Topology and Dynamics of Biological Networks

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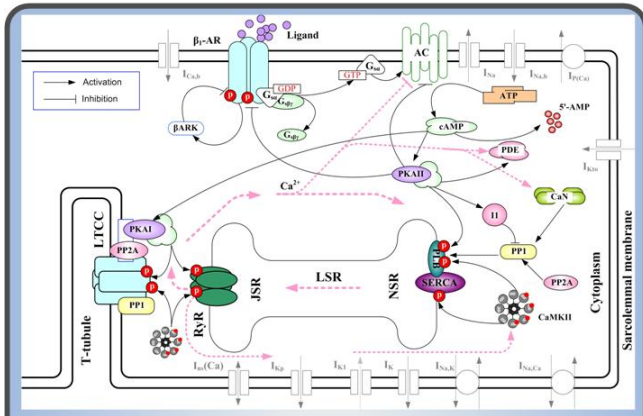
2010. 1. 11

Outline

- Systems Biology
- Reverse Engineering of Biological Networks
- Network Topology and Dynamics

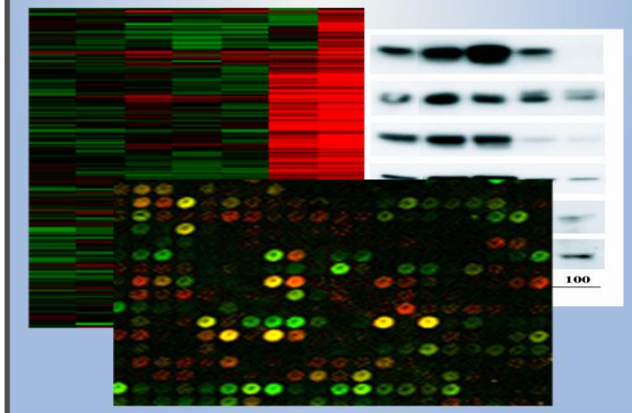
What is Systems Biology?

Biological Information



Cell & Molecular Interactions

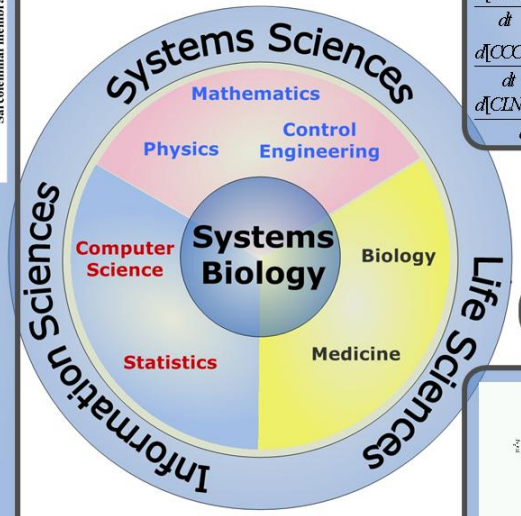
+



Experimental Data

Modeling

Analysis



Prediction

Verification

Mathematical Modeling

$$\frac{d[Ca^{2+}]}{dt} = -k_1[Ca^{2+}]^4[CaM] + k_{-1}[Ca^{2+}/CaM]$$

$$\frac{d[CaM]}{dt} = -k_1[Ca^{2+}]^4[CaM] + k_{-1}[Ca^{2+}/CaM]$$

$$\frac{d[Ca^{2+}/CaM]}{dt} = k_1[Ca^{2+}]^4[CaM] - k_{-1}[Ca^{2+}/CaM] - k_2[Ca^{2+}/CaM][CLN]$$

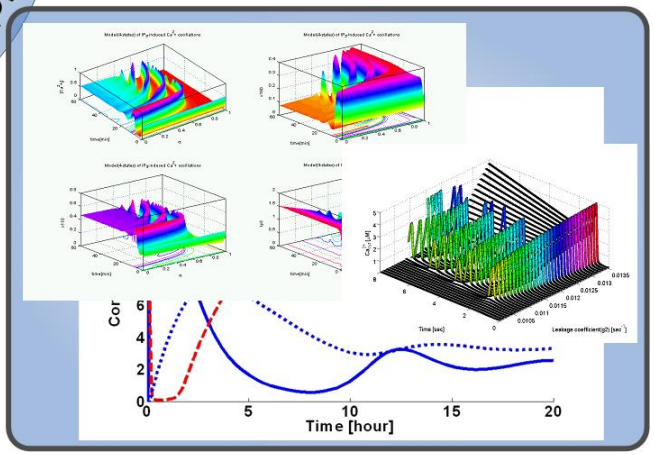
$$\vdots$$

$$\frac{d[MCIP]}{dt} = \frac{V_{max}[NFAT_{cyt}(t-\tau)]^6}{[NFAT_{cyt}(t-\tau)]^6 + K_6} - k_3[CLN/Ca^{2+}/CaM][MCIP]$$

$$\frac{d[CCCM]}{dt} = k_3[CLN/Ca^{2+}/CaM][MCIP] - k_{-3}[CLN/Ca^{2+}/CaM/MCIP]$$

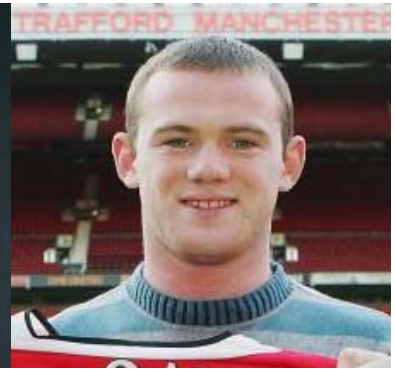
$$\frac{d[CLN/MCIP]}{dt} = -k_5[Ca^{2+}/CaM][CLN/MCIP] + k_{-5}[CLN/Ca^{2+}/CaM/MCIP] + \dots$$

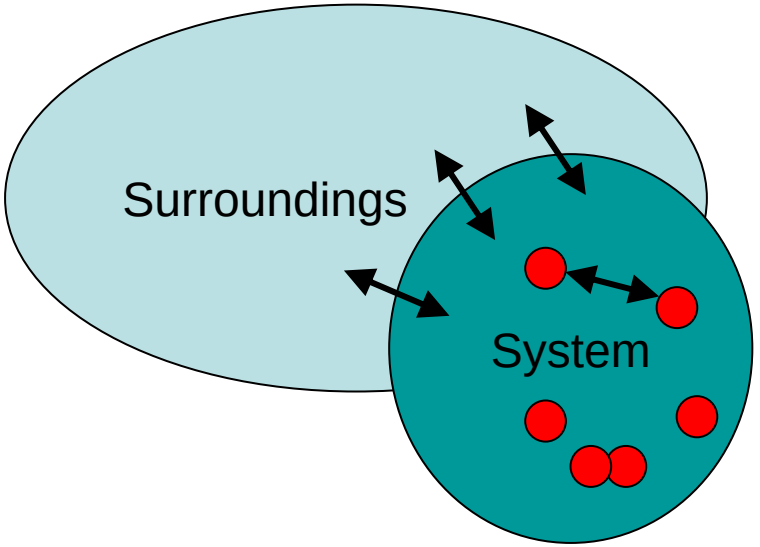
Simulation & Analysis



If we have all the information on each player in a soccer team. Then, can we predict the play of this team?



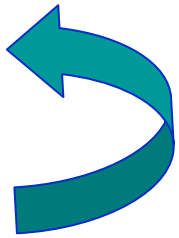



Systems Biology Research

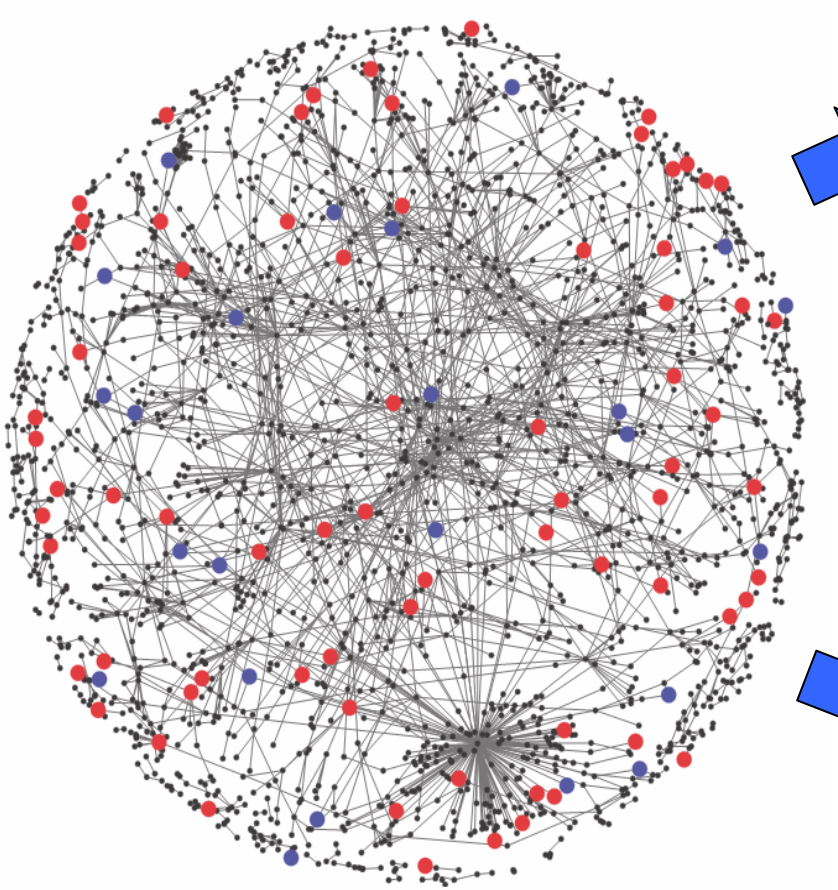
The Prerequisites:

