

# The International Symposium on Optimization and Systems Biology

August 8-10, 2007, Beijing, China

# Welcome to OSB 2007

Local Organizer



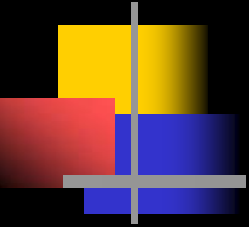
Organizers



Sponsors



# Computational Systems Biology on Networks and Dynamics



## 計算系統生物学

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At molecular level

*From computational viewpoint*



# Systems Biology?

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Instead of analyzing individual components or aspects of organism,

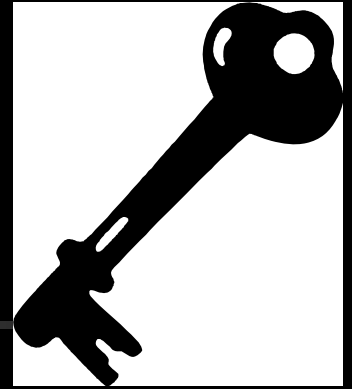
**systems biology** is to study an organism, viewed as a **dynamical** or **interacting network** of genes, proteins and biochemical reactions,

which eventually give rise to life.



# Keywords

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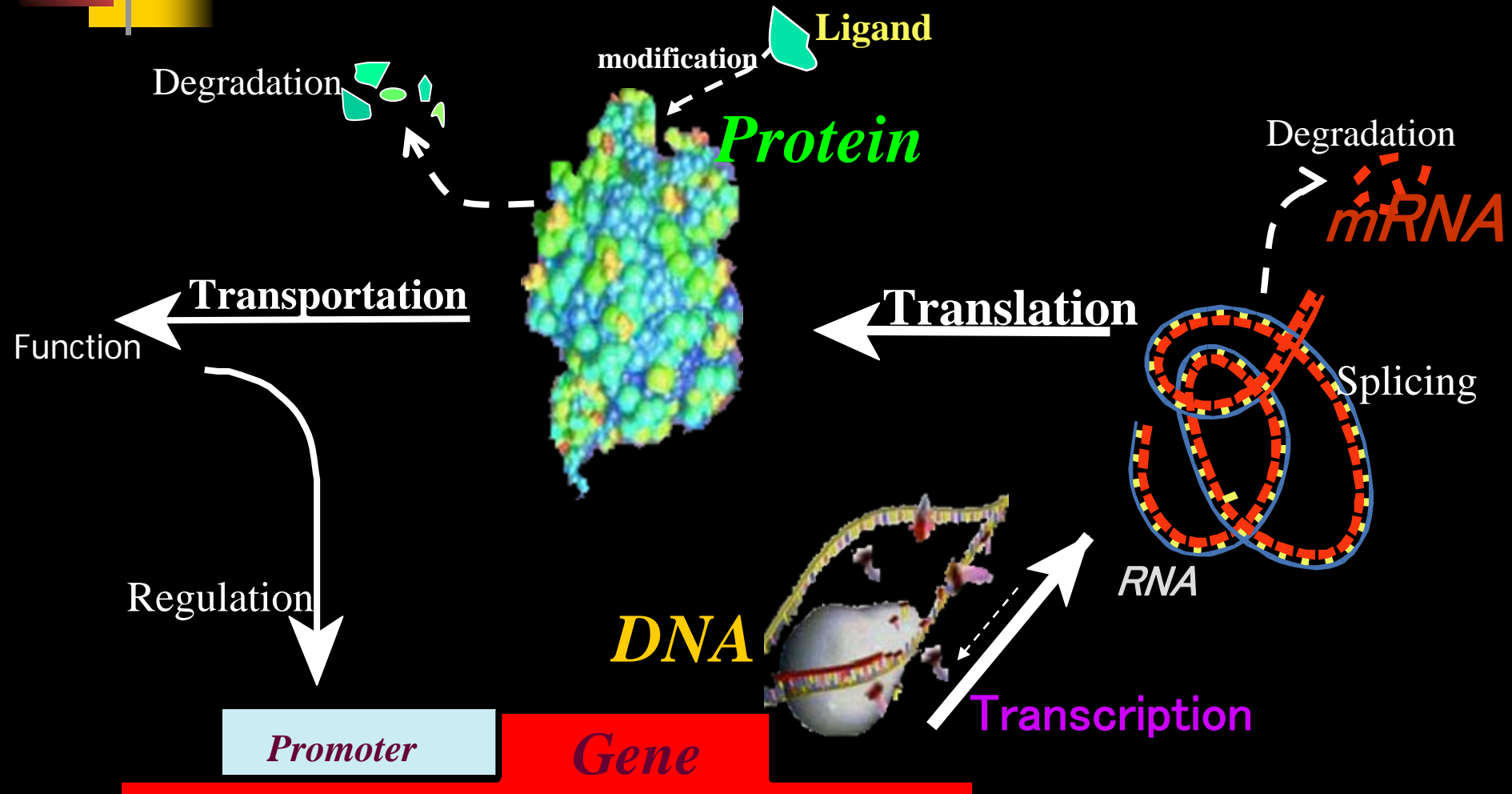


- System (component->system)
- Integration
- Network
- Dynamics (static->dynamic)
- Interaction

**from theoretical and engineering  
perspectives**

# Dynamics in Biological System:

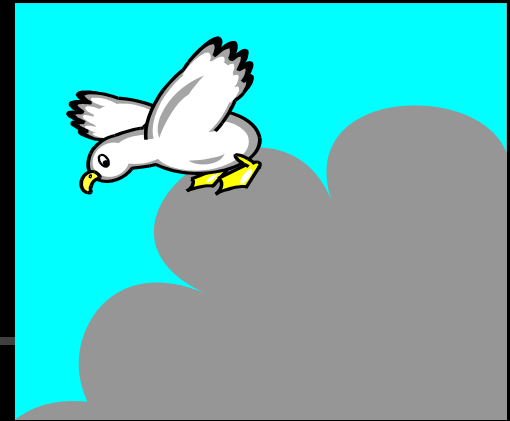
## --- Central Dogma of Biology





# Overview

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- Motivation
- Areas
- Perspective

**Pursue frontier works from theoretical  
and engineering perspectives**



# Motivation

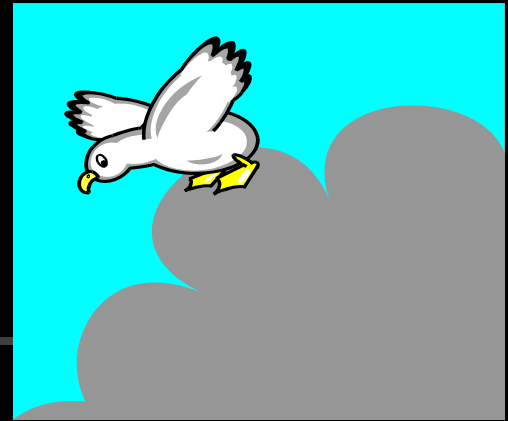
- Motive: Burgeoning high-throughput data are driving the integrative study from describing **phenomena** to understanding **design principle, mechanism**, from studying **components** to understanding **functional network** for biological systems, entire cell, organ, and even organisms.
- New Frontier: **systems biology**
- Area: An emerging multi-**interdisciplinary** field



# Overview

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- Motivation
- Areas
- Perspective





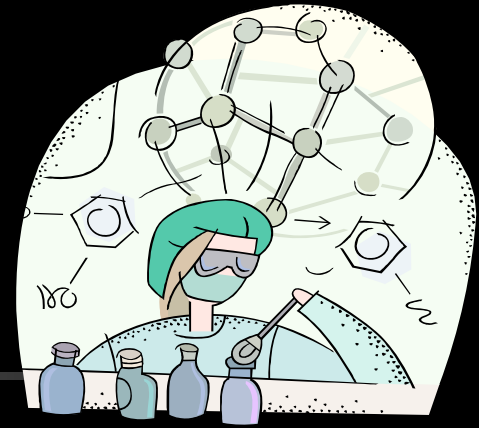


# Areas of Research

## Three areas of research

- 1. **Molecular systems biology**  
(Dynamics, Network)
  - 2. **Molecular biology**  
(Synthetic Bio, Experiments)
  - 3. **Computational systems biology**  
(Static, Tool, Database)
- } interdisciplinary

# 1. Molecular Systems Biology



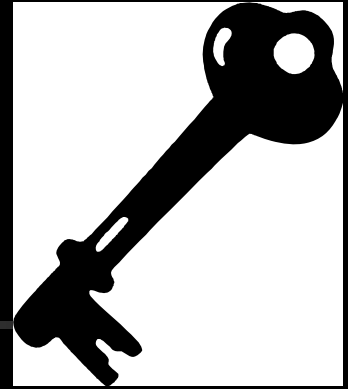
One of the grand challenges in Systems Biology is to build a complete and high-resolution description of molecular topography and connect molecular interactions with physiological responses.

- Instead of analyzing individual components or aspects of organism, systems biology is to study an organism, viewed as a **dynamical or interacting network** of genes, proteins and biochemical reactions which give rise to life.



# Keywords

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- Dynamics
- Network
- Integration
- Engineering
- Optimization

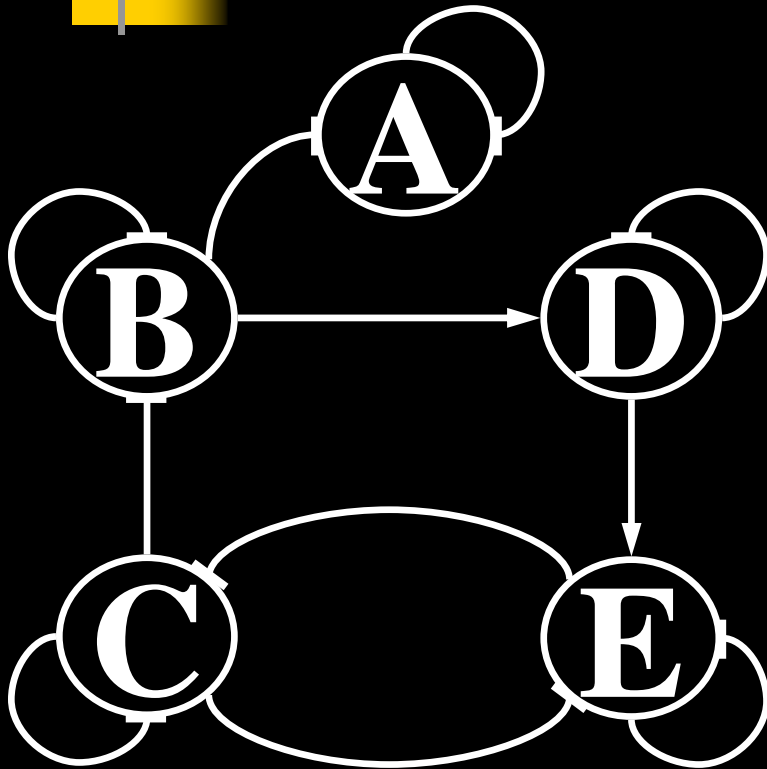
# The main topics on

## Dynamics and Networks

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- Nonlinear dynamical models and nonlinear analysis at molecular level.
- Quantitative simulation of cellular dynamics.
- Molecular communication
- Inferring gene regulatory network, and signal pathways of biological systems
- Finding motifs and conserved substructures of protein interaction networks, GRN

# Modeling gene regulatory network



**Gene Network**

**Biochemical Reaction Network**  
**Mass Action Law**

Difficulties

**Nonlinearity, noises and delays**

Models

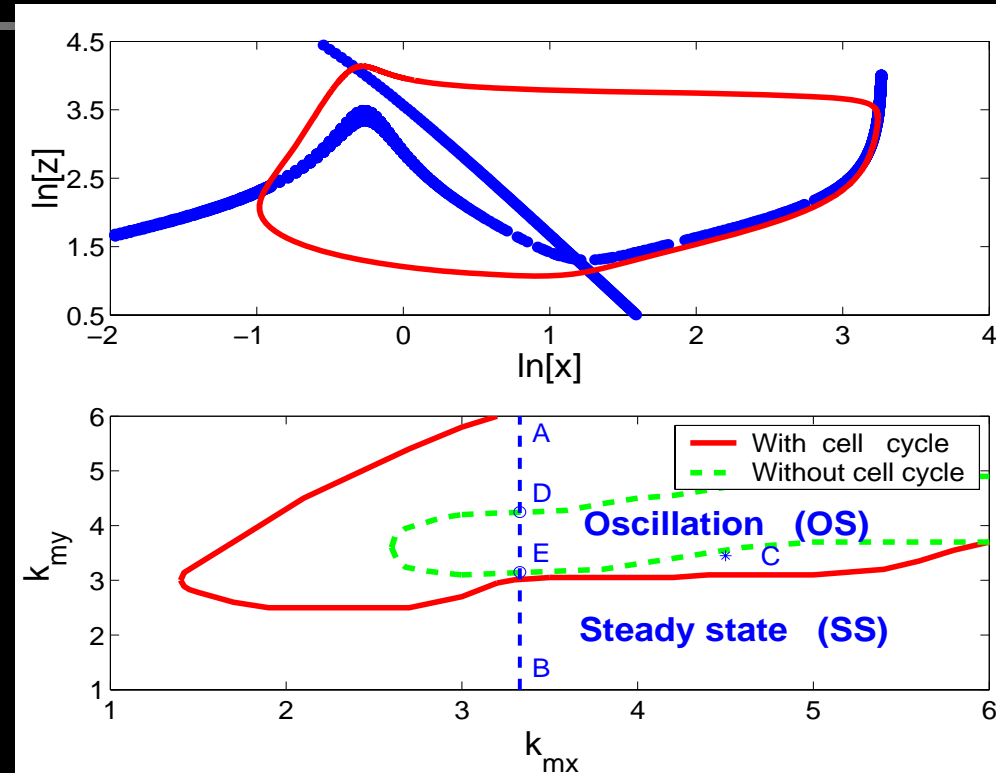
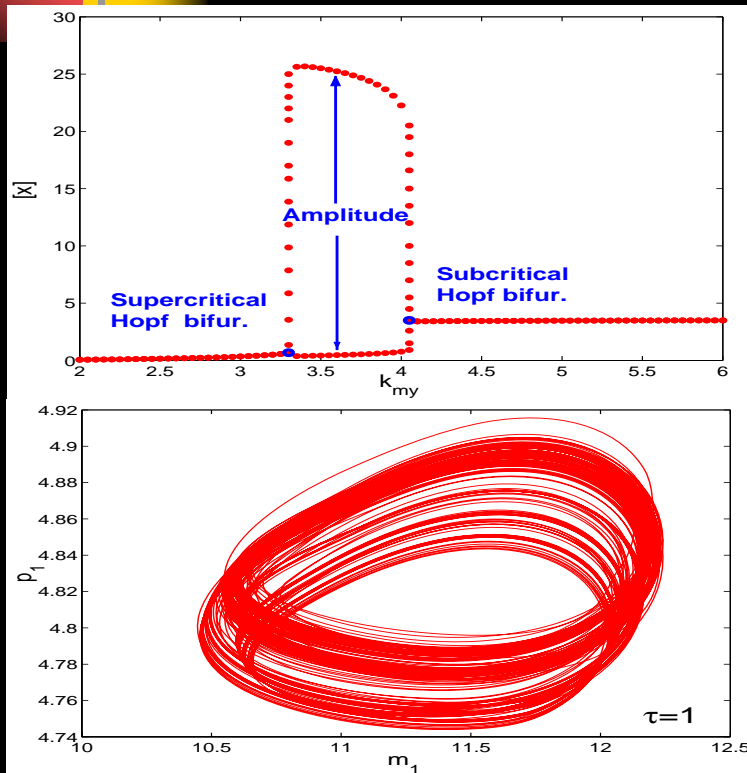
**Monotone Dynamical Systems**  
**Lur'e systems**

reduce complexity without significant approximation

**Network Theory**

- Nodes are mRNAs, proteins
- Arrows represent interactions
- Monotone dynamical system

