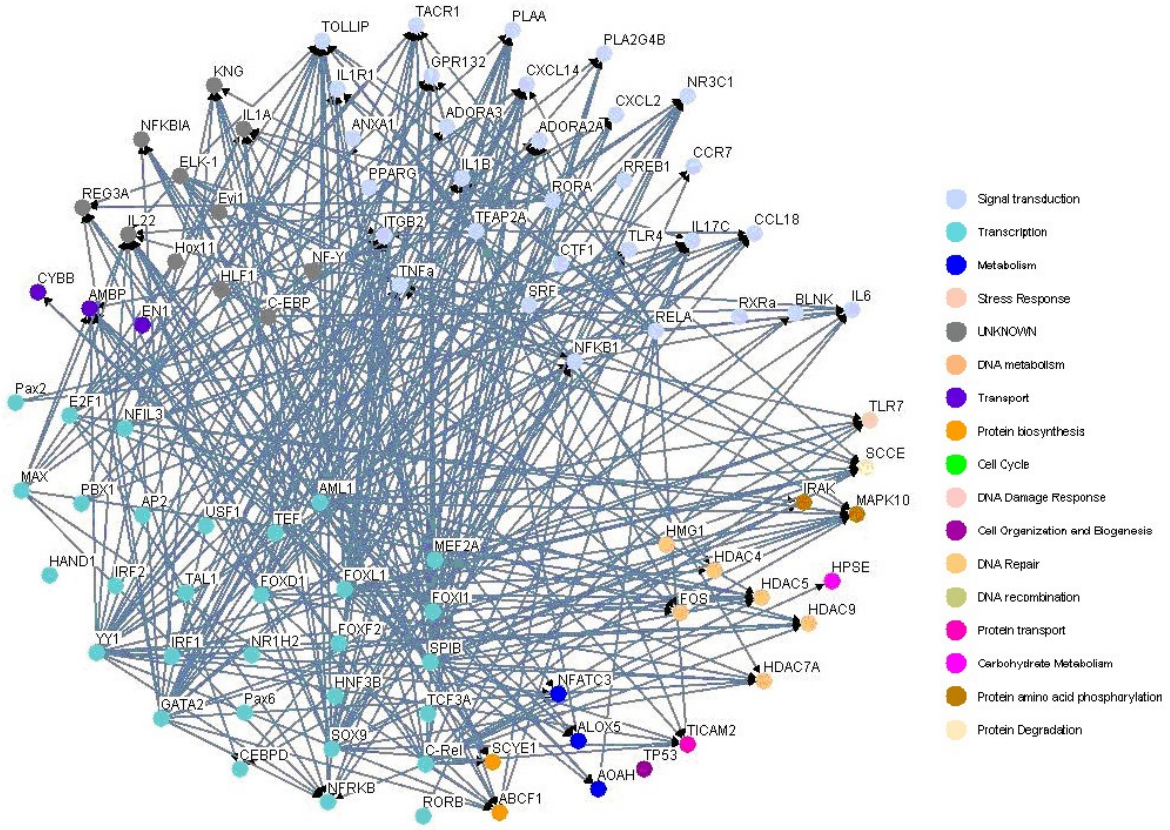


Application of system biology



Immune System

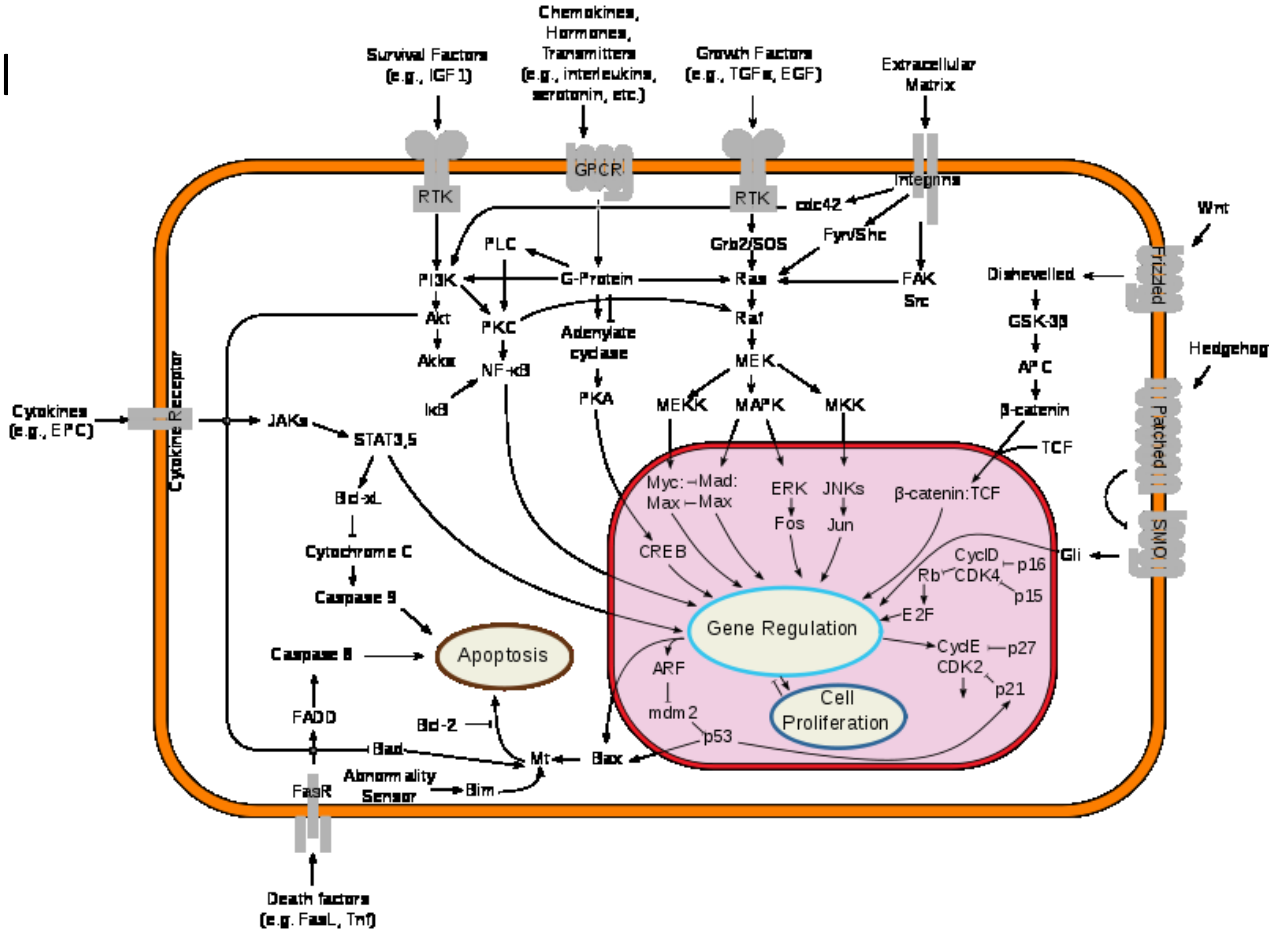
- **The inflammatory transcriptional gene network in immune system with LPS**



Chen *et al. BMC Medical Genomics* 2008 **1**:46 doi:10.1186/1755-8794-1-46

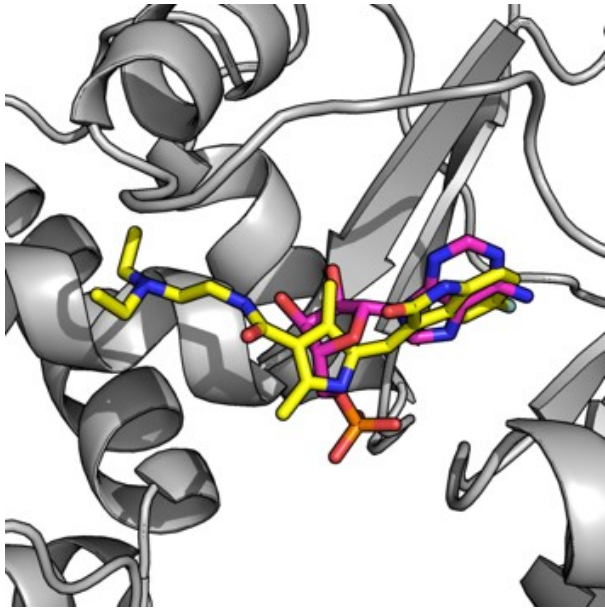
signal transduction pathway

- Cross talk as a network
- Fine tuning in ada|



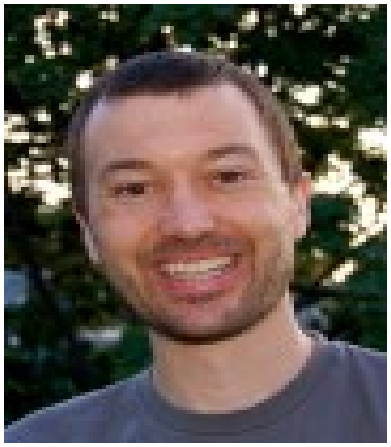
Drug discovery

- Identify drug target
- To inhibit growth of cell (host /pathogen)
- Discovery of new targeted drug
- *In silico* drug studies
- predicting biological responses in different disease condition



Reengineering bact. Metabolic pathway

- To create new function
  - Bio-fuel synthesis
  - Bio-degradable spp.