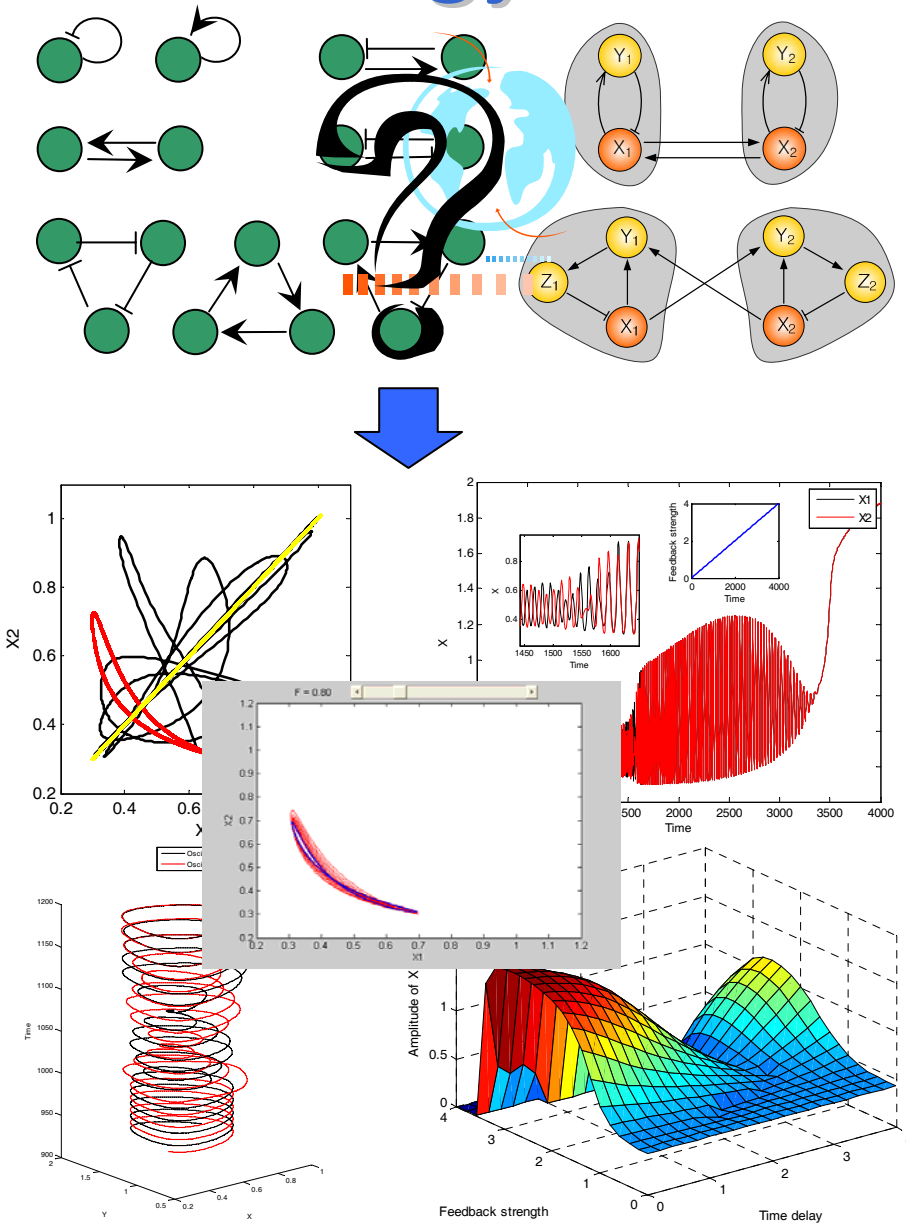
"Experiments" should be quantitative!

"Modeling" should be predictive!

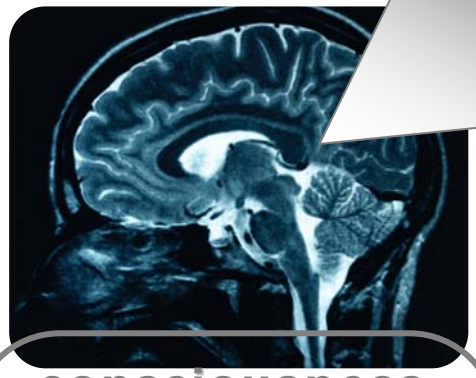


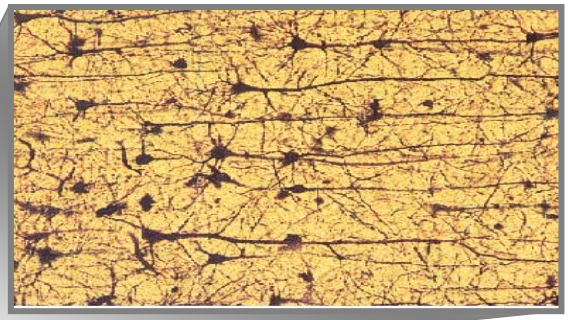
Network Systems Biology

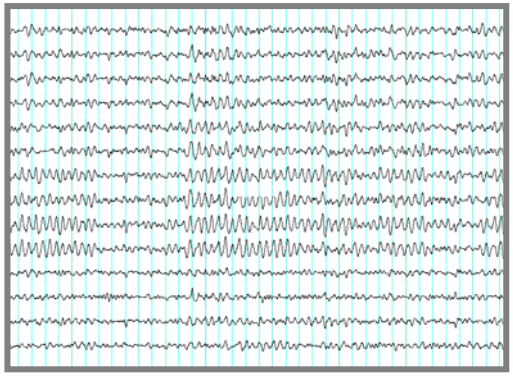


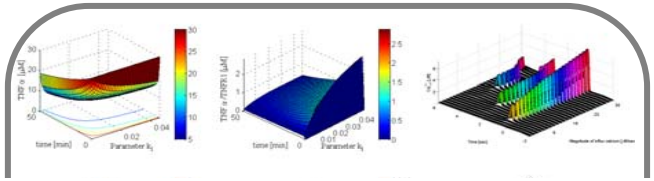


Brain Systems Biology

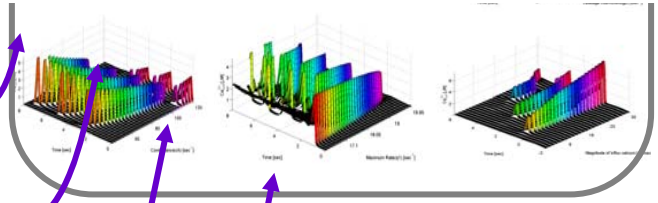


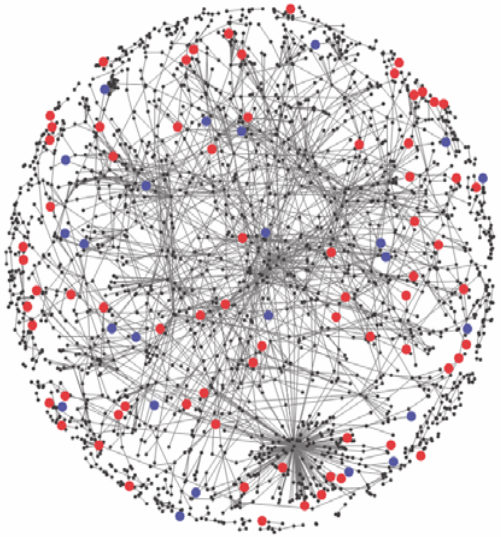






Emergent Properties





consciousness

decision making

creative thinking

memory

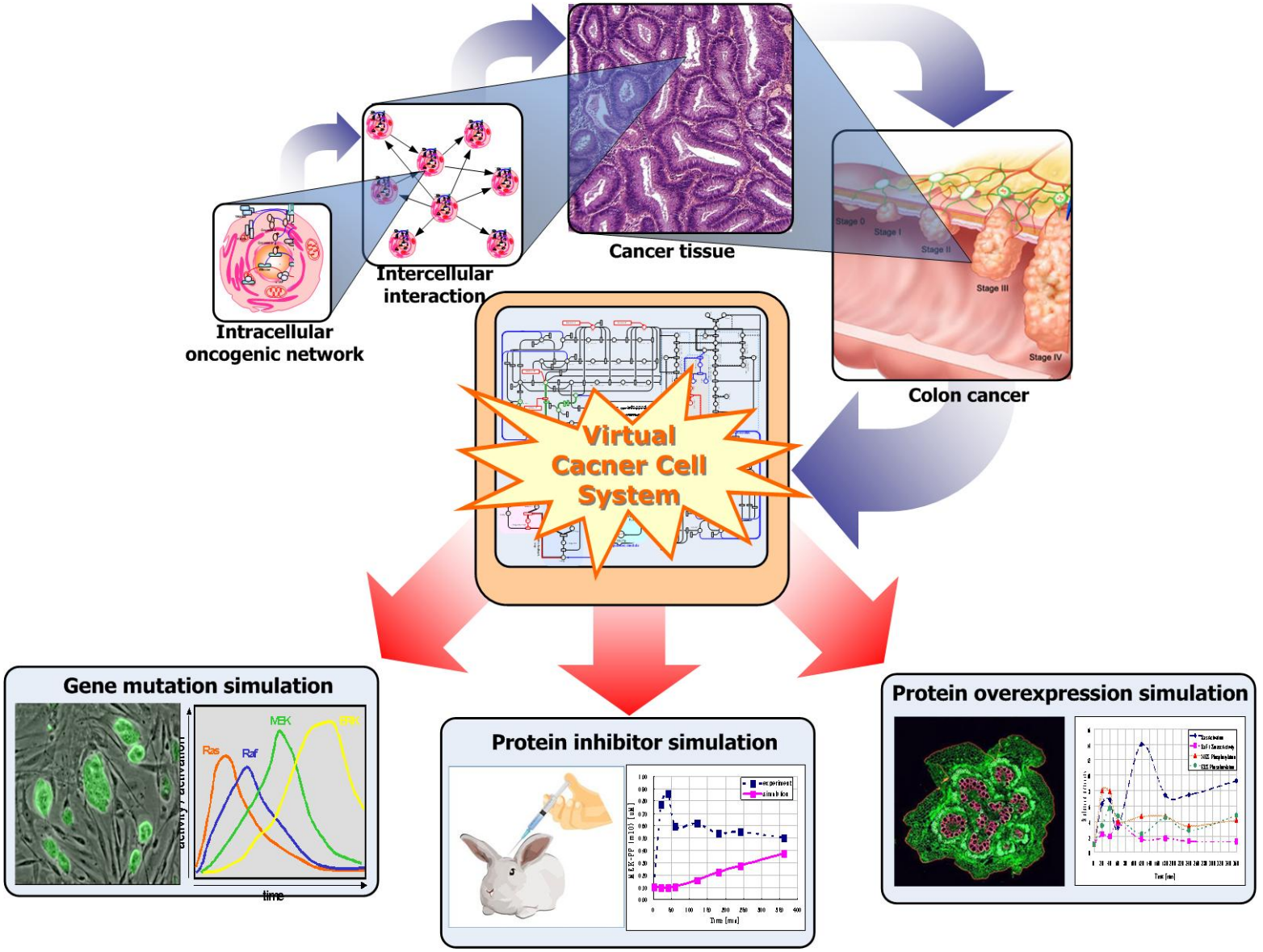
learning

recognition

⋮

Brain Functions

Cancer Systems Biology

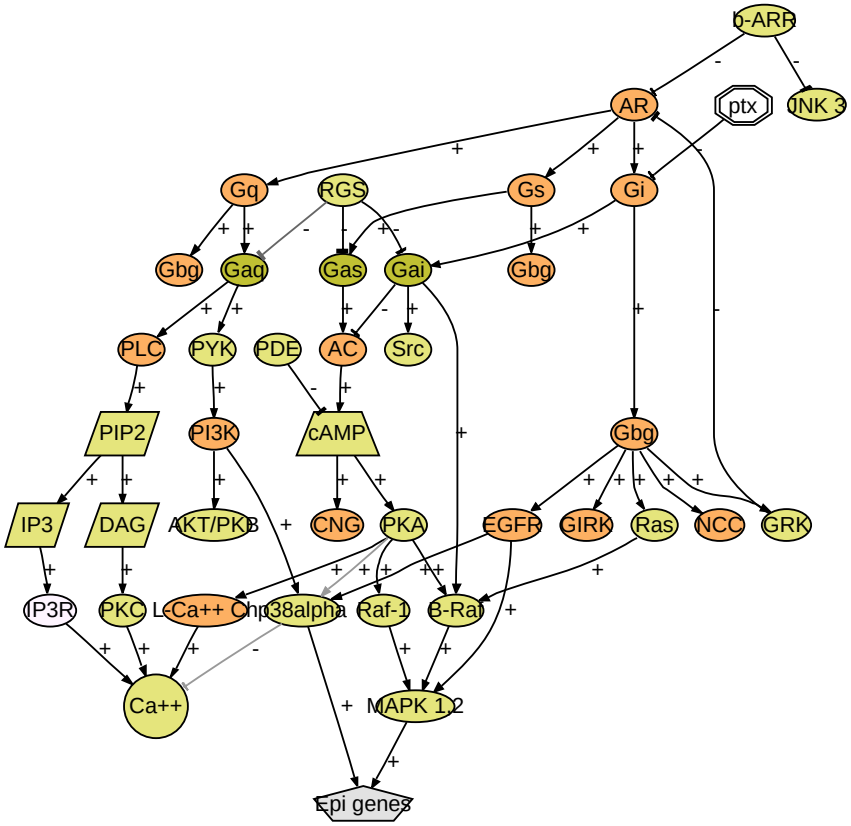


Biological Networks

Node
- Protein
- Gene
- Metabolite
- mRNA
- ...