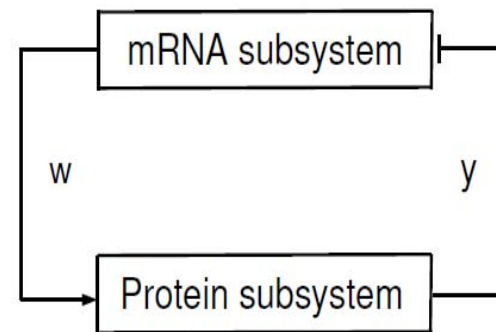
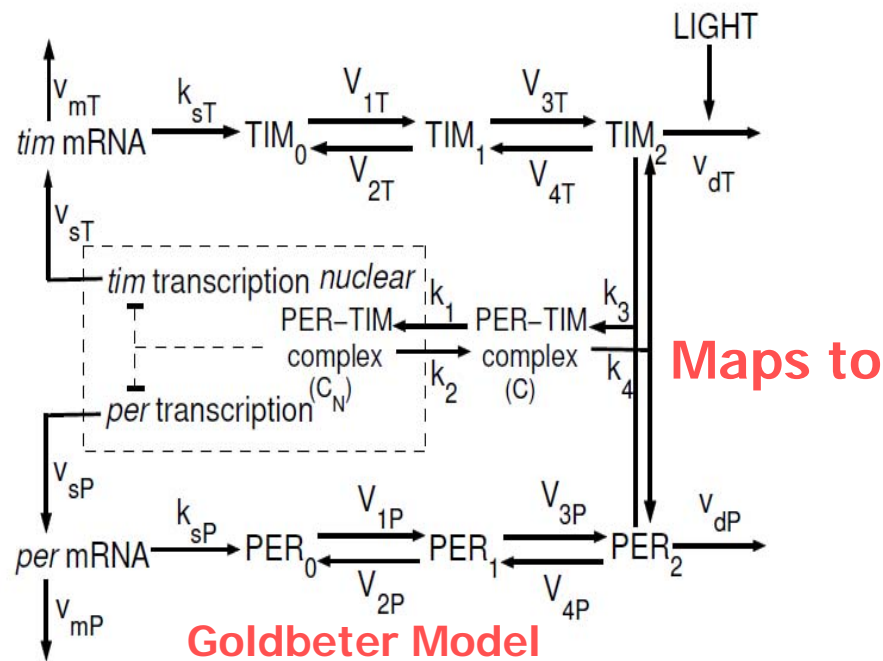
# Nonlinear Analysis



## Effects of Cell Cycle on Cellular Dynamics (degradation factor)

Apply nonlinear theory, e.g. stability and bifurcation analysis to identify essential mechanism of cell cycle, chemotaxis, quorum sensing (gain insights)

# Reducing complexity by control theory



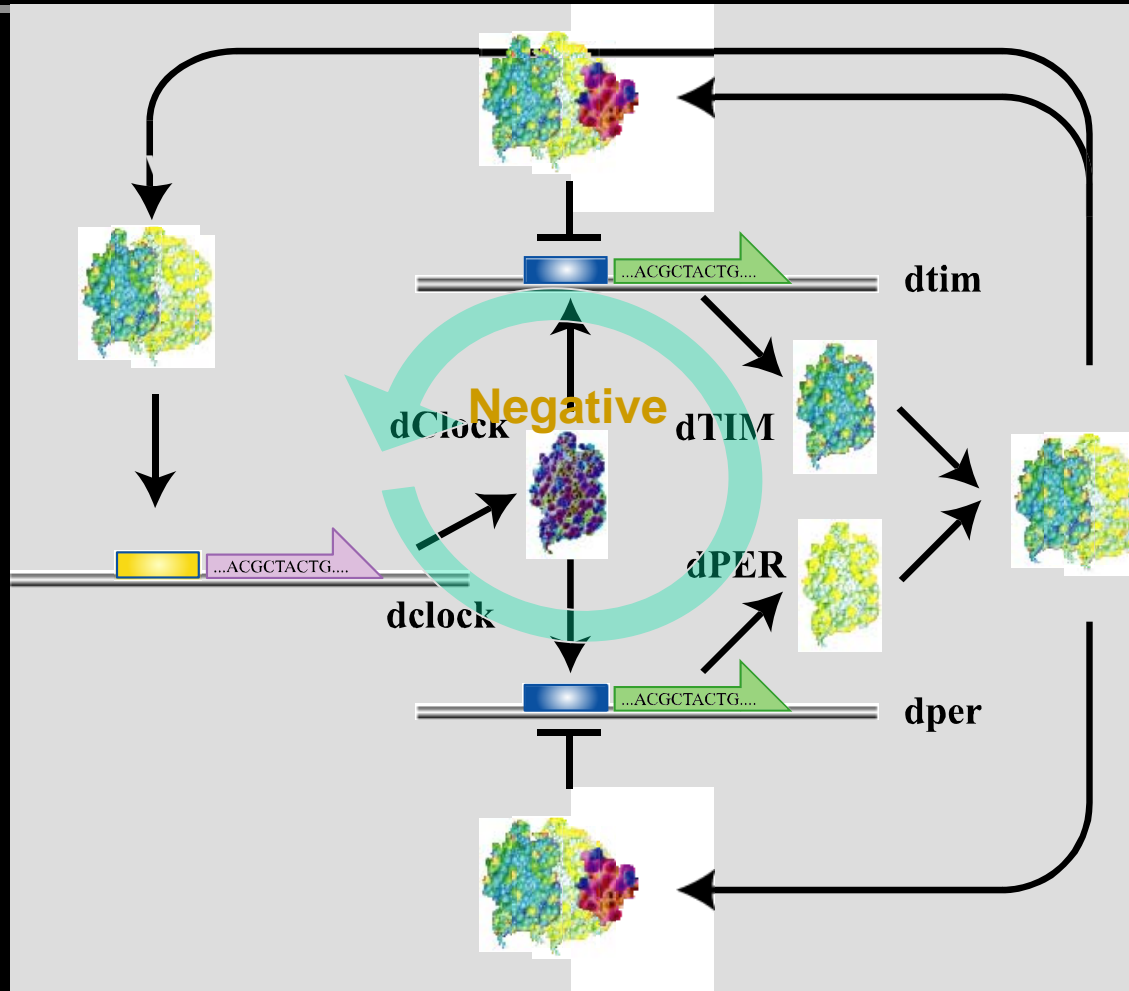
Monotone System

By applying a wealth of control theory and exploiting the special structures, many biological systems can be reduced to simple forms

Jet lag

(a) Scheme of the model for circadian oscillations in *Drosophila* involving negative regulation of gene expression by PER and TIM. (b) Its feedback closure form with inputs and outputs, by which the regulation mechanism can be understood and the system can be significantly reduced.

# Analysis of Circadian Rhythm



A typical example is to analyze circadian oscillators, and control the biological rhythms, which may have therapeutic application.

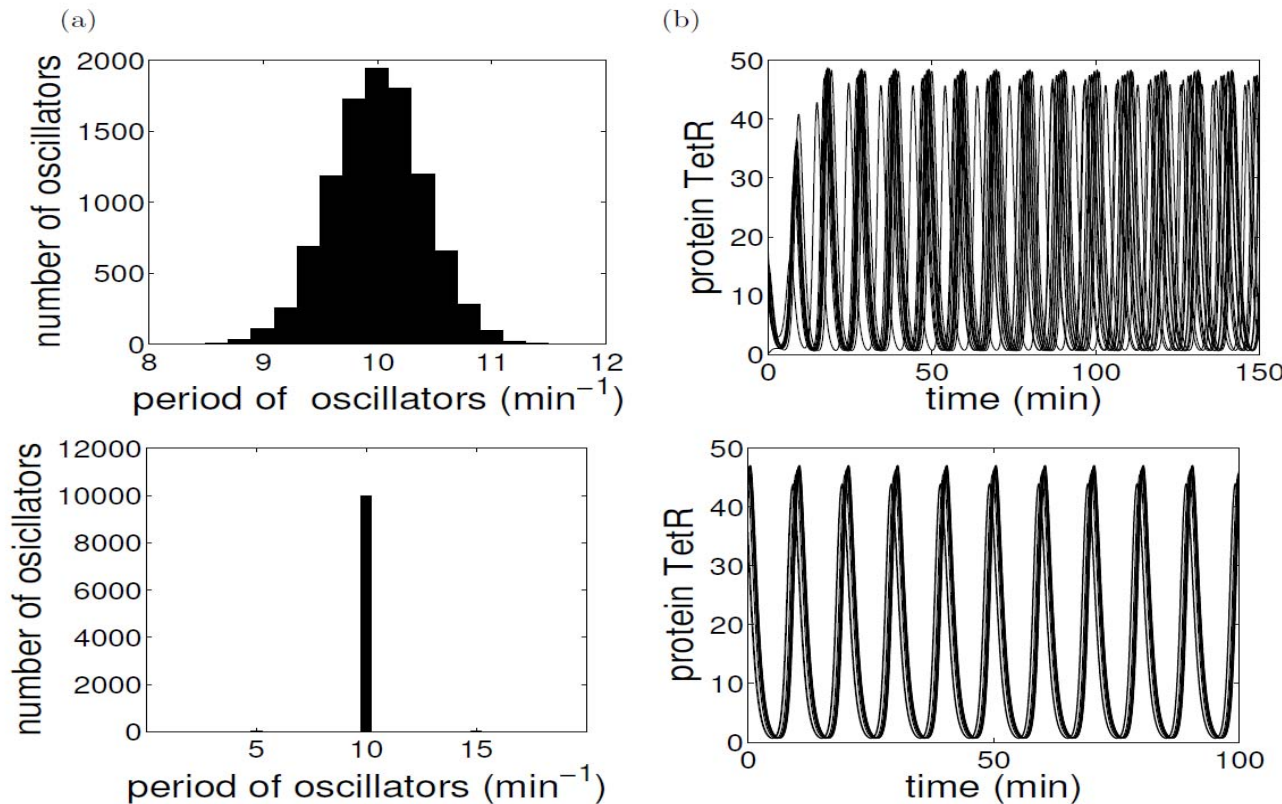


*Drosophila*

Natural oscillator



# Control cellular dynamics by impulse inputs (Synchronization)



**Control strategy is an effective way to change the cellular dynamics, for instance, synchronizing bio-oscillators by impulse control.**

Entrainment of the 10,000 coupled repressilators by periodically injecting coupling AI into the common extracellular medium. (a) Asynchronous oscillations of protein TetR for 10 randomly chosen oscillators in the absence of injection. (b) Synchronization induced by the periodic injection

# Cellular communication: essential for all living organisms at molecular level

- For multicellular organisms
  - complex pattern structures are created from identical and unreliable components via communication