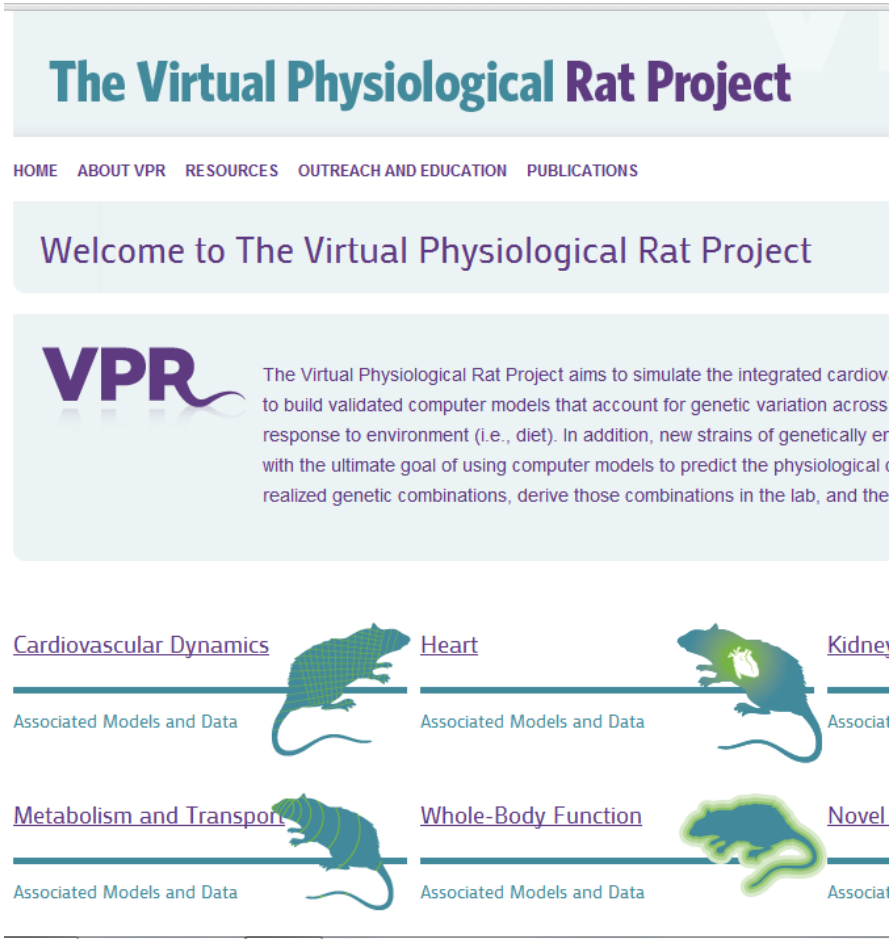
David Savage Ph.D.
Assistant Professor of Biochemistry and Molecular Biology, UC-Berkeley

Why systems biology: Synthetic biology aims to reengineer bacterial metabolism pathways to create new functions (such as making fossil fuel alternatives, medicines or other interesting molecules), but understanding metabolism enough to engineer it requires a systems approach.

https://sysbio.med.harvard.edu

http://virtualrat.org/

- The Virtual Physiological Rat
- to simulate the integrated cardiovascular function
- to build validated computer models that account for genetic variation across rat strains and physiological response to environment (i.e., diet).
- to predict the physiological characteristics of not yet realized genetic combinations,



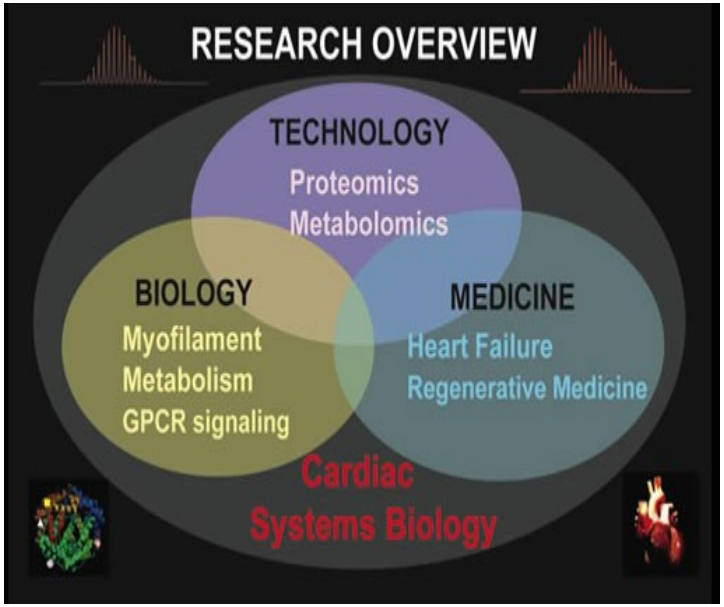
http://genome.tbdb.org/annotation/genome/tbdb/SysBioHome.html