Link
- Protein-protein interaction (PPI)
- Protein-DNA interaction
- Enzyme reaction
- …

Examples
- Protein-protein interaction network
- Signaling pathway
- Gene regulation network (GRN)
- Metabolic network (pathway)



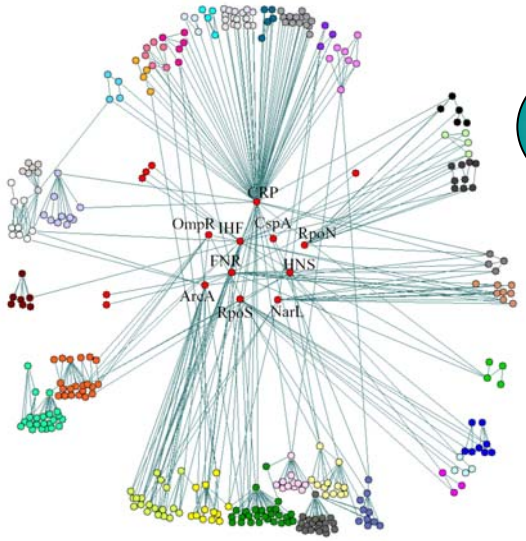
Adrenergic Pathway (STKE)

Gene Regulation Network

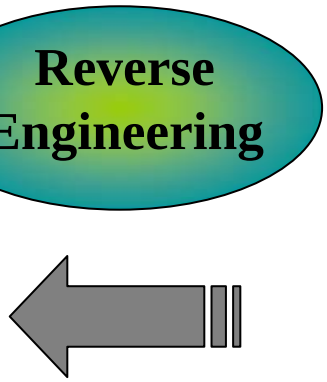
- Genes are able to regulate one another's expression levels via proteins called *transcription factors*.
- We will call the set of genes that regulate transcription of a specific gene its *regulators*.
- The network of regulatory relations among genes throughout the genome is called a *gene regulation network*.

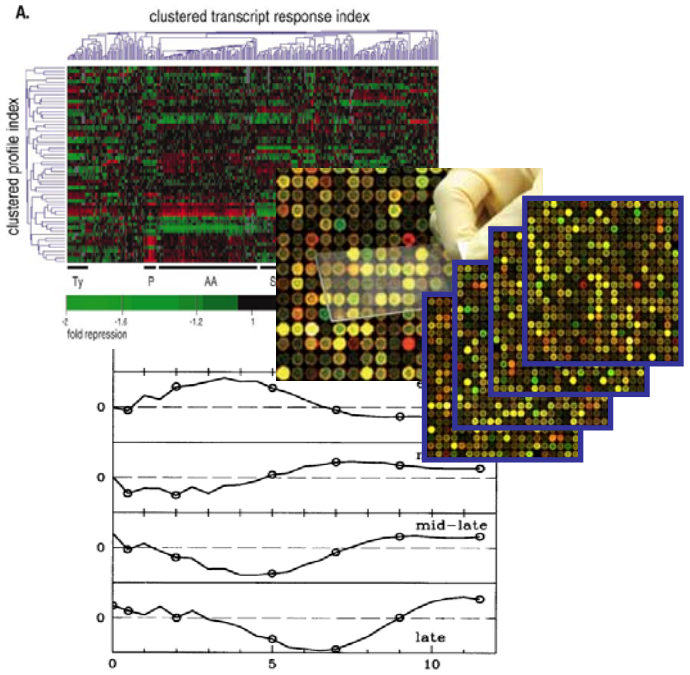
Reverse Engineering

Reverse Engineering means building a network structure from the observed gene expression patterns.



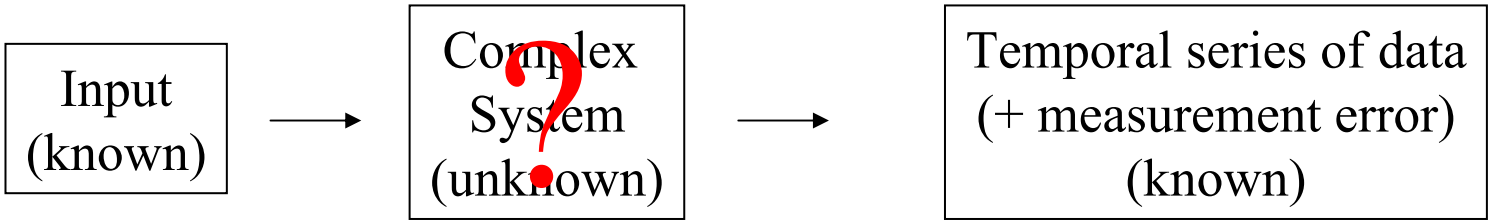
Network structure



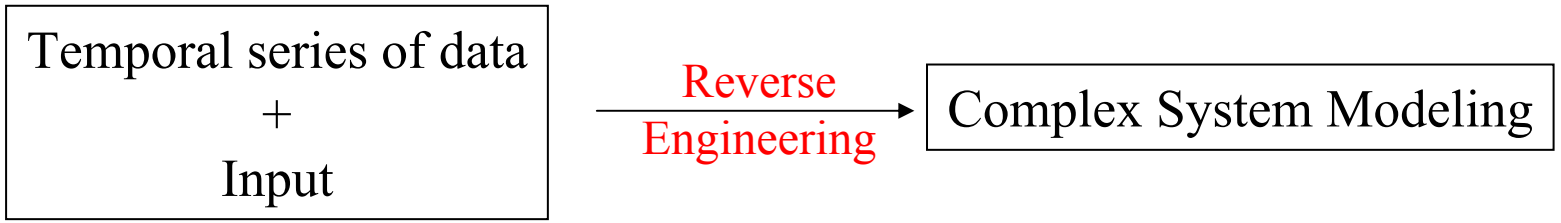


Observed data

Reverse Engineering



Temporal dynamics, between one state of the system and another, are necessary to infer the structure of the system.

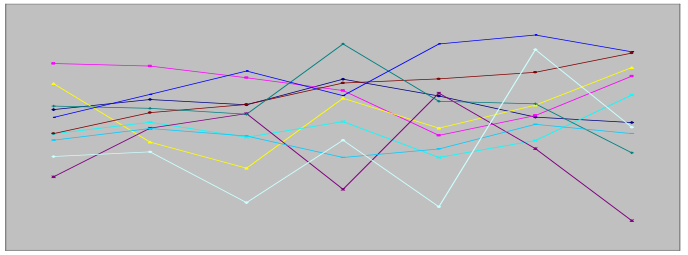


Reverse Engineering of Gene Regulatory Network

- Problems
  - Too many genes
  - Too few measurements
  - Missing and incorrect values
  - Complexity (time/space)
- Various Approaches
  - Logical rules (Boolean network)
  - Statistical approach (Bayesian network, dynamic Bayesian network)
  - Differential equation model (linear or nonlinear models)
  - Neural network (nonlinear model)
  - Genetic algorithm

Reverse Engineering

- Reverse engineering biomolecular regulatory networks uses the followings as input data:
  - Experimental expression profiles
    - cDNA Microarray data
    - ChIP-chip data
  - Sequence or annotations
    - Binding motif
    - Gene annotations

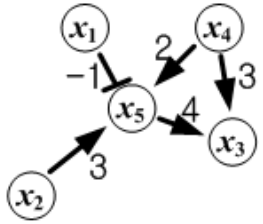


Input

Reverse engineering

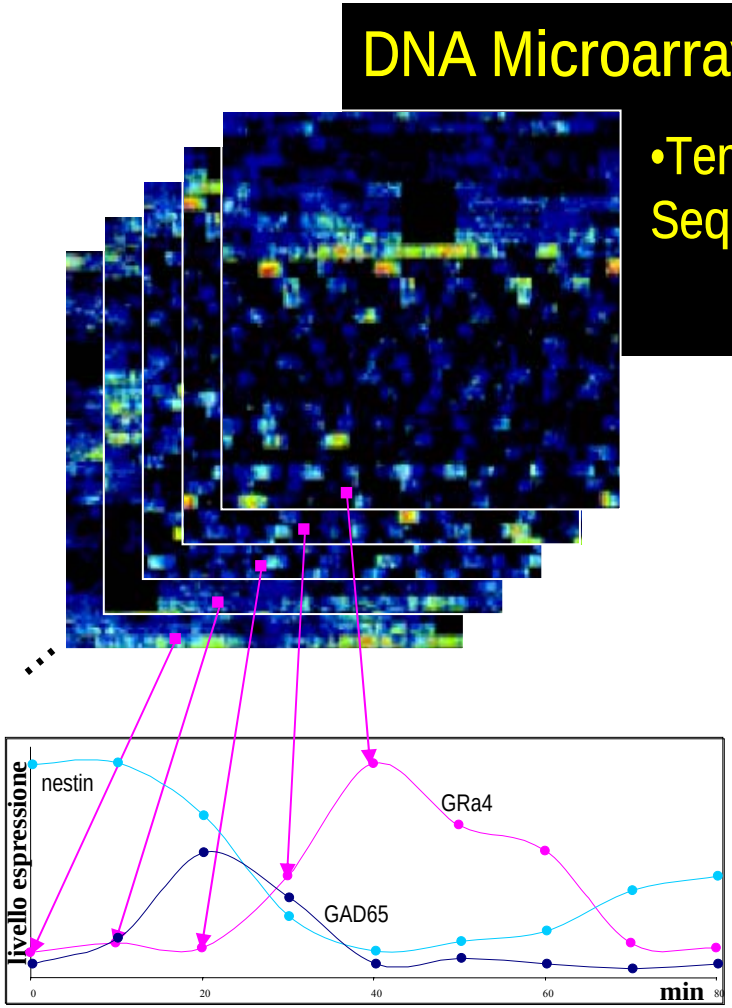
- The output of reverse engineering biomolecular networks can be
  - Directed or undirected graph
  - Adjacency matrix
  - Regulation matrix
  - Interaction network of modules

$$\begin{pmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 3 & 4 \\ 0 & 0 & 0 & 0 & 0 \\ -1 & 3 & 0 & 2 & 0 \end{pmatrix}$$