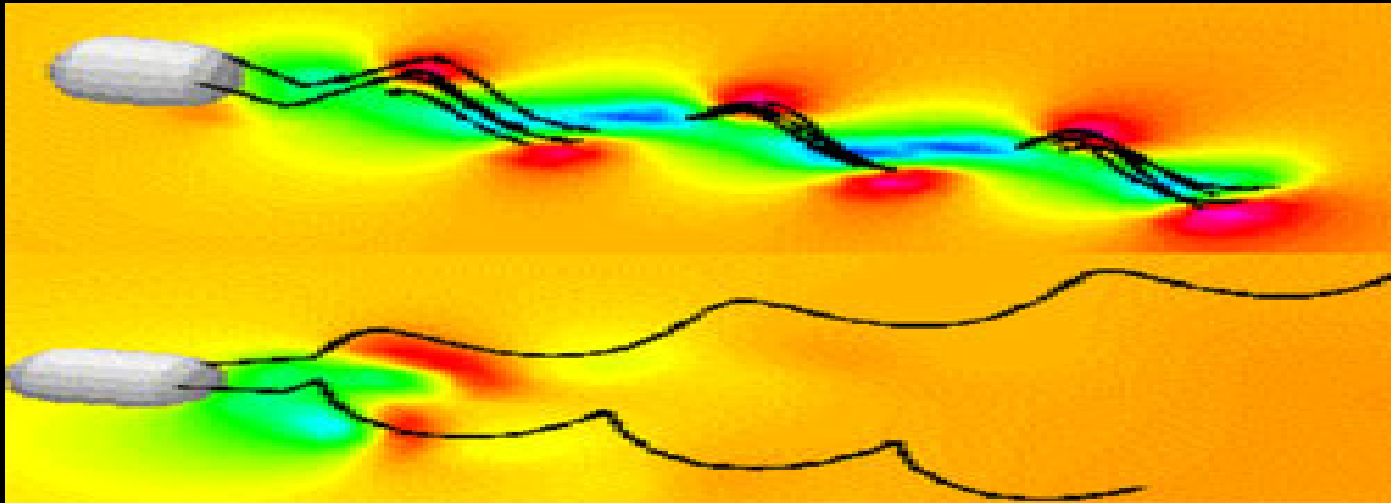
Sea star

Communication is accomplished by first transmitting individual cell information via signal molecules to neighboring cells, then exchanging information among these signal molecules and further generating a global cellular response at the level of tissues, organs and bodies

collective  
behavior,  
cooperative  
behavior,  
synchroniza  
tion

For bacteria

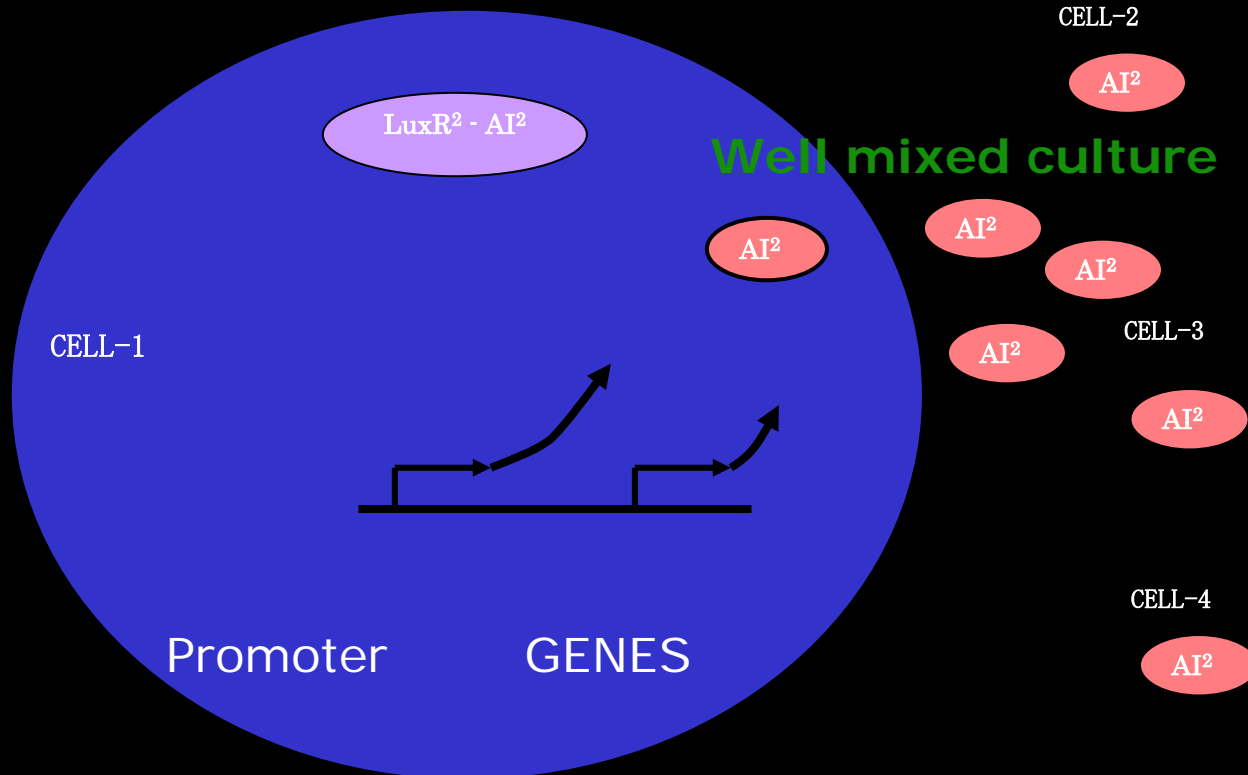
- various social behaviors are displayed due to intercellular communication



*E.coli*

Signal transduction in Chemotaxis: communication strategy

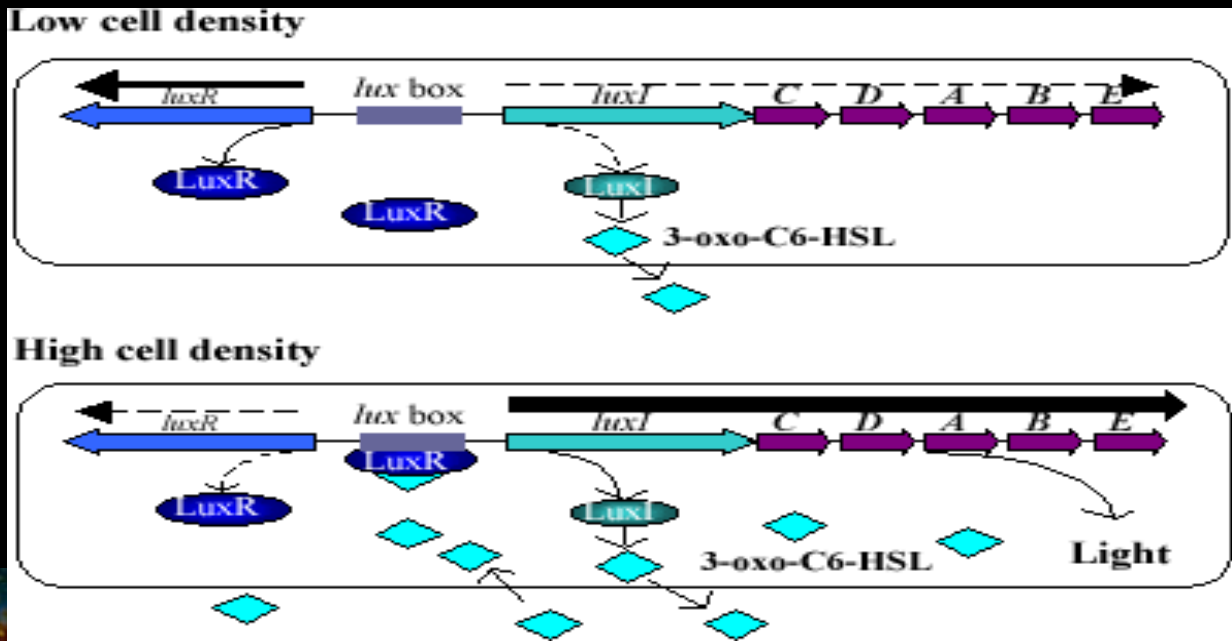
Cell communication is accomplished by diffusing AIs to environment, which enter cells as signal molecules to regulate gene expression.



The ability to communicate between cells is an absolute requisite to ensure appropriate and robust coordination of cell activities at all levels of organisms under an uncertain environment. To understand the mechanism of molecular communication is an essential topic with systems biology, which requires both mathematical and biological knowledge.

Such circuit is engineered on plasmids and assumed to grow in E.coli, based on quorum sensing.

*Quorum sensing : coupling between environment and cells*  
*A bacterium is effectively communicating, to detect and respond to signals (autoinducer: AI) produced by the surrounding bacteria*



gene regulatory network



synthetic net

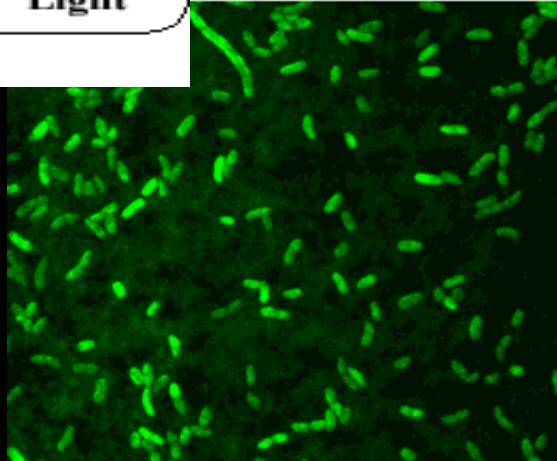
bioluminescence

host



*squid*

*V. fischeri*

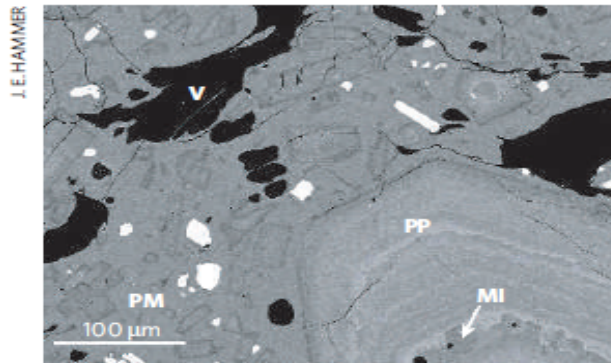




# Commentary to *PRL* by *NATURE*

NATURE | Vol 439 | 5 January 2006

NEWS & VIEWS



**Figure 1 | Photomicrograph of a plagioclase phenocryst with a melt inclusion.** This backscattered electron image shows the microtexture of a Mount St Helens lava-dome sample erupted in September 1981. PM, plagioclase microlite; PP, plagioclase phenocryst; MI, melt inclusion; V, vesicle (relict vapour bubble).

plagioclase phenocrysts form in a magma reservoir but then grow considerably during an eruption. In their new paper<sup>1</sup>, they support and expand this idea with analyses of the melt inclusions found in phenocrysts (Fig. 1).

Melt inclusions are intriguing aberrations of 'normal' crystal growth. They preserve information about the history of the phenocryst, but are difficult to interpret because the conditions in which they form are unknown, the degree of chemical communication with the outside melt may vary, and post-entrapment processes can modify the original compositions. To address these problems, Blundy and Cashman<sup>1</sup> analysed more than 100 inclusions from six eruptions of Mount St Helens during 1980 that varied in intensity from quiescent lava effusion to sustained explosive activity. They interpret a large range in observed

conditions, and the remainder as the result of the eruption itself in which partial degassing of the melt happened too quickly for crystallization to occur. There is an alternative interpretation, however, that is consistent with the traditional understanding of plagioclase phenocrysts. Variable H<sub>2</sub>O may arise from fluctuations in the CO<sub>2</sub> and H<sub>2</sub>O content of magma within the reservoir. Such fluctuations would corroborate the view of the reservoir as an open system subject to periodic influxes of new magma<sup>10</sup>.

Most importantly, Blundy and Cashman's interpretation of the melt-inclusion data reinforces the idea that crystallization during an eruption affects the style of intermediate-intensity eruptions<sup>8,11</sup>. The correlation between crystallinity and melt-inclusion H<sub>2</sub>O content raises an intriguing chicken-and-egg issue, however. Does degassing-induced crystallization occur only when ascent rates and flow regimes in the magma conduit produce conditions favourable for rapid crystal growth? Or through its influence on magma viscosity, can the solidification process reduce the intensity of an eruption already in progress?

Events at Mount St Helens in 1980 have inspired many studies, the latest being this report<sup>1</sup> detailing changes in melt chemistry at unprecedented spatial and temporal resolution. With the volcano again obliging investigators with new magma since early 2004, a renewed effusion of research is sure to follow.

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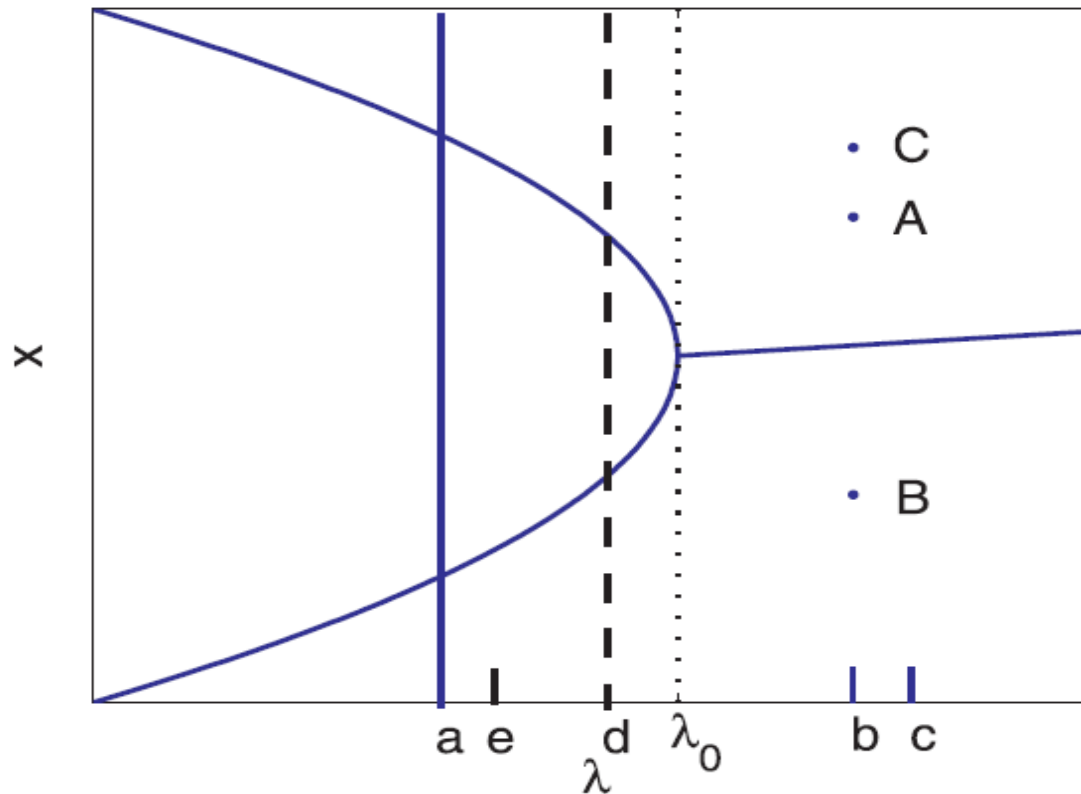
## BIOLOGICAL PHYSICS

# Harmonies from noise

Michael Springer and Johan Paulsson

**Do random environments make for random responses to them? Mathematical models suggest that this is not always the case — adding noise could create synchronous oscillations in cell-cell signalling systems.**

# Transient Resetting: A Novel Mechanism for Synchrony



**Figure 1.** A Schematic Bifurcation Diagram with a Normal (Supercritical) Hopf Bifurcation for Illustrating the Transient Resetting Mechanism  
DOI: 10.1371/journal.pcbi.0020103.g001

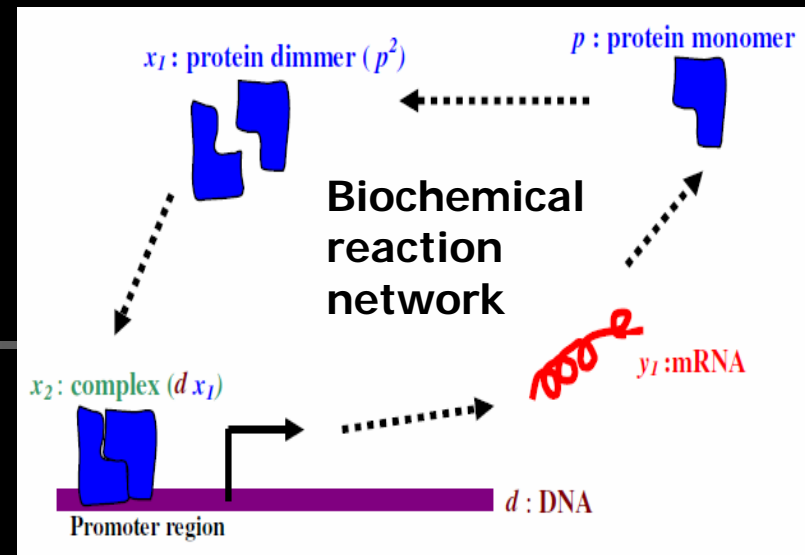
For uncoupled biological oscillators with Stimuli, this mechanism can unify and extend many existing results on (deterministic and stochastic) stimulus induced synchrony. Transient resetting is a possible mechanism for synchronization in many biological organisms, which might also be further used in the medical therapy of rhythmic disorders.