- **TB Systems Biology Program**
- experimentally map and computationally model the molecular pathways of *M. tuberculosis* under conditions relevant to TB pathogenesis.
- established a collaborative network that will perform systematic profiling using
  - ChIP-Seq,
  - transcriptomics,
  - proteomics,
  - glycomics,
  - metabolomics, and
  - lipidomics
  - during both in vitro and in vivo growth and

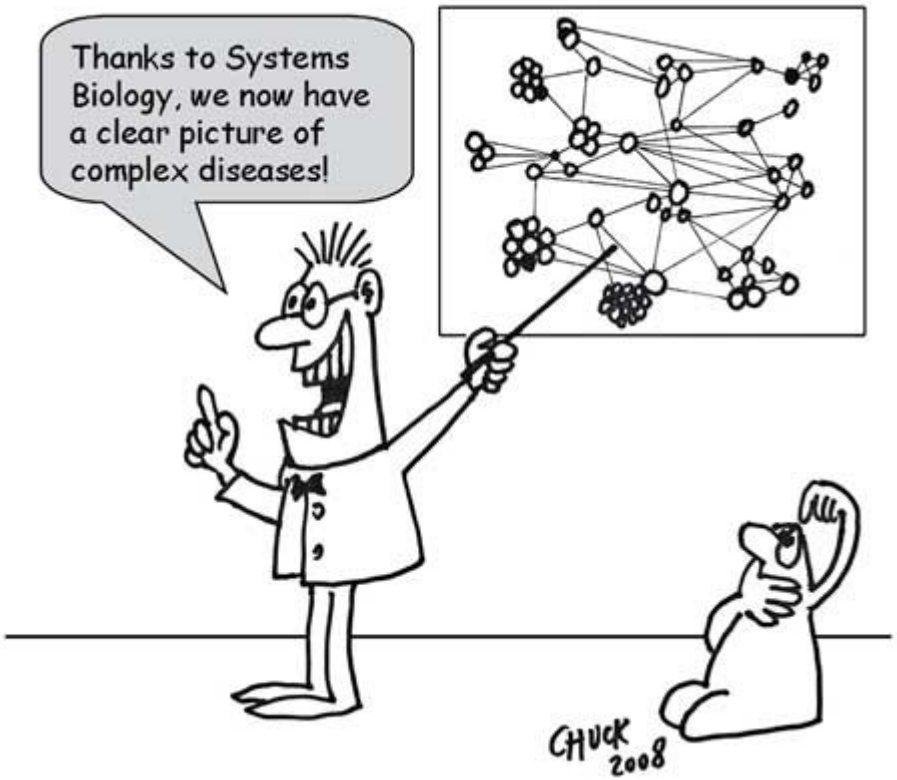
- will integrate these data into predictive computational models
- regulatory and metabolic networks

Medicine

- Pathogenesis of disease
- Treatment
- prevention



Q&A


Thanks to Systems Biology, we now have a clear picture of complex diseases!
CHUCK 2008

Reference

- Dr. Carlo Cosentino, School of Computer and Biomedical Engineering, Department of Experimental and Clinical Medicine, Università degli Studi Magna Graecia, Catanzaro, Italy, http://bioingegneria.unicz.it/~cosentino
- Wikipedia.org, google.com

- The final exam questions comprise questions from:
- 1.Dr.Sakawrat Khanthawong (SK) 10 points, (10 MCQs)
- 2.Dr.Surasakdi Wongrattanacheewin 20 points, (4+1 MEQs) 4 of DNA and amino acid sequence analysis and 1 of Comparative genomics
- 3.Dr.Yaovaluck Chamkramol (YC) 10 points, (1 MEQ) Microarray analysis
- 4.Dr.Sorujsiri Charoensudjai (SC) 10 points, (5 MEQs) Structural genomics
- 5.Dr.Wises Namwat (WN) 10 points, (6 MEQs; System biology)
- 6.Dr.Umaporn Yordpratum (UY) 10 points, (5 McQs+3 MEQs)GWAS
- Total 70 points (25 % of total points in the course)
- No questions from , Dr.Virphong, Dr.Wichittra, Dr.Kiattichai,
- MCQ: multiple choice question
- MEQ: multiple Essay question