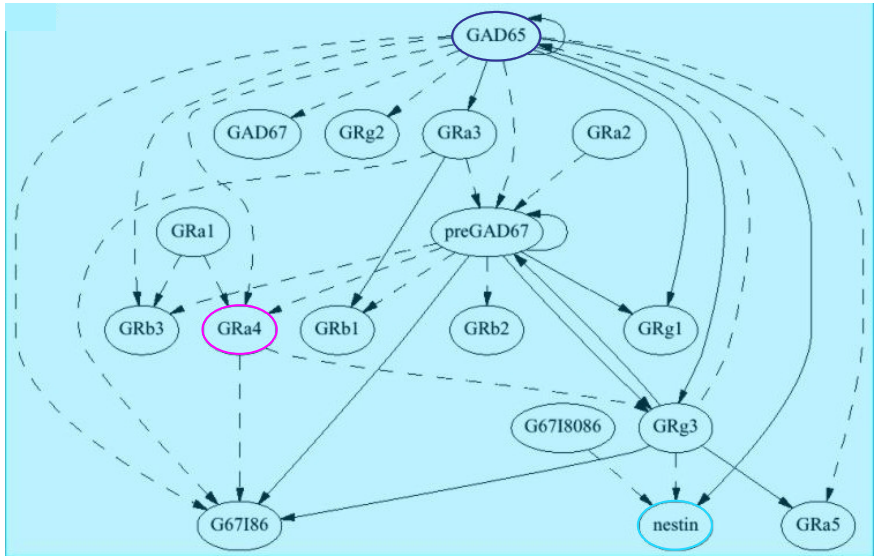


Output

From Microarray Data to the Gene Network



REVERSE ENGINEERING NETWORKING



Differential Equation Model

$$\frac{dx_i(t)}{dt} = R_i \cdot f\left(\sum_{j=1}^{N} w_{ij} \cdot x_j(t) + \sum_{k=1}^{K} v_{ik} \cdot u_k(t) + B_i\right) - \lambda_i \cdot x_i(t)$$

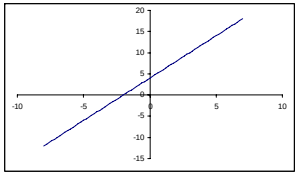
Activation constant gene i

Control strength of gene j on gene i

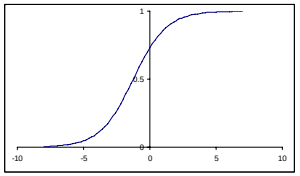
External input and their control strength on i

Gene i degradation law

Activation function of gene i



Linear f(.)



Sigmoidal f(.)

Gene j expression level

Gene i basal activation level

Reverse Engineering Methods

- Boolean Method
  - Discretized expression levels
  - Find a Boolean function explaining the relationships of discretized data
- Bayesian Method
  - Use the Bayesian rules
  - Network learning
- Regulation Matrix Method
  - Assume a nonlinear ODE model

$$\frac{dX}{dt} = f(X, P)$$

  - Linearize the nonlinear model near steady states

$$\frac{dX}{dt} = AX$$

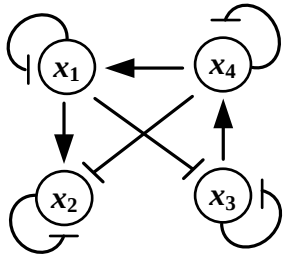
or

$$X_{t+1} = AX_t$$

  - Find a regulation matrix A

Regulation Matrix Methods #1

- Van Someren et al. (Proc. ICSB, 2000)
  - Time-series data
  - Solve $X_{t+1} = AX_t$
  - Reduce the network size (clustering)
  - Transform under-determined problems into over-determined problems



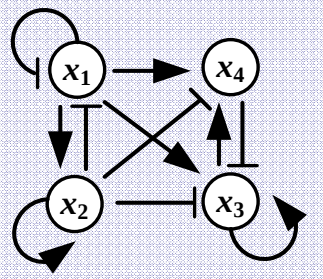
True network

$$X_1 = (0.19 \quad 0.03 \quad 0.97 \quad 0.48)^T$$
$$X_2 = (0.24 \quad 0.08 \quad 1.01 \quad 0.53)^T$$
$$X_3 = (0.29 \quad 0.12 \quad 1.05 \quad 0.58)^T$$
$$X_4 = (0.33 \quad 0.16 \quad 1.09 \quad 0.62)^T$$
$$X_5 = (0.37 \quad 0.20 \quad 1.12 \quad 0.66)^T$$

Find A such that

$$AX_t = X_{t+1}$$
$$(t = 1, 2, 3, 4)$$

$$A = \begin{pmatrix} -1.03 & -0.11 & 0.05 & -0.01 \\ 0.13 & 0.78 & 0.04 & -0.02 \\ 2.12 & -0.93 & 1.64 & -1.96 \\ 0.99 & -0.42 & 0.36 & -0.02 \end{pmatrix}$$



Regulation Matrix Methods #2

- Yeung et al. (PNAS, 2002)
  - Steady state data
  - Solve $\frac{dX}{dt} = AX + B$
  - Singular Value Decomposition

$$x_0 = \begin{pmatrix} 0.19 & 0.03 & 0.97 & 0.48 \end{pmatrix}^T$$

$$X = \begin{pmatrix} 0.48 & 0.20 & 0.26 \\ 0.07 & 0.03 & 0.03 \\ 0.91 & 1.26 & 0.96 \\ 0.47 & 0.53 & 0.78 \end{pmatrix}$$

$$B = \begin{pmatrix} 0.50 & 0.00 & 0.00 \\ 0.00 & 0.00 & 0.00 \\ 0.00 & 0.50 & 0.00 \\ 0.00 & 0.00 & 0.50 \end{pmatrix}$$

(i) Use SVD to decompose X^T

$$X^T = UWV^T$$

(ii) Find a special solution A_0 of $\dot{X} = AX + B$

$$A_0 = \left(\dot{X} - B\right) U \, \mathrm{diag}\left(1/w_j\right) V^T$$

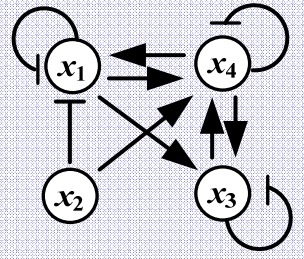
with $1/w_j$ taken to be zero if $w_j = 0$

$$\Rightarrow A = A_0 + CV^T \text{ is the general solution}$$

$$(C = (c_{ij}) \text{ where } c_{ij} = 0 \text{ if } j < \dim(\ker(X^T)))$$

(iii) Find A such that A is as sparse as possible

$$A = \begin{pmatrix} -1.34 & -0.48 & 0.03 & 0.45 \\ 0.03 & -0.04 & -0.00 & -0.01 \\ 0.71 & 0.08 & -0.75 & 0.68 \\ 0.28 & 0.20 & 0.51 & -1.29 \end{pmatrix}$$



Regulation Matrix Methods #3

- Kholodenko et al. (PNAS, 2002)
  - Parameter perturbation data
    - Steady state data before/after perturbation
  - Construct an interaction network of gene modules
    - Calculate global interactions R_p
    - Calculate local interactions using chain rules

$$x_0 = \begin{pmatrix} 0.19 & 0.03 & 0.97 & 0.48 \end{pmatrix}^T$$

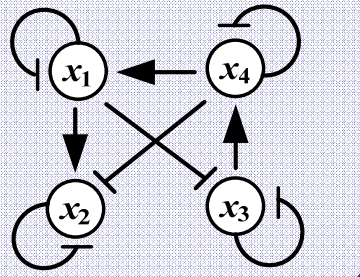
$$X_p = \begin{pmatrix} 0.27 & 0.19 & 0.30 & 0.32 \\ 0.05 & 0.04 & 0.06 & 0.06 \\ 0.93 & 0.97 & 1.38 & 0.91 \\ 0.47 & 0.48 & 0.65 & 0.68 \end{pmatrix}$$

$$R_p = \left(R_{ij} \right)$$

$$R_{ij} \approx 2 \frac{\dfrac{x_i^s\left(p_j + \Delta p_j\right)}{x_i^s\left(p_j\right)} - 1}{\dfrac{x_i^s\left(p_j + \Delta p_j\right)}{x_i^s\left(p_j\right)} + 1}$$

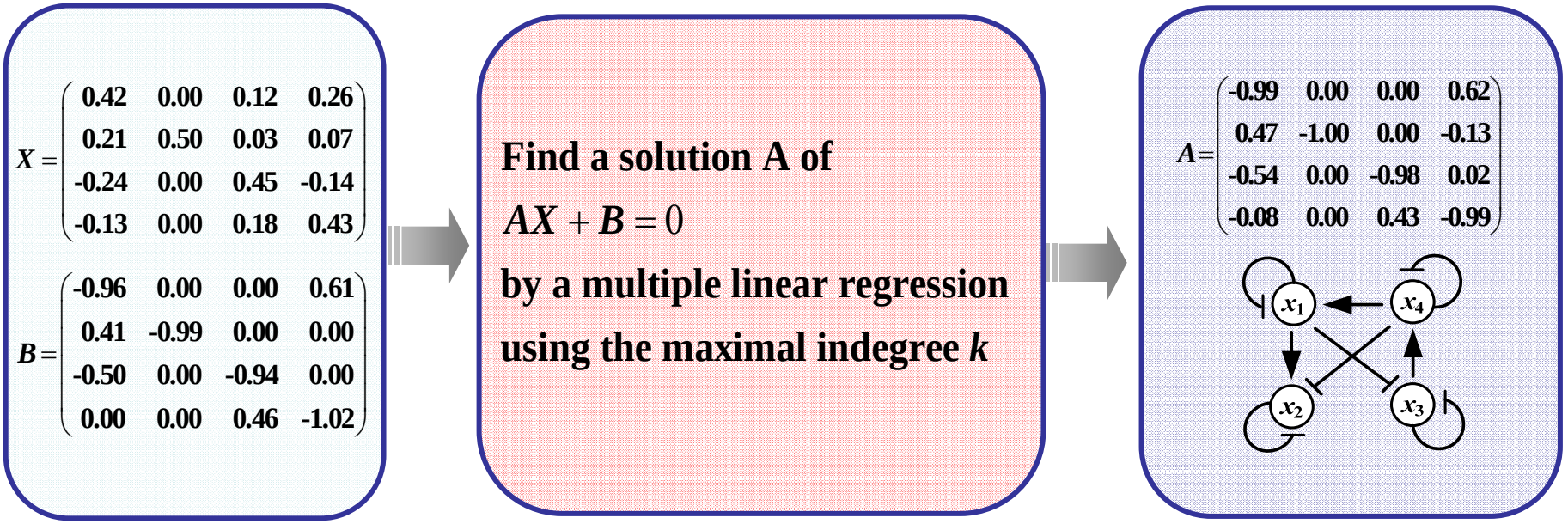
$$A = -\left[\mathrm{diag}\left(R_p^{-1} \right) \right]^{-1} R_p^{-1}$$

$$A = \begin{pmatrix} -1.00 & 0.00 & 0.01 & 1.49 \\ 1.84 & -1.00 & 0.02 & -0.49 \\ -0.10 & 0.00 & -1.00 & -0.03 \\ 0.02 & 0.00 & 0.88 & -1.00 \end{pmatrix}$$