Independent Oscillators

# Quantitative Simulation in a Cell

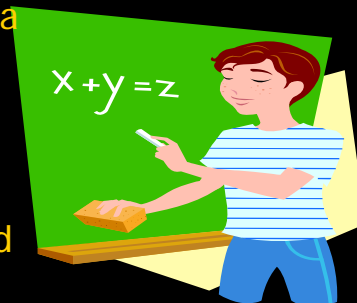
## Stochastic Simulation

- Biochemical master equation
- Monte Carlo simulation for cellular dynamics
- Fokker-Planck equation
- Langevin equation, SDE
- Cumulant equation
- ODE



Simulation for such network requires enormous computational power.

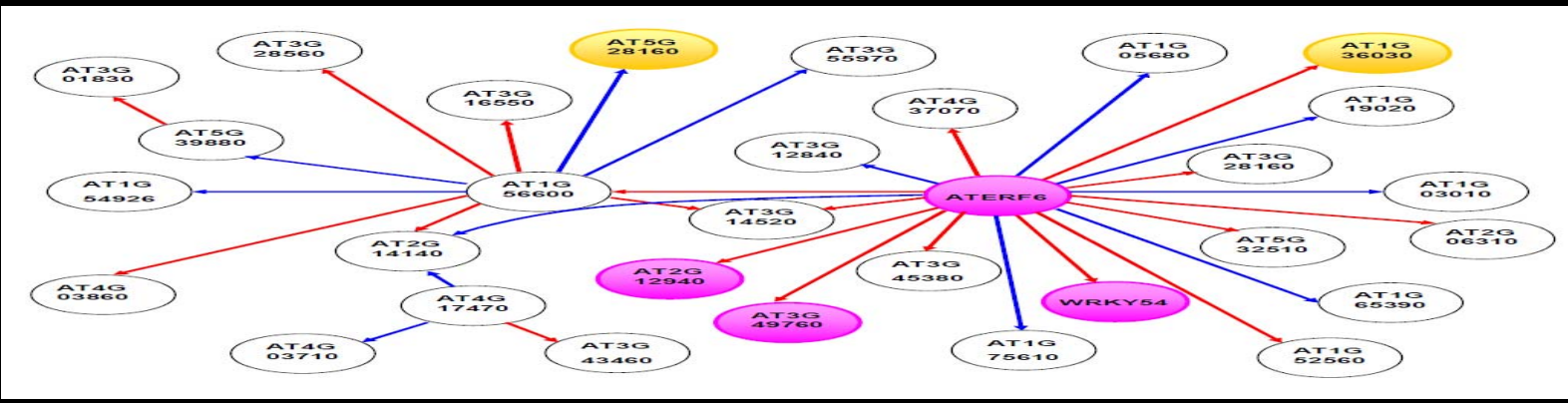
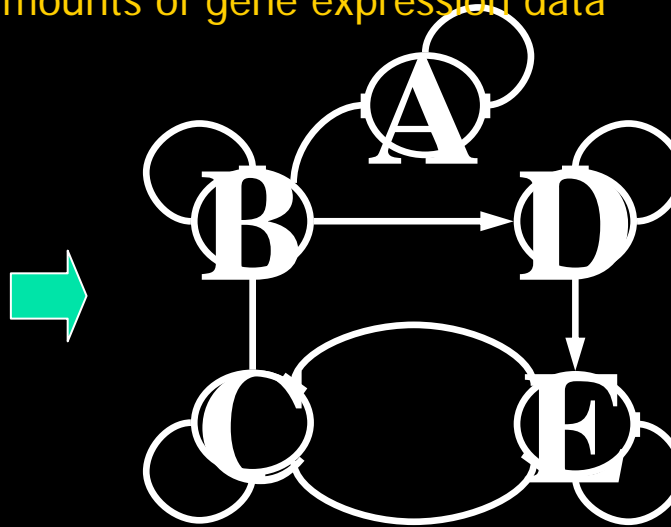
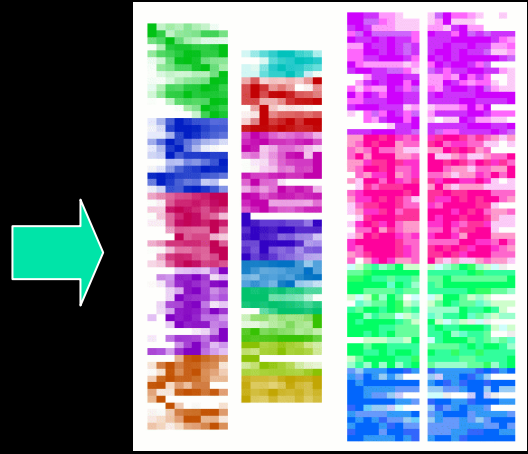
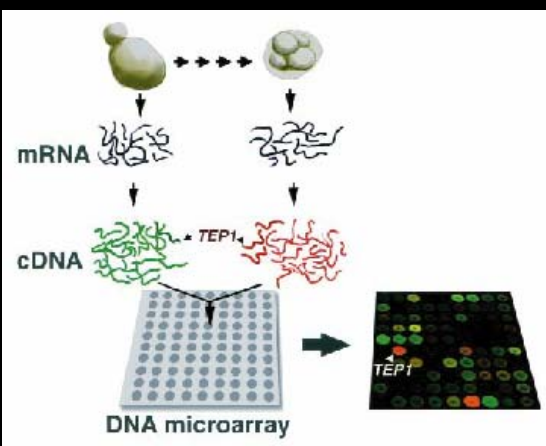
In contrast to the qualitative analysis, quantitative computation provides the detail information. Biological system can be viewed as a biochemical reaction network, which generally can be defined as master equation with both stochastic fluctuations and discrete changes.





# Inferring Gene Networks

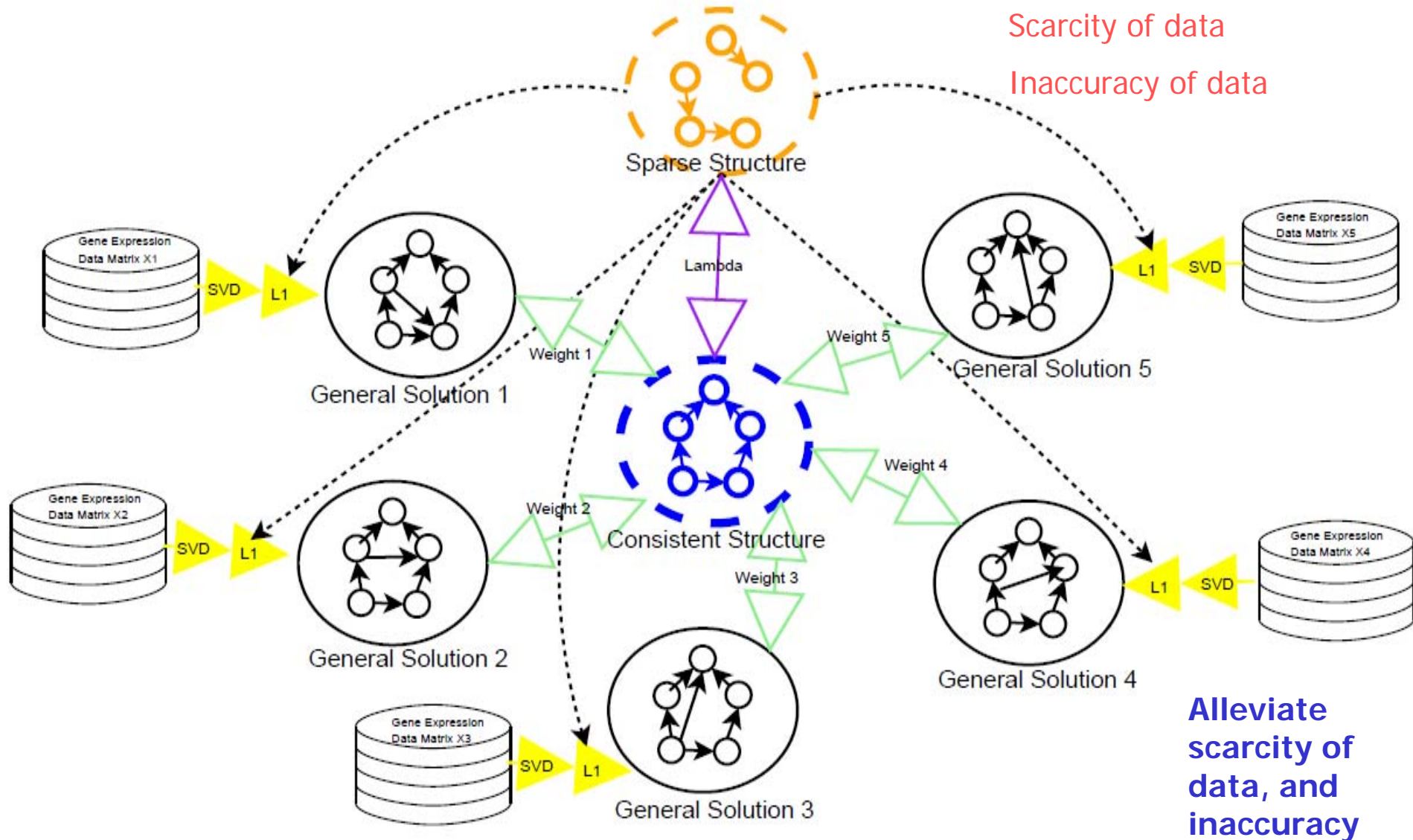
Microarray technologies have produced tremendous amounts of gene expression data



Inferred network in *Arabidopsis thaliana*, from stress response datasets in shoots.

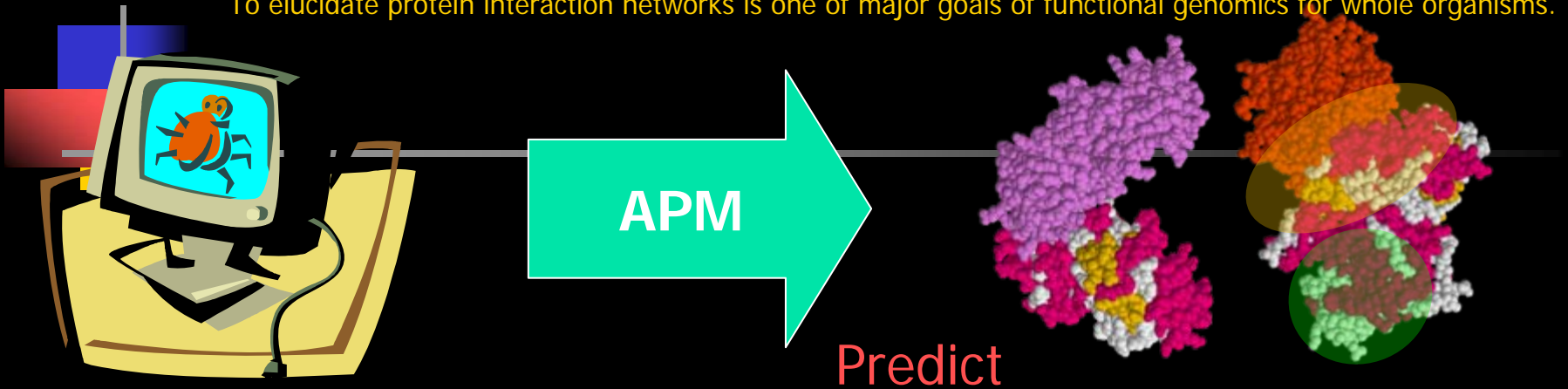
Software, GRNInfer, is available on line !

# Inferring Gene Network by Multiple Datasets

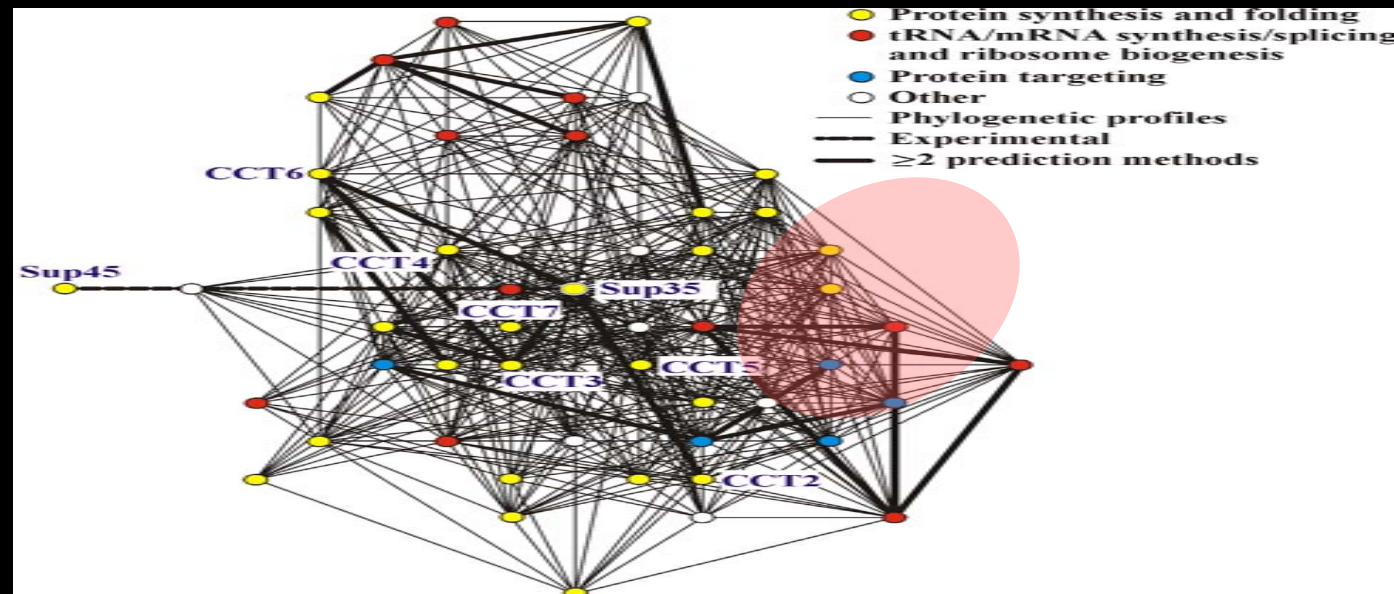


# Inferring Protein Network from experiment data

To elucidate protein interaction networks is one of major goals of functional genomics for whole organisms.



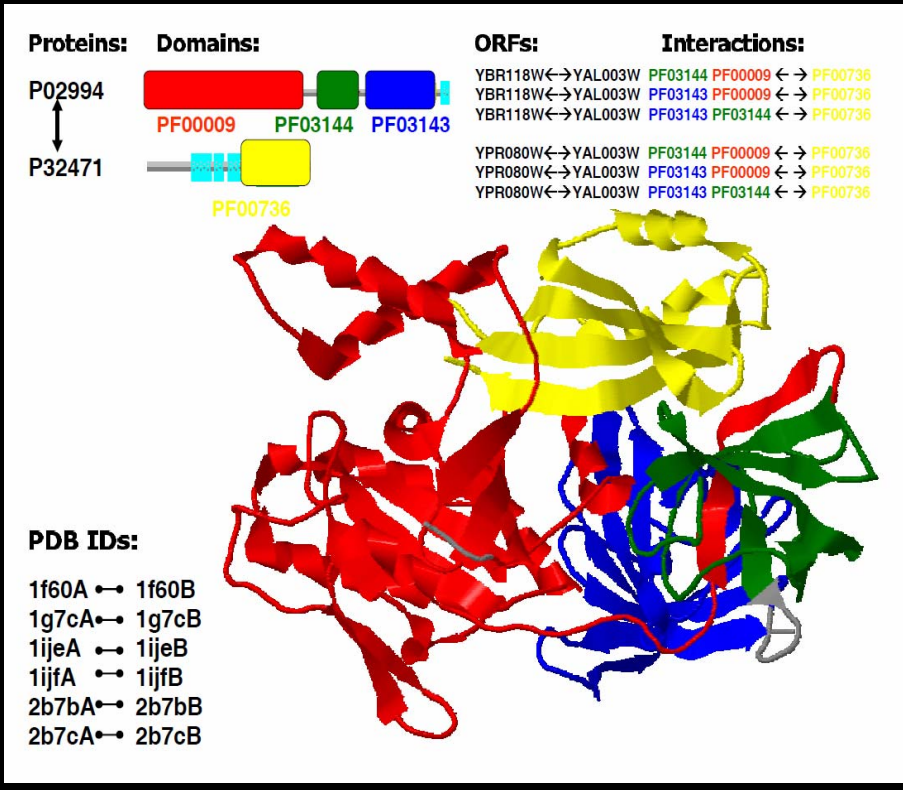
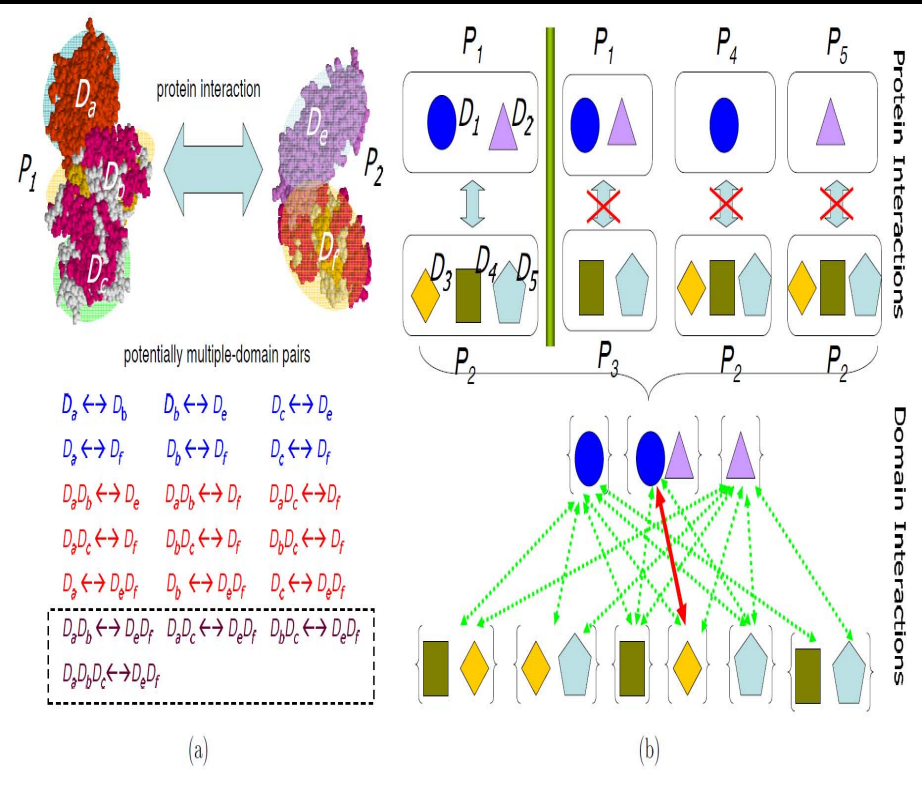
Due to recent advances of biotechnology, data of protein-protein interaction can be generated by experiment, such as two-hybrid assay, co-immunoprecipitation and chIP-chip approach.



Sup 35 Interaction Network



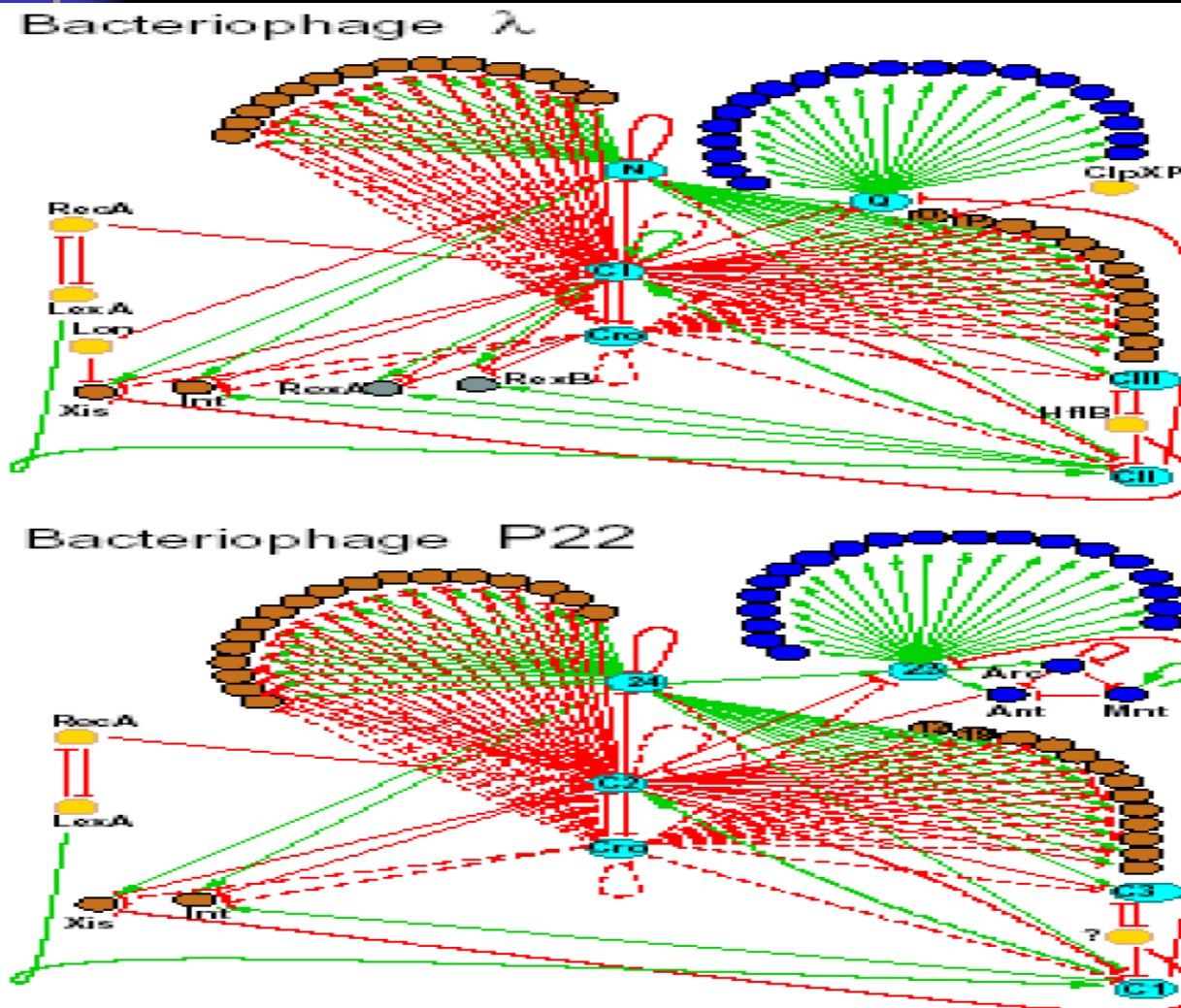
# Multi-domain interactions



Super-domains, strongly cooperative domains

Domain cooperation plays an important role in facilitating the protein-protein interactions

# Network motif, signal pathway, evolution



Various organisms differ not only because of differences of constituting proteins, but also because of their networks. Hence, it is essential to address similarities and differences in networks by comparative network analysis

Alignment of gene and protein networks

*Scale-free,  
small-world*

# Identify signaling network from PPI and Microarray data

$$\text{Min} \sum_{i=1}^{|V|} \sum_{j=1}^{|V|} a_{ij} e_{ij} + \lambda \sum_{i=1}^{|V|} \sum_{j=1}^{|V|} e_{ij}$$

$$\text{s.t. } e_{ij} \leq x_i$$

$$e_{ij} \leq x_j$$

$$\sum_j e_{ij} \geq 1, \text{ if } i \text{ is a membrane protein or TF}$$

$$\sum_j e_{ij} \geq 2x_i, \text{ if } i \text{ is not a membrane protein or TF}$$