Regulation Matrix Methods #4

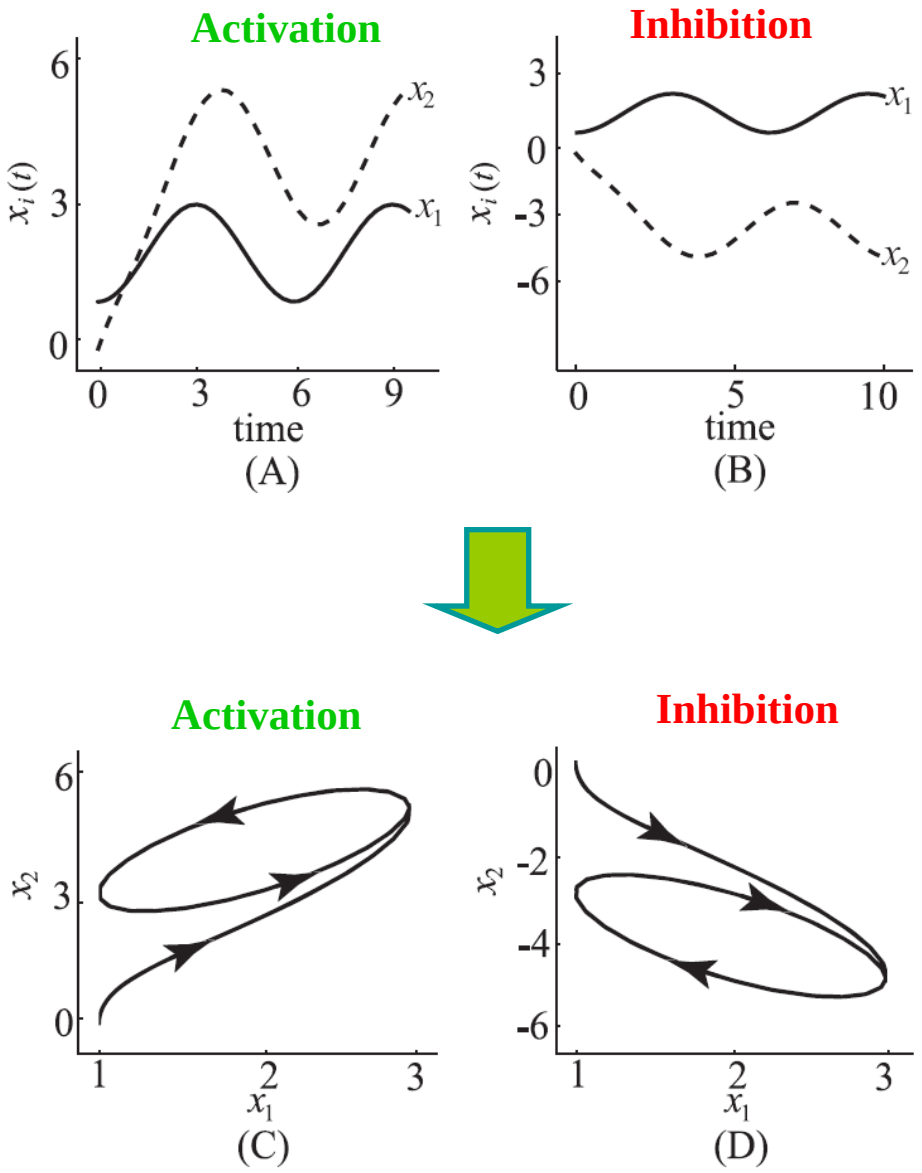
- Gardner et al. (Science, 2003)
  - Solve $0 = \frac{dX}{dt} = AX + B$
  - Biomolecular networks are mostly sparse
    $\Rightarrow$ Introduce a maximal indegree constraint
  - Multiple linear regressions



Limitations in Reverse Engineering

- Intrinsic noise
- Experimental noise
- Various time delays between nodes
- Time complexity
- Insufficient data for large scale networks
- Sometimes, non-deterministic regulations

Inferring Biomolecular Regulatory Networks from Time-Series Expression Profiles



Inferring Biomolecular Regulatory Networks from Time-Series Expression Profiles

- Two measures to quantify the interaction properties and to systematically infer the regulatory relation: **slope index (SI)** and **winding index (WI)**.
- **SI** : a measure to determine the regulatory type (activation or inhibition)
- **WI** : a measure for the direction of such regulation.

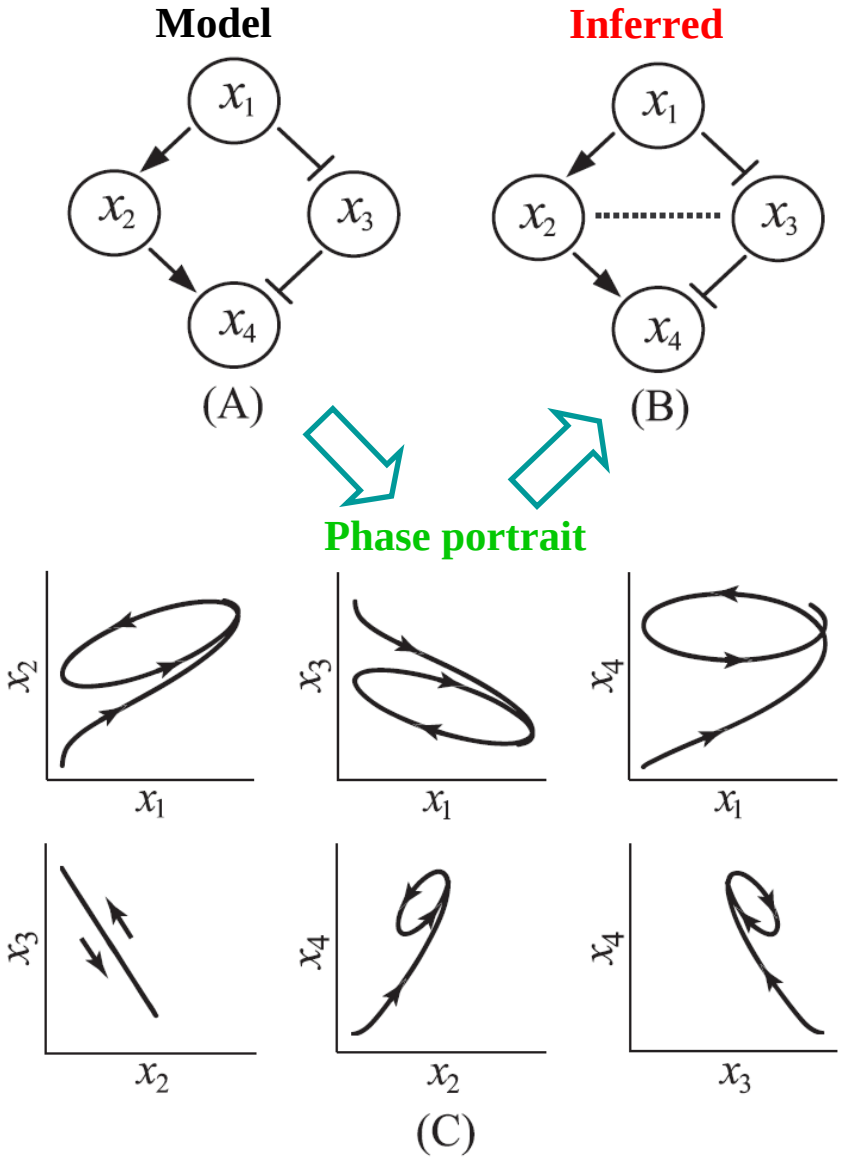
$$SI(x_1, x_2) = \frac{1}{k-1} \sum_{i=1}^{k-1} \text{sign}\left(\frac{x_2(i+1) - x_2(i)}{x_1(i+1) - x_1(i)}\right)$$

$$WI(x_1, x_2) = \frac{1}{k-2} \sum_{i=1}^{k-2} \text{sign}(d(i))$$

$$d(i) = \det \begin{bmatrix} x_1(i) & x_1(i+1) & x_1(i+2) \\ x_2(i) & x_2(i+1) & x_2(i+2) \\ 1 & 1 & 1 \end{bmatrix}$$

Inferring Biomolecular Regulatory Networks from Time-Series Expression Profiles

- A synthetic gene network of four nodes

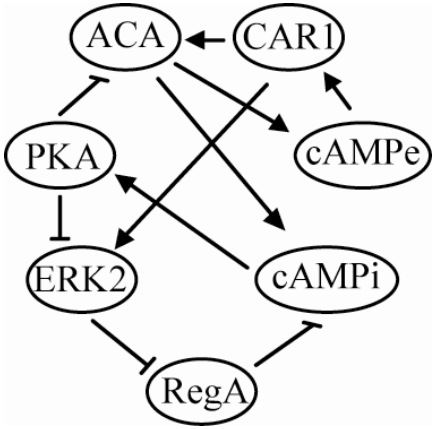


- Fig. (A) is the posited regulatory network of example system.
- Fig. (C) shows corresponding phase portraits. We can presume activating regulations in (x_1,x_2), (x_2,x_4), and inhibiting regulations in (x_1; x_3), (x_2,x_3), (x_3, x_4).
- The inferred whole regulatory network is illustrated in Fig. (B)
- We compute the SI and WI for the phase portraits.

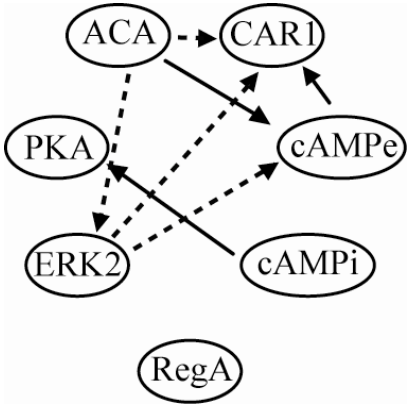
a \ b	x_1	x_2	x_3	x_4
x_1	-	0.4/0.8	-0.4/-0.8	0.0/0.8
x_2	0.4/-0.8	-	-1.0/0.0	0.6/1.0
x_3	-0.4/0.8	-1.0/0.0	-	-0.6/-1.0
x_4	0.0/-0.8	0.6/-1.0	-0.6/1.0	-

Example

- *Dictyostelium discoedium* Network



- Inferred Network



- Performance Comparison

	Bayesian network	Dynamic Bayesian network	The proposed scheme
True positive ratio	4/18 (22%)	2/9 (22%)	3/7 (43%)
True negative ratio	18/24 (75%)	25/33 (76%)	28/35 (80%)

Merits & Limitations

- Merits
  - Simple!
  - Low complexity!
  - Fast calculations!
  - Applicable to measuring time-delays!

- Limitations
  - … still cannot handle highly nonlinear networks
  - … still cannot handle systems with time-varying coefficients

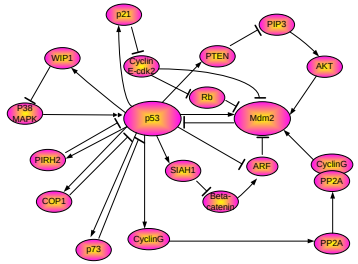
Network Motif

- Complex cellular behaviors can be seen as a result of interactions of numerous intracellular or extracellular biomolecules.
- To figure out cellular behaviors, it is important to investigate the topology of cellular circuits and corresponding dynamical characteristics.
- As a way of conducting such investigations, network motifs have been proposed and studied in various cellular circuits.
- Network motif examples
  - Feedforward loops in gene transcriptional networks
  - Feedback loops in signaling networks
- The dynamic characteristics of feedforward and feedback loops is well known.

A

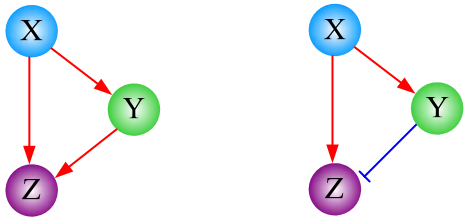
<Gene transcriptional network in *E. coli* >

B



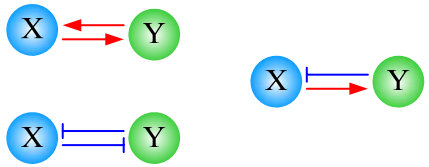
<p53 signaling network >

C



<Feedforward loops >

D

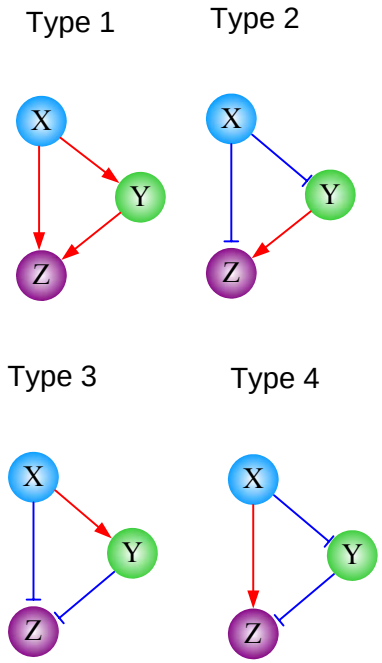


<Feedback loops >

Coherent Feedforward Loops

- There are 4 types of coherent feedforward loops (Fig. A)
- Coherent feedforward loops induces delays in response
  - AND logic case
    - Type 1 and Type 4 induce delays in response when the stimulation on X appears while Type 2 and Type 3 induce delays when the stimulation on X disappears (Fig. B)
  - OR logic case
    - Type 2 and Type 4 induce delays in response when the stimulation on X appears while Type 1 and Type 3 induce delays when the stimulation on X disappears (Fig. C)

A



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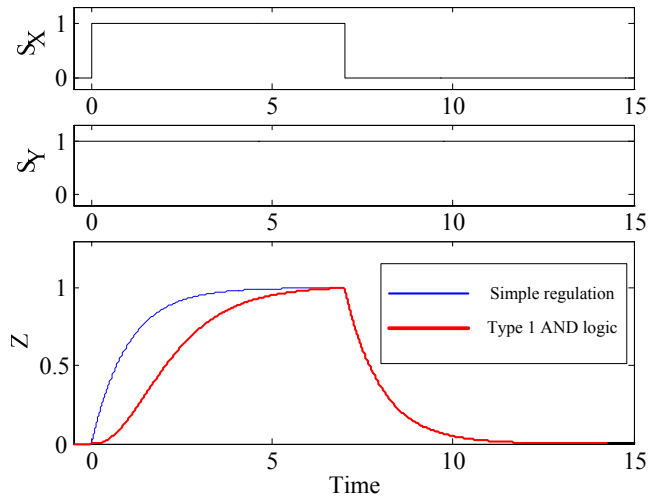

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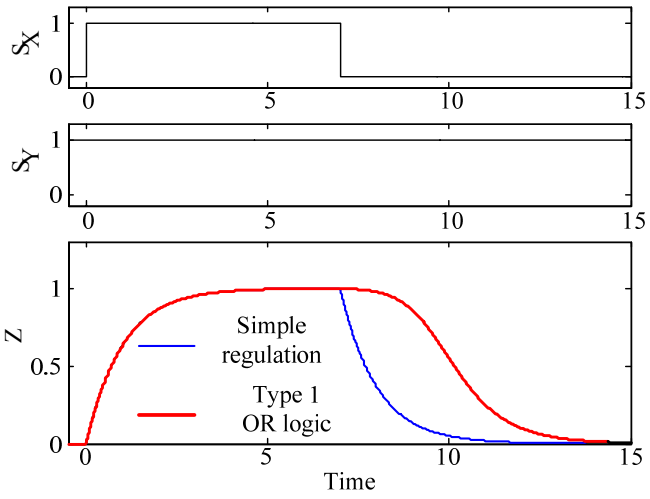
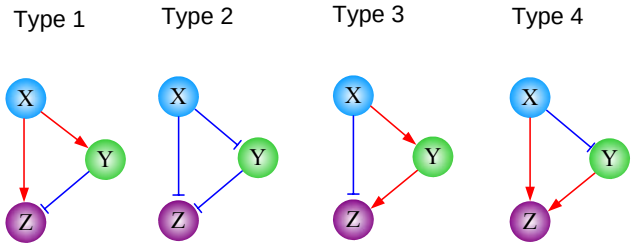


<S_X and S_Y denote the stimuli given on X and Y, respectively >

Incoherent Feedforward Loops

- There are 4 types of incoherent feedforward loops (Fig. A)
- Incoherent feedforward loops accelerate responses (Fig. B)
  - Type 1 and Type 4 accelerate responses when the stimulation appears while Type 2 and Type 3 accelerate responses when the stimulation disappears
- Incoherent feedforward loops induces biphasic responses
  - Temporal biphasic (Fig. C)
  - Dose (stimulus) biphasic (Fig. D)

A



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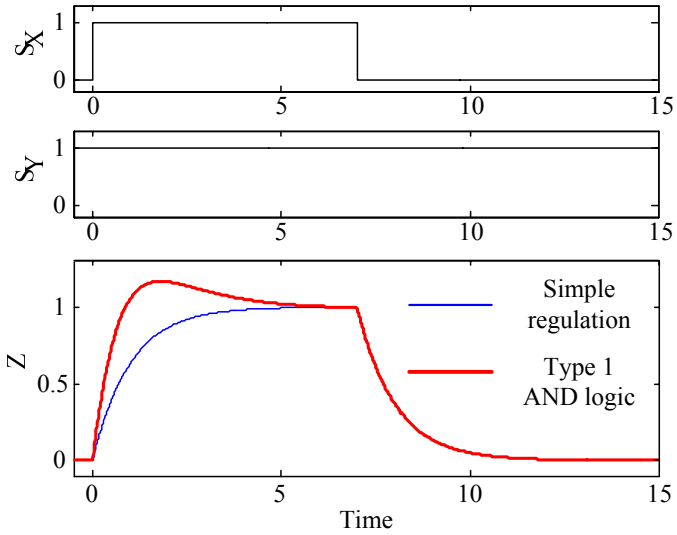
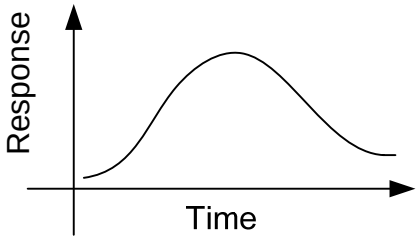


C



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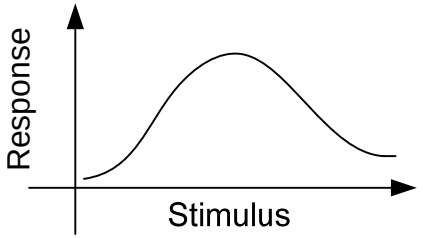
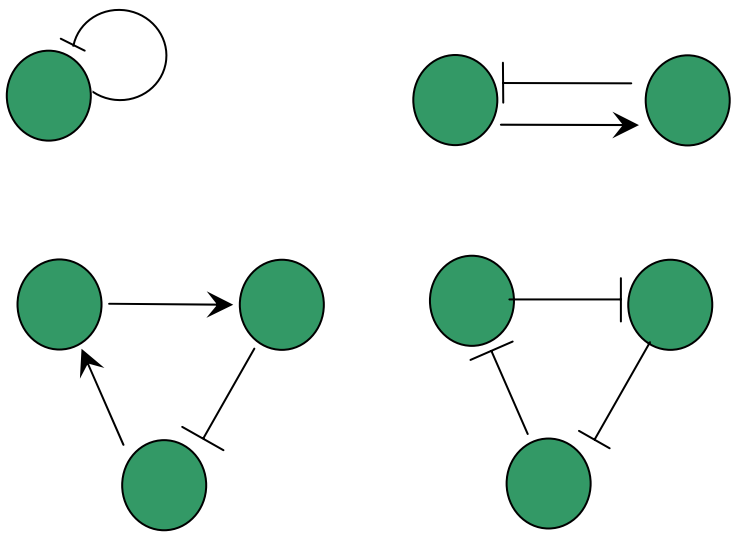
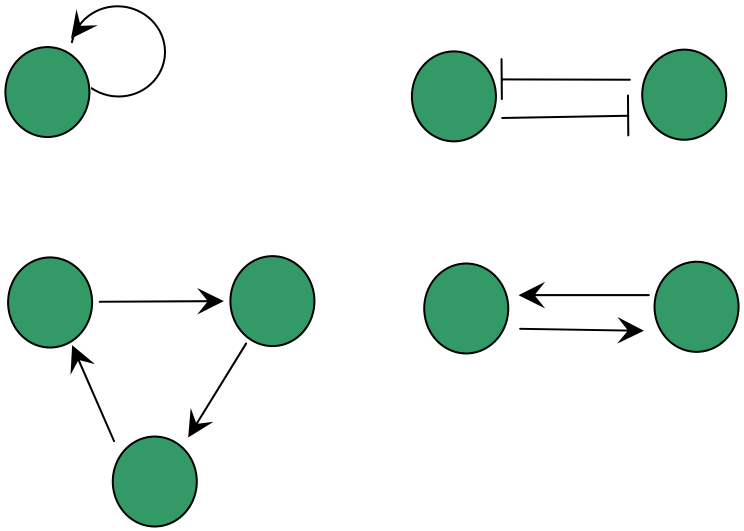


Feedback Loops

- Feedback loops may be positive or negative, depending upon the parity of the number of negative interactions in the loop.
- Negative feedback loops tend to act within biological systems to maintain homeostasis.
- Systems involving negative feedback loops tend to settle to a steady state.
- Positive feedback loops promote multistationarity; that is, the existence of a number of different stable states.