$$x_i = 1, \text{ if } i \text{ is a membrane protein or TF}$$

$$x_i \in \{0, 1\}, i = 1, 2, \dots, |V|$$

$$e_{ij} \in \{0, 1\}, i, j = 1, 2, \dots, |V|$$

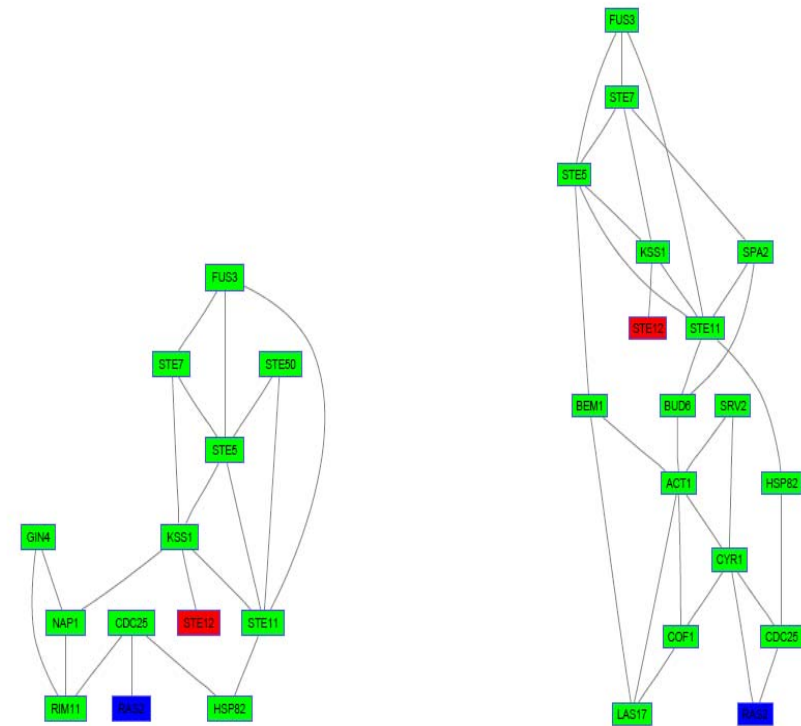


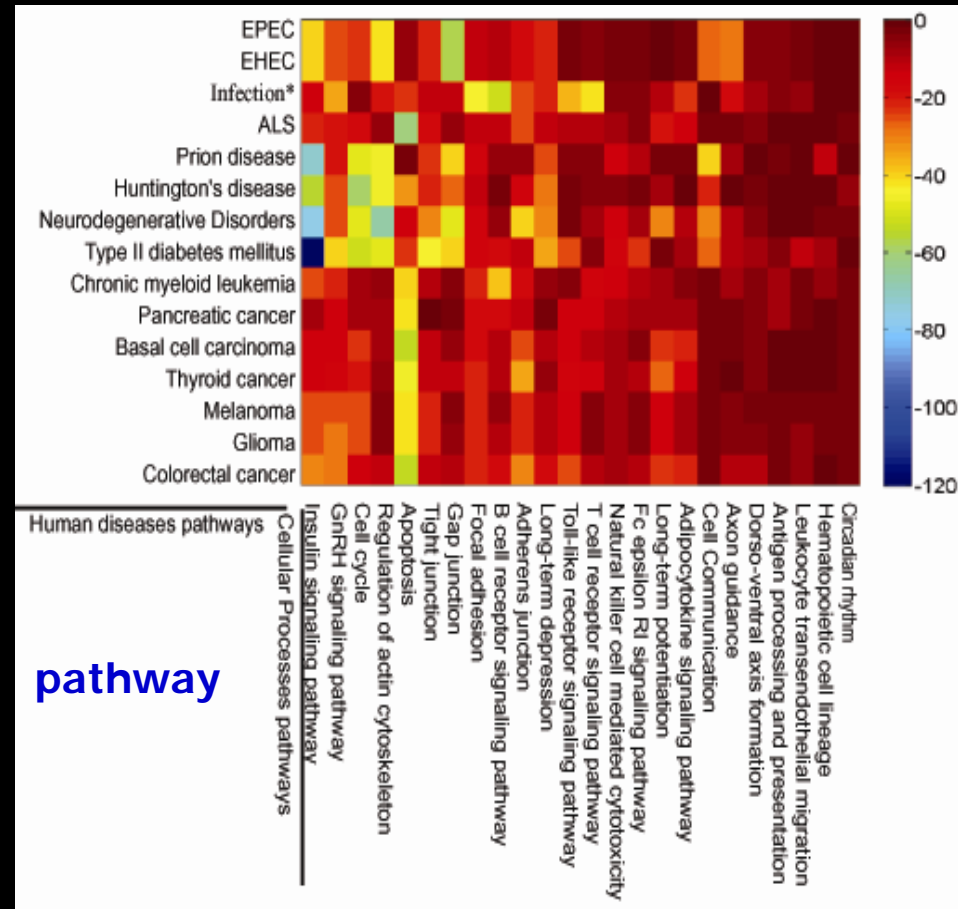
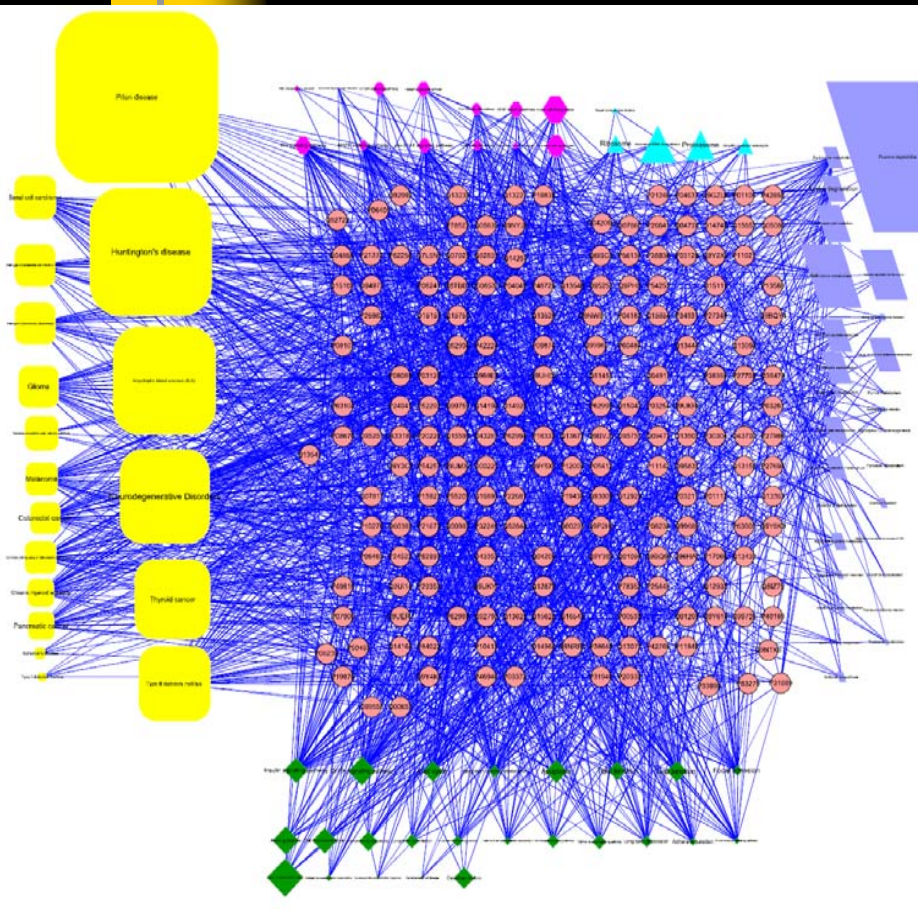
Figure 4. The signaling network for filamentous growth invasion.

By mathematical programming, we can identify the signal pathway or network



# Hubs and network motifs: diseases and their pathogenesis

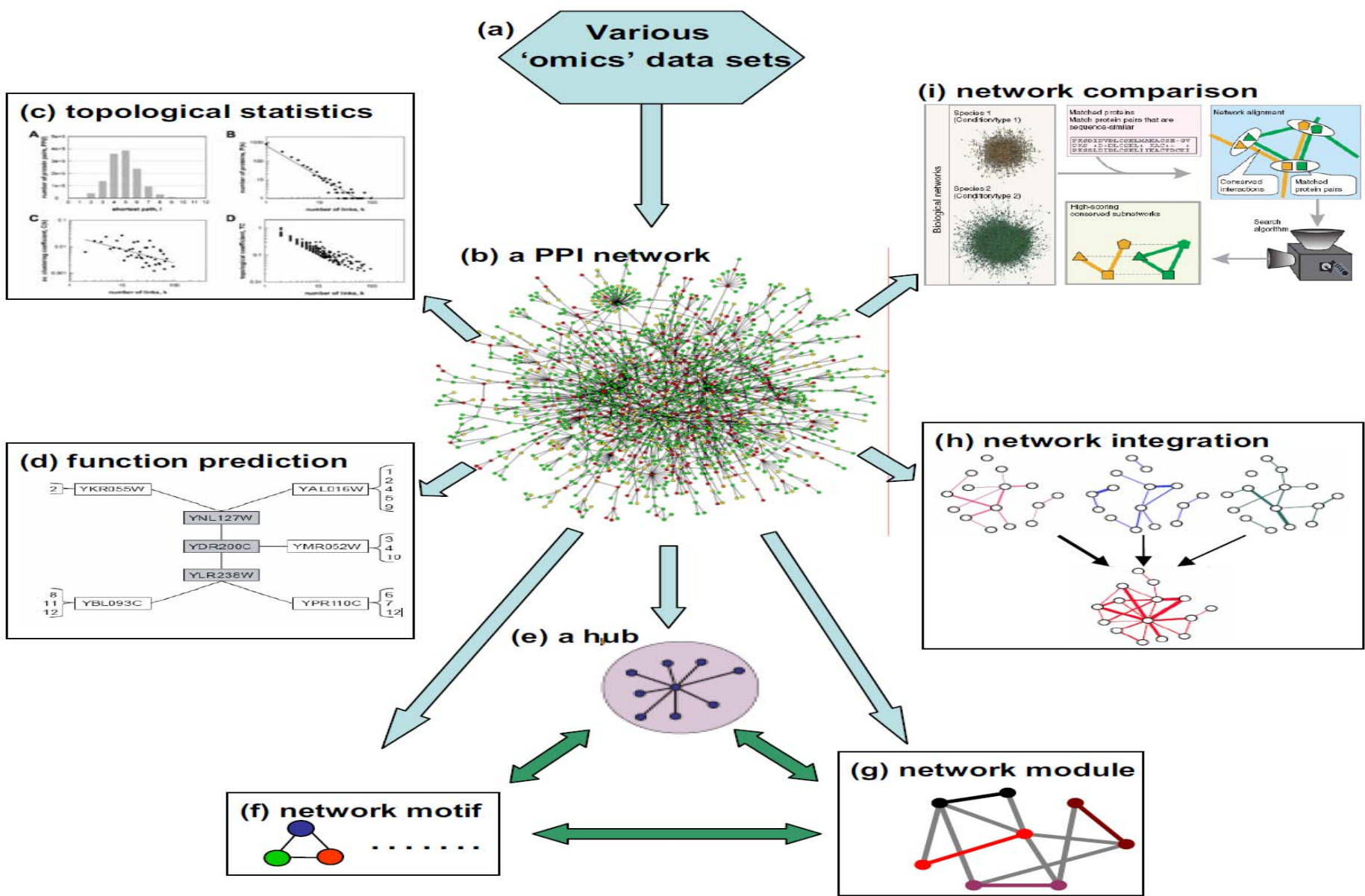
Connectors: derived from a network with motifs and hubs



pathway

One mechanism of diseases may be attributed to the connectors that activate or initiate interactions between disease pathways and causation pathways, thereby eventually leading to diseases.

# Research for Molecular Networks





## 2. Molecular Biology (experiments, synthetic biology)



- Synthetic biology is a new area of research that combines science and engineering in order to design and build novel biological functions and systems.

Aim: Research is aimed to combine knowledge from various disciplines including molecular biology, engineering and mathematics to design and implement new cellular behaviors.

Goal: The goal is both to improve the quantitative understanding of natural phenomenon as well as to foster an engineering discipline for obtaining new complex cell behaviors in a predictable and reliable fashion.



# Main Topics on Engineering

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- Gene switching network and experiment
- Gene oscillating network and experiment
- Biosensor network and related experiment
- Study on differentiation of stem cells
- Drug target screen and identification

based on synthetic biology

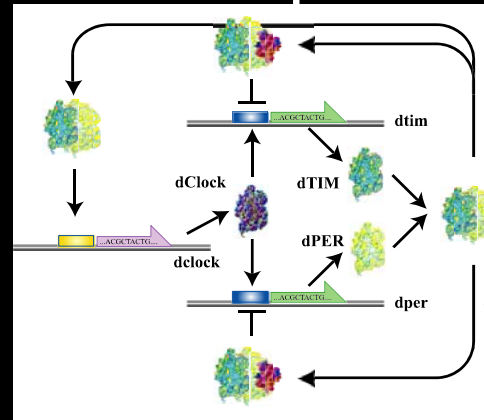
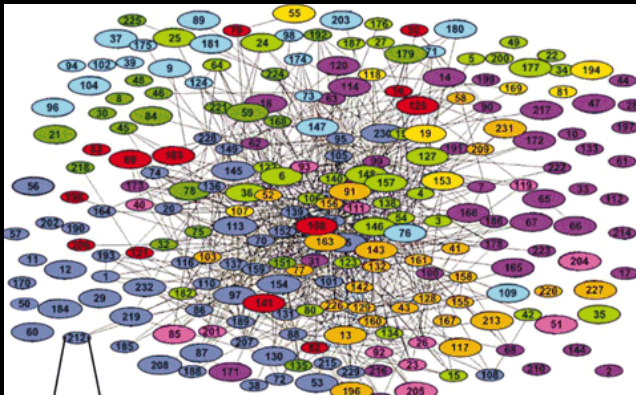
# Approach by Synthetic Biology

## Forward engineering

In contrast to the reverse engineering, the synthetic gene network is a forward engineering

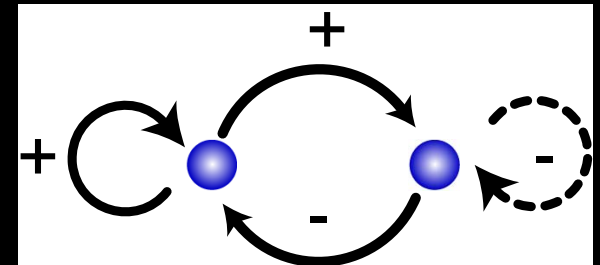
- Analyze and understand essential structure mechanism with simple environment

Complicated gene network



Analysis

subnetwork ? (e.g. circadian rhythm)



# Designing Gene Switch *Journal of Theoretical Biology '04*

## (toggle switch in *E.coli*)

1. A state

2. Switching

**An artificial gene network which has multistable states !**

**A mathematical interpretation**

1. A stable equilibrium point.

2. Transition between two stable equilibrium points

Experiment data well agreed with theoretical results, which implies that mathematical model is a powerful tool for designing network