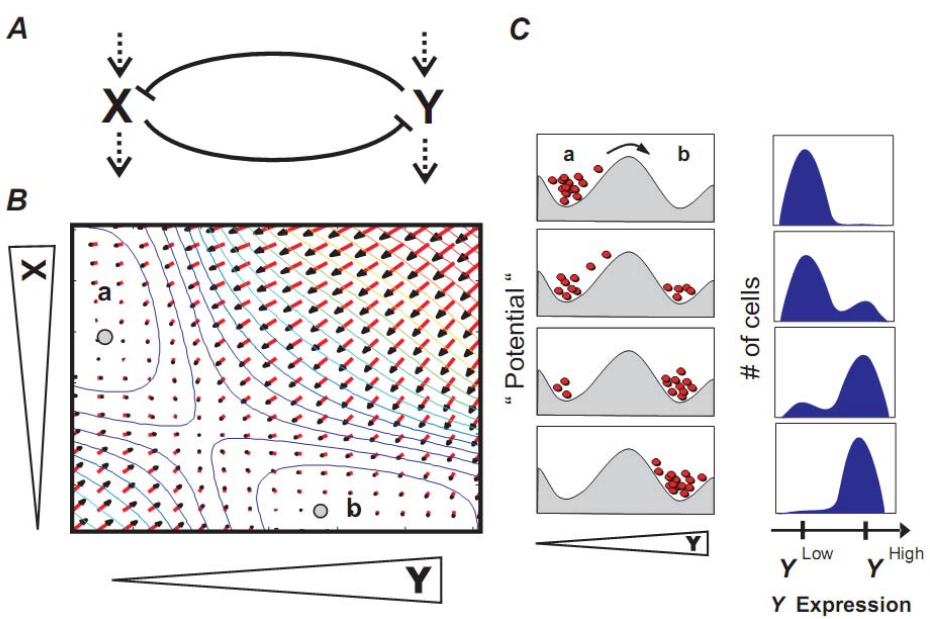
<Negative feedback>

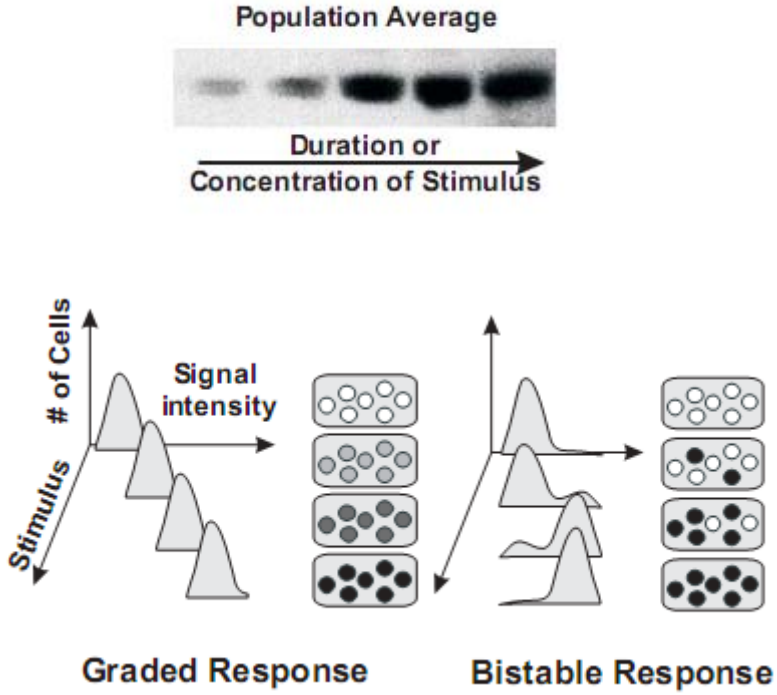


<Positive feedback>

Bistability (multistationarity)

- Multistationarity is essential to development, since different cell types represent different stable states in the gene expression space of the organism.
- Multistationarity is also fundamental to the development of bistable switches in regulatory networks, in which there are two stable states, between which the system can be moved by an external stimulus.



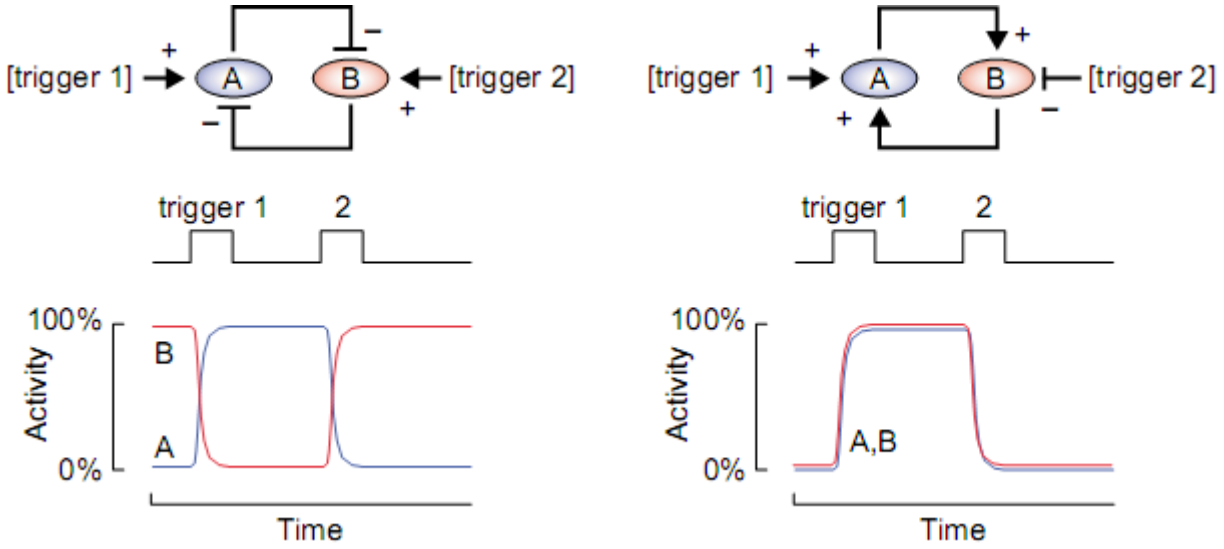


<Bistable dynamics in a double-inhibition feedback system>

(BMC Cell Biol. 7:11 (2006))

Positive Feedbacks and Memory

- Bistable switches induced by positive feedbacks are essentially a memory for the cell, since the state in which it finds itself is dependent upon the history of the system.

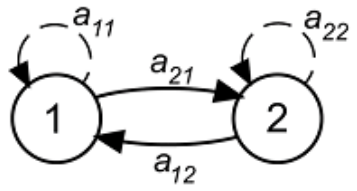


(Current Opinion in Chemical Biology 6:140-148 (2006))

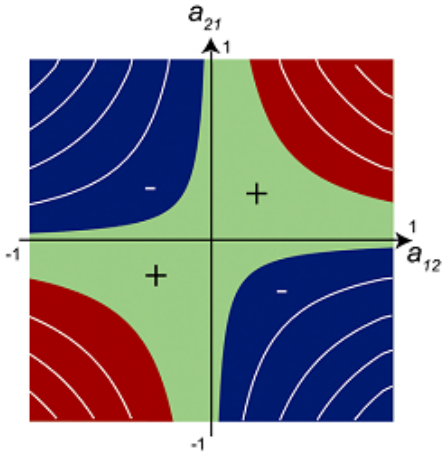
Dynamic Behaviors of a Two-Node Feedback Loop

- Consider a two-node feedback with nodes and edged labeled (assume $a_{ii}<0$ (i=1,2)) (Fig. A)
- $a_{12}*a_{21}<0$ => negative feedback (- region in Fig. B)
- $a_{12}*a_{21}>0$ => positive feedback (+ region in Fig. B)
- For small perturbation from steady-state, the system can be stable (green), oscillatory (blue), or unstable (red) (Fig. B).
- The stability regions vary as the values of self-degradation terms a_{11} and a_{22} change.
- The more stable the open-loop nodes (i.e., more negative a_{11} and a_{22}), the greater the regions of closed loop stability.
- However, if a_{11} and a_{22} are close in sign and magnitude, the size of the oscillatory regions increases.

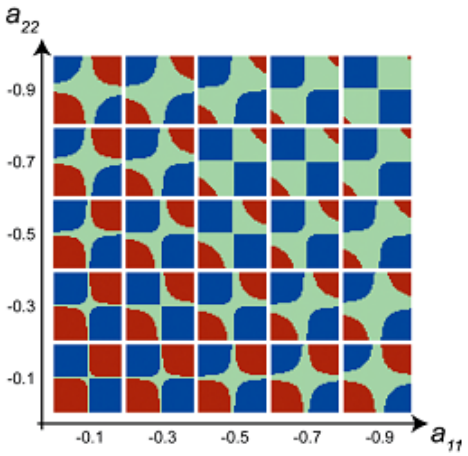
A



B



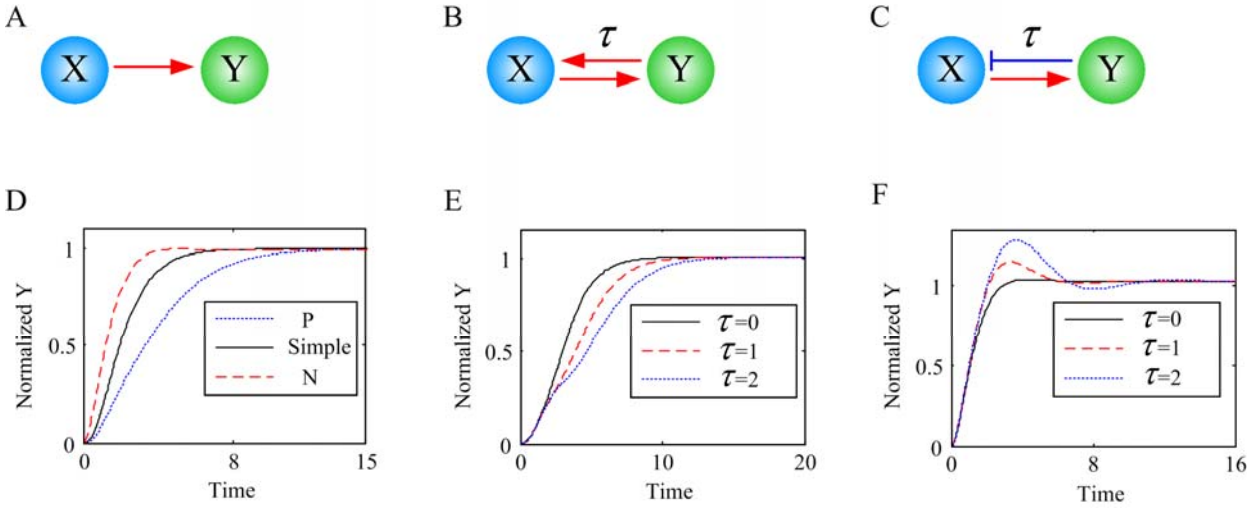
C



(PLoS Biology 3:11 (2005))