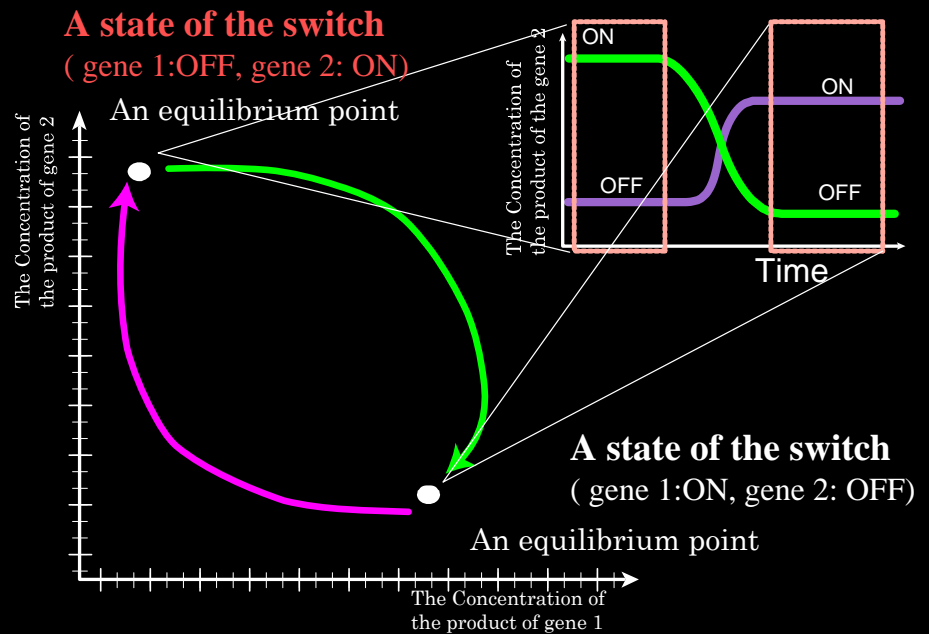
Ex.: ✓ **A gene toggle switch**

✓ A gene oscillator

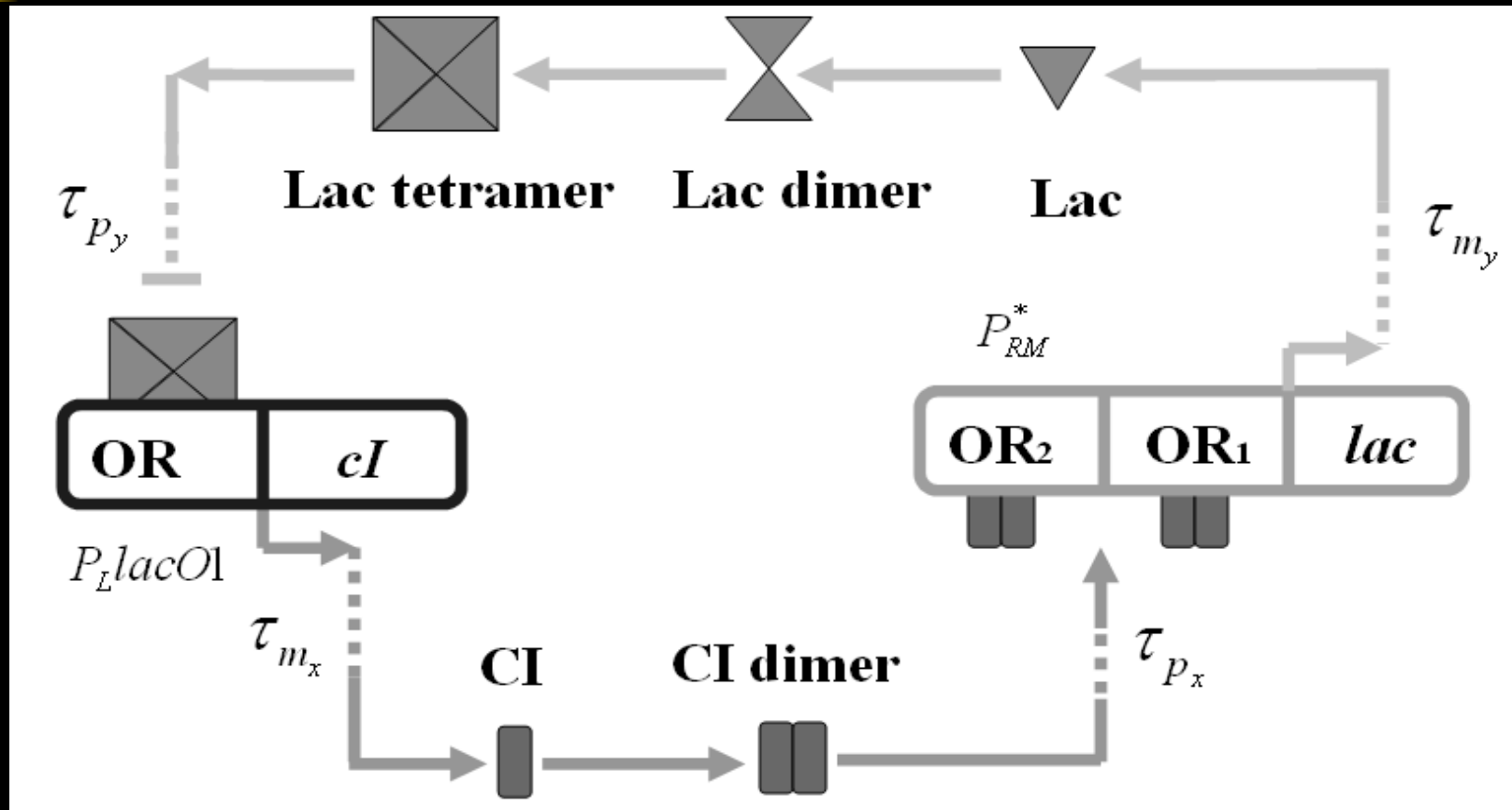
### Applications

- Medicine ( gene therapy )
- Biotech
- Bio-computer

Mathematical model can be used to design an artificial gene network which has desirable functions.



# Designing Gene Network (Oscillating Network)



There exist various periodic oscillations with different time scales ranging from less than a second to more than a year, which may allow for living organisms to adapt their behaviors to a periodically varying environment

# Repressilator

A typical oscillating network is repressilator, which is constructed on plasmids, and transformed into simple organisms, *E. coli*.

transfect cloned gene network into a host

*E. coli*

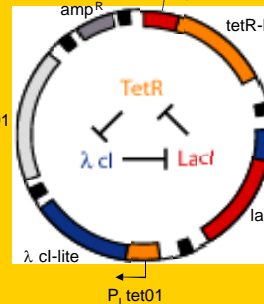


*E. coli*

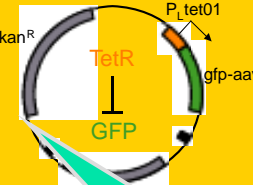


By GFP, measure the dynamics of gene expression

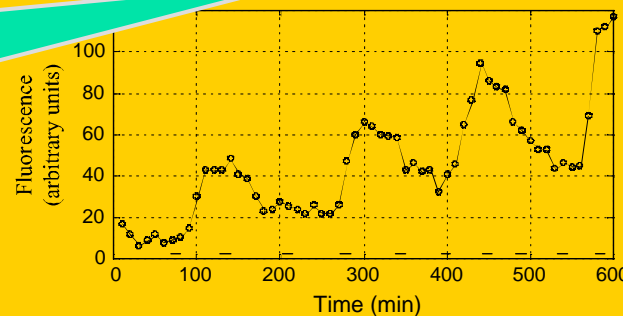
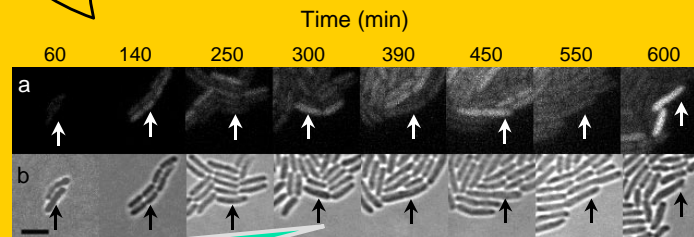
Plasmid



Reporter

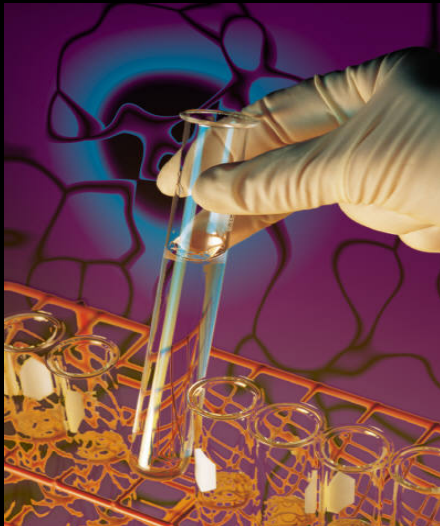


Construct artificial gene network on plasmids (vectors)

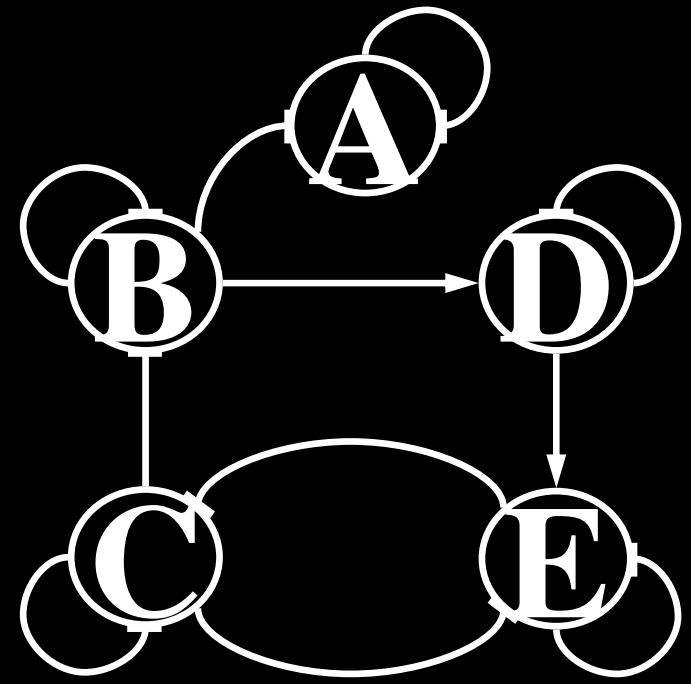


# Refining network by RNAi

- RNAi silence experiments are also conducted in several key or pivotal genes (with dense connections to others) to improve the confidence.



RNAi perturbation



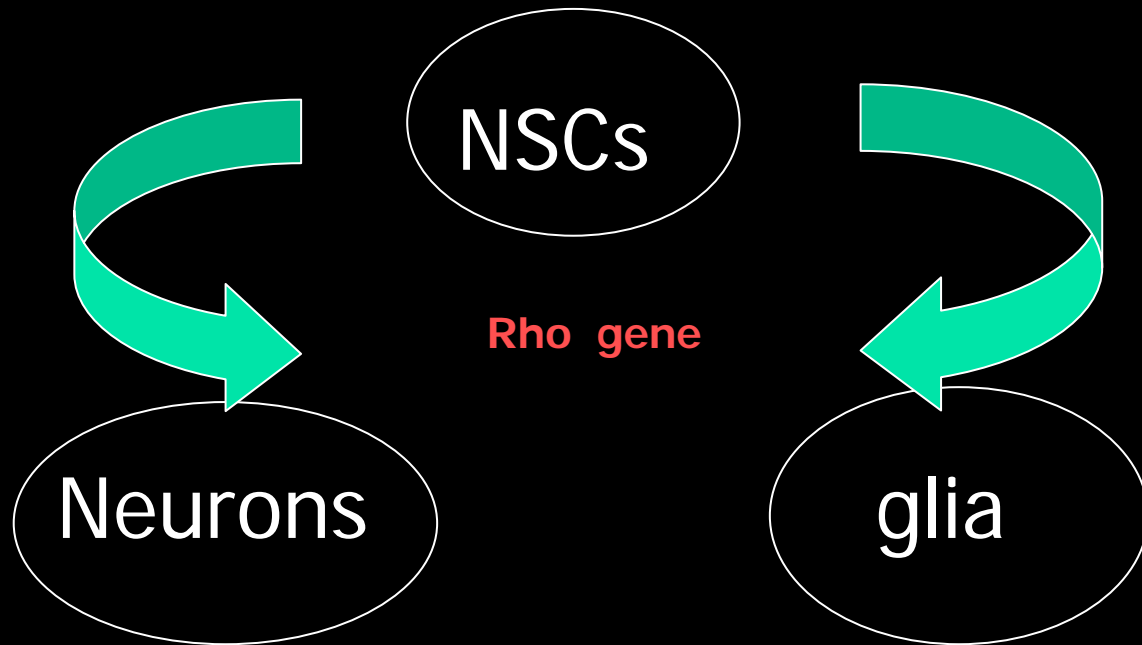


# Neural Stem Cells (NSC)

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- Differentiation : subtype of progenitor cells in the nervous system

NSCs are expected to apply for treatment of nervous system diseases, such as Parkinson, Huntington's disease, and spinal cord injury.



*Mouse*





# 3. Computational Systems Biology

(static problem, tools, database)

- Computational systems biology is the use of techniques from mathematics, informatics and computer science to solve biological problems.
- Research in computational systems biology often overlaps with bioinformatics.





# Main Topics on Optimization

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- Protein structure analysis and function prediction
- Haplotype reconstruction
- Identifying protein by Mass Spectrometry
- Inferring protein-protein interaction network by experimental data
- Neuron image processing (Neuroinformatics)

Software PTG is available on line !

Disease genes mapping  
Drug design

# SNP & Haplotype

NP-hard class

- SNP: Single Nucleotide Polymorphism
- Haplotype: A set of closely linked genetic markers present on one chromosome which tend to be inherited together (not easily separable by recombination).



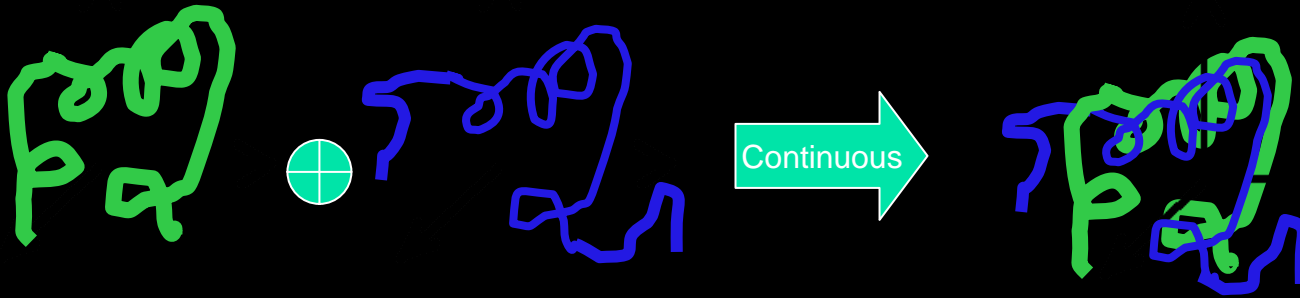
Set of SNP polymorphisms: a SNP haplotype

Tree-grow method

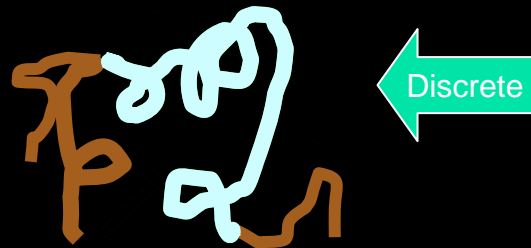
Parsimony principle, phylogenetic tree, frequency

# Protein Structure Alignment

## 1. Optimally superimpose two structures



## 2. Further find the regions of closest overlap in a three-dimension space.

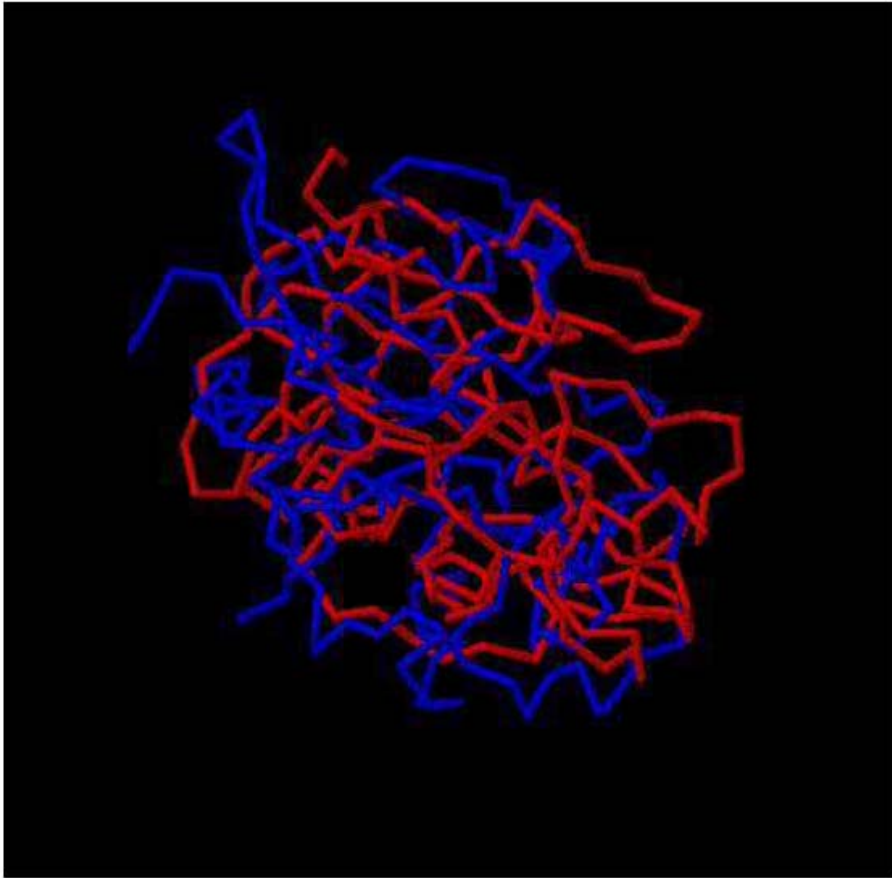


Structure alignment plays a key role in protein structure prediction, fold family classification, motif finding, phylogenetic tree reconstruction

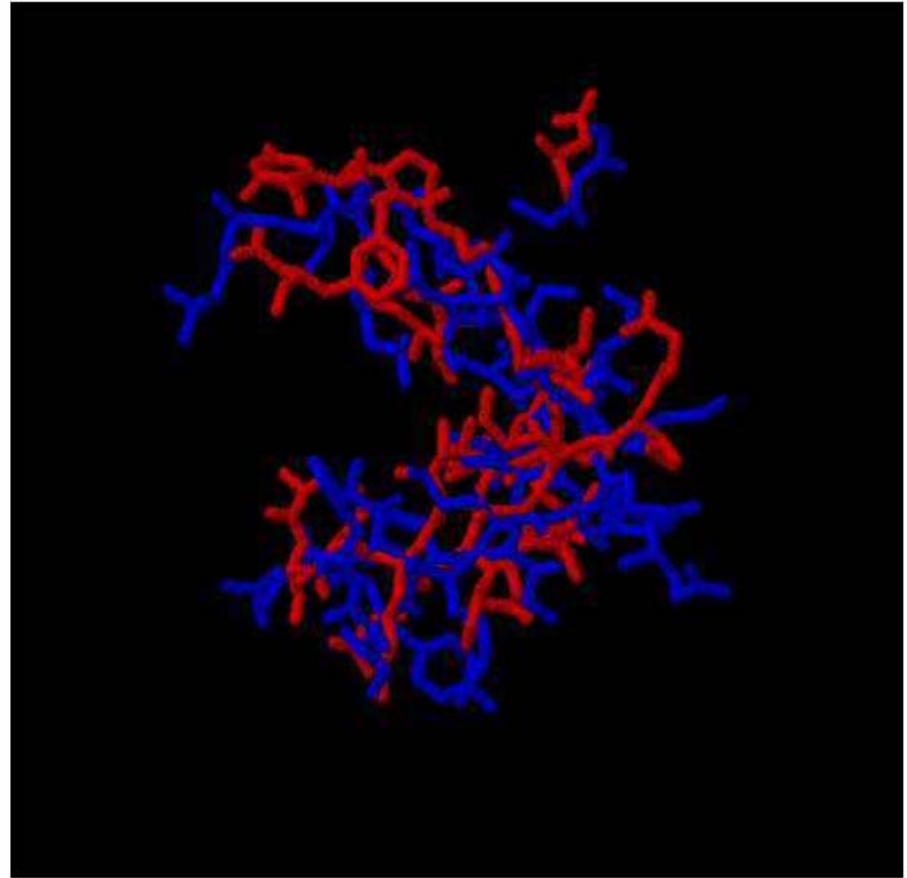
\*Combinatorial optimization problem : NP-hard

\*Pairwise sequence alignment: polynomial time algorithm (DP)

# Local Alignment to Identify Active Site



(a) Alignment result of 1tpo and 2act.



(b) Detail of active site match.

# Structure- Function Relationships



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- ◆ Can we predict the function of protein molecules from their sequence?

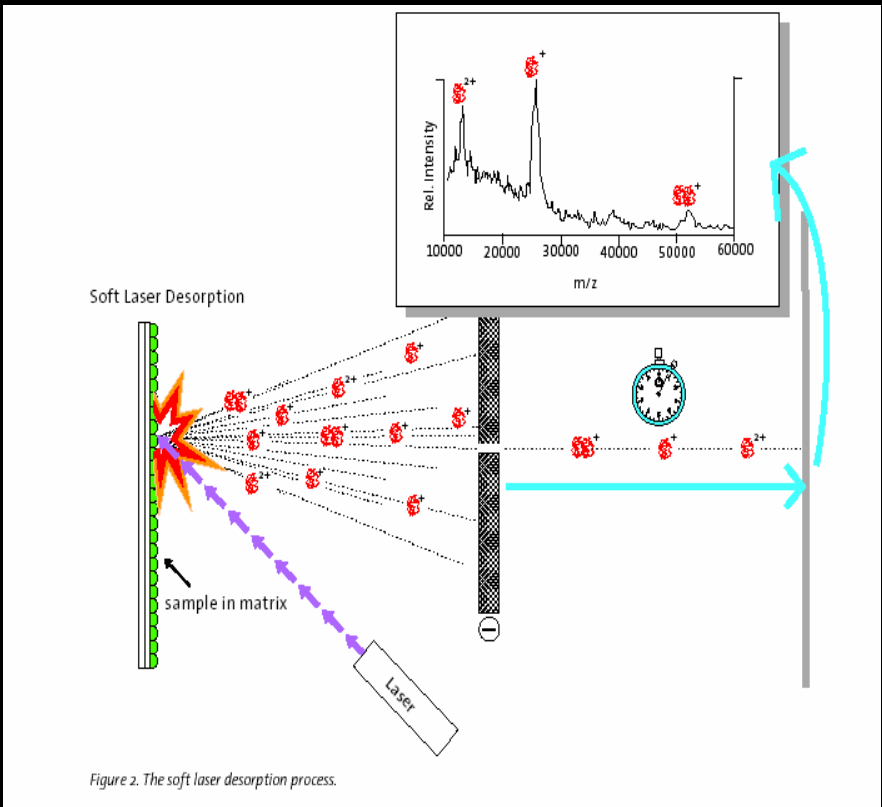
**sequence > structure > function**

- ◆ Conserved functional domains = motifs
- ◆ Prediction of some simple 3-D structures ( $\alpha$ -helix,  $\beta$ -sheet, membrane spanning, etc.)

Secondary structure: 80% accuracy

# Mass Spectrometry to identify protein

## Matrix-Assisted Laser Desorption/Ionization (MALDI)



# Function prediction by Machine Learning

Table 1: Summary of data descriptions						
Data sets	# Samples	Positive samples		Negative samples		Classification tasks
		Min	Max	Min	Max	
PCB00019	1357	10	168	592	670	55
PCB00020	11944	10	771	566	587	246
PCB00022	11944	10	1013	555	587	191
PCB00028	11373	10	1301	503	573	199

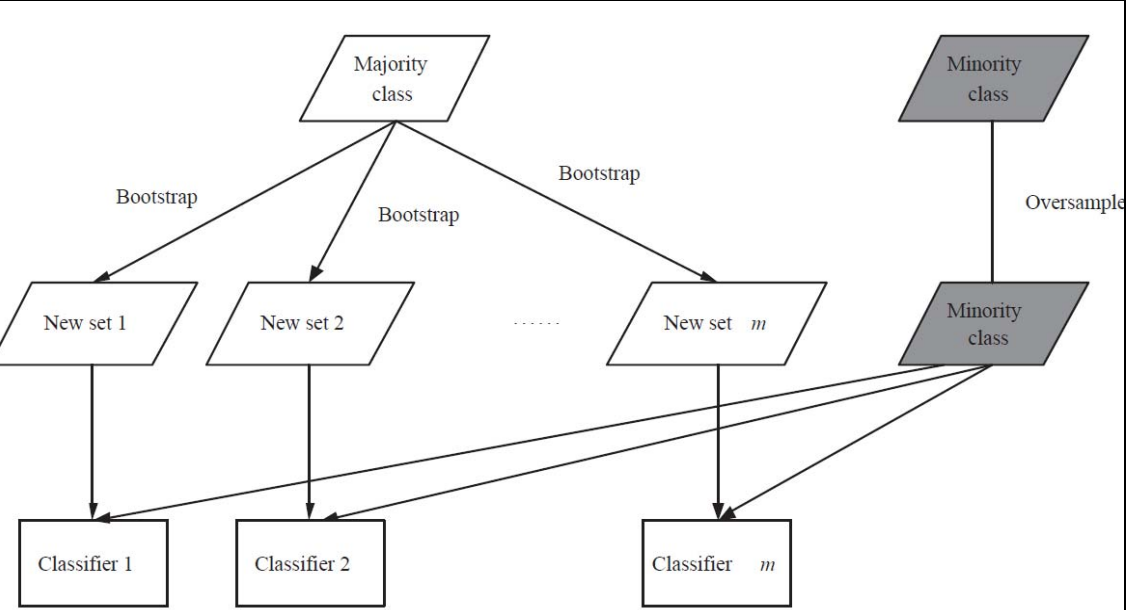


Figure 2: Schematic for EnClassifier

**Imbalance data: a new algorithm to overcome the imbalanced problem with a new sampling technique and a committee of classifiers. Then, classifiers trained in different feature spaces are combined together to further improve the accuracy of protein function prediction**






# Website for Papers and Software

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- <http://www.isb.shu.edu.cn>
- <http://intelligent.eic.osaka-sandai.ac.jp>
- <http://zhangroup.aporc.org/>

# List of Major Publications

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---

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- **Shanghai University**: Dr. R-Q. Wang, Prof. Z.Liu, etc.
- **Osaka Sangyo University**: Dr. R-S.Wang



# Upcoming Books

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## *Optimization !*

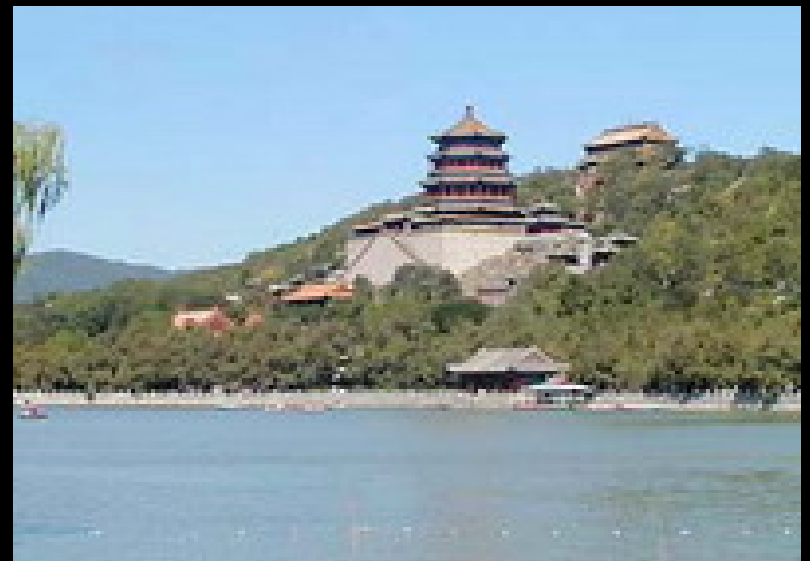
- L.Chen, R.Wang, X.Zhang, *Biomolecular Network: Computational Methods and Applications in Bioinformatics and Systems Biology*, *John Wiley & Sons*, 2008

## *Dynamics !*

- L.Chen, R.Wang, C.Li, K.Aihara, *Modelling Biomolecular Networks: Structures and Dynamics*. *Springer-Verlag*, London, 2008.
- 陳、吳、王、章、系統生物學導論、*科学出版社*、2008



# Thank you



Enjoy rich cultural heritage of Beijing, and further China during your stay !