Single Feedback Loops

- The roles of positive feedback loops (Fig. B)
  - Signal amplification
  - Slow response (Fig. D)
  - Bistability & hysteresis
- The roles of negative feedback loops (Fig. C)
  - Homeostasis (oscillation & attenuation)
  - Signal adaptation or desensitization
  - Noise filters
  - Fast responses (Fig. D)
- The time delays between nodes in a feedback loop affect its dynamics
- Larger time delays between nodes in a positive feedback loop induce slower responses (Fig. B &E)
- Larger time delays between nodes in a negative feedback loop induce oscillations with larger amplitudes (Fig. C & F)

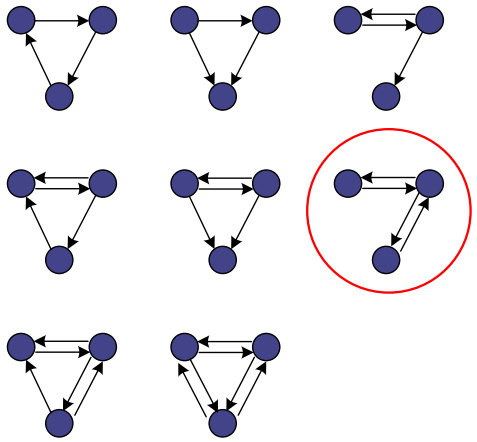


<Single feedback loops and their dynamical properties >

Coupled Feedback Loops

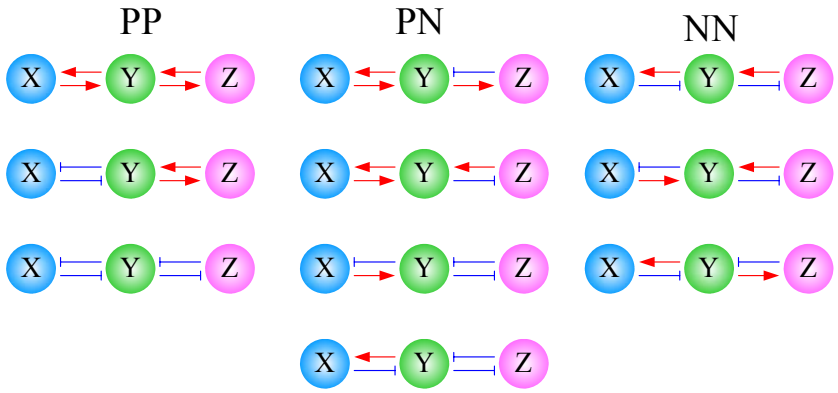
- Feedback loops have been considered as playing important roles in keeping cellular homeostasis, producing sustained oscillations, and making critical decisions such as cell fate decision and cell development decision.
- Interestingly, feedback loops are often found as a coupled structure rather than a single isolated form in various cellular circuits. What does it mean?
- We can represent such coupled feedback loops with topologically equivalent three-node networks by simplifying serial connections (Fig. A)
- Three basic modules of the coupled feedback structures : PP, PN, and NN (Fig. B)

A



<All possible network structures with three nodes >

B



<Coupled feedback structures >

Mathematical modeling

- X activates Y

$$dY/dt = V_X (X / K_{XY})^H / 1 + (X / K_{XY})^H - K_{dY} Y + K_{bY}$$

- X represses Y

$$dY/dt = V_X / 1 + (X / K_{XY})^H - K_{dY} Y + K_{bY}$$

- Both X and Z activate Y

$$dY / dt = V_Y ((X / K_{XY})^H + (Z / K_{ZY})^H) / (1 + (X / K_{XY})^H + (Z / K_{ZY})^H) - K_{dY} Y + K_{bY}$$

- Both X and Z repress Y

$$dY / dt = V_Y / (1 + (X / K_{XY})^H + (Z / K_{ZY})^H) - K_{dY} Y + K_{bY}$$

- X activates Y but Z represses Y

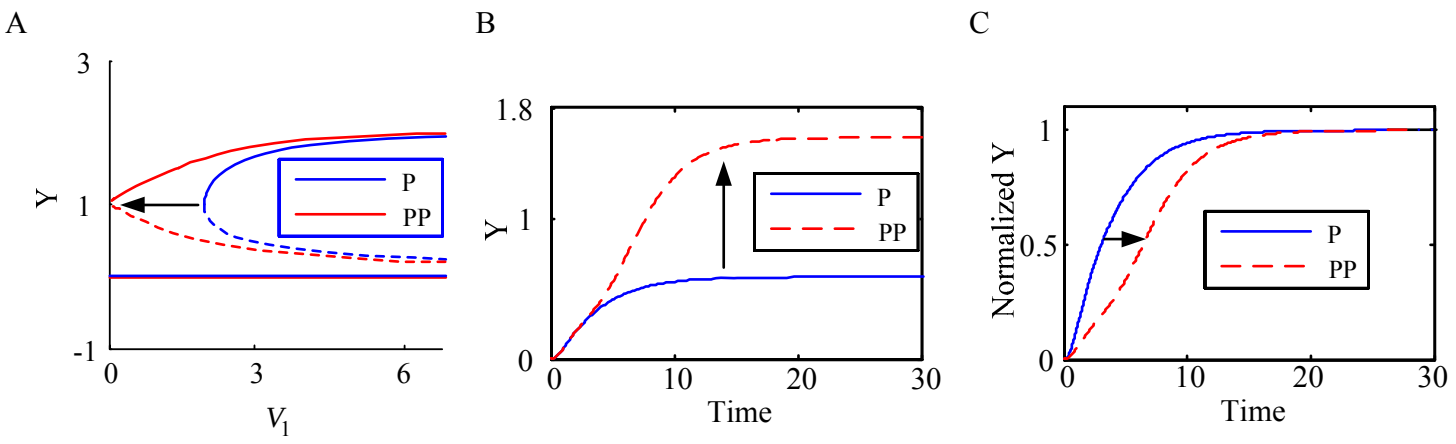
$$dY / dt = V_Y (X / K_{XY})^H / (1 + (X / K_{XY})^H + (Z / K_{ZY})^H) - K_{dY} Y + K_{bY}$$

Coupled Feedbacks: PP

- Example circuits of PP.

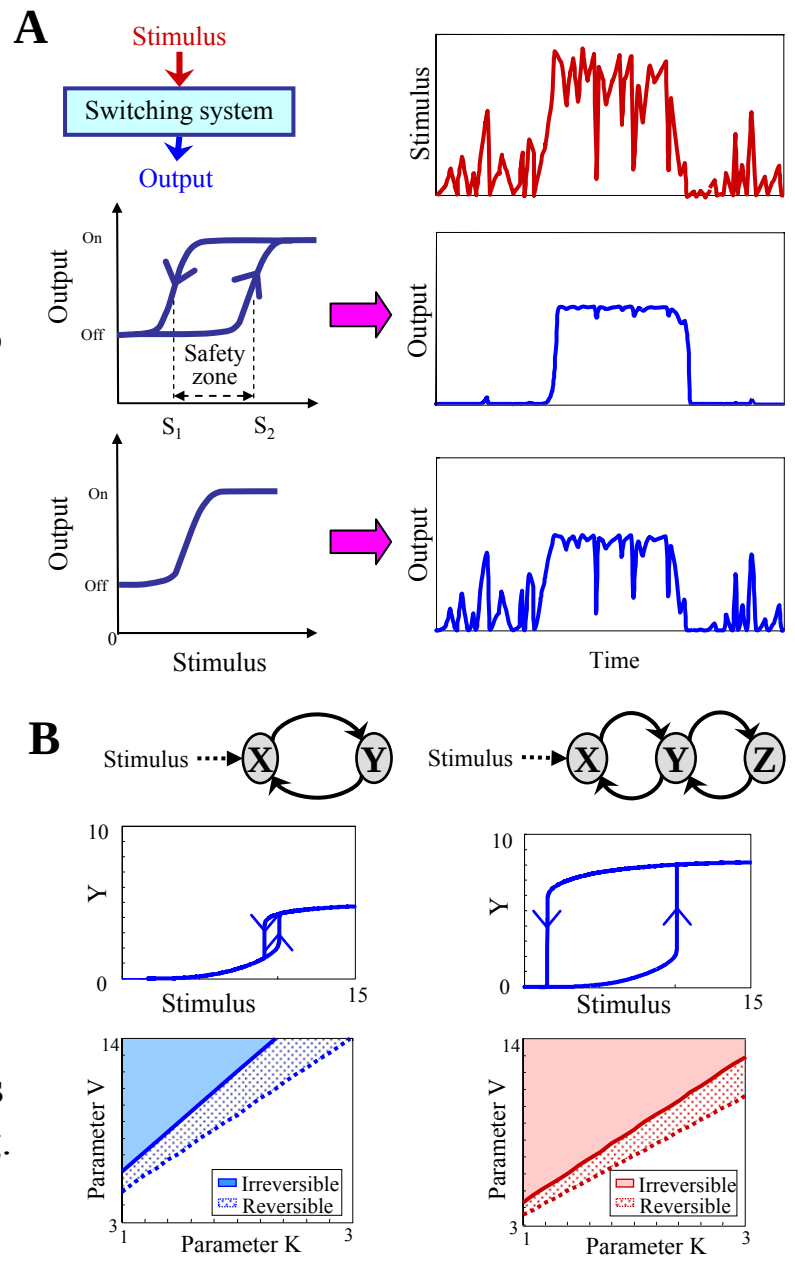
Related network	Coupled feedback loops	Related network	Coupled feedback loops
Ca2+ spikes /oscillations	IP3R → Ca^{2+}_{cyt} → IP3R RYR → Ca^{2+}_{cyt} → RYR	Mitotic trigger in *Xenopus*	Weel ⊣ cdc2 ⊣ weel Cdc25 → cdc2 → Cdc25
Muscle cell fate specification	CDO → MyoD → CDO Akt2 →MyoD → Akt2	Mitotic trigger in *Xenopus*	Myt1 ⊣ cdc2 ⊣ Myt1 Cdc25 → cdc2 → Cdc25
Muscle cell fate specification	CDO → MyoD → CDO Myostain → MyoD → Myostain	Start of cell cycle in budding yeast	Sic1 ⊣ cdc28 ⊣ Sic1 Cln → cdc28 → Cln
Galactose-signaling network in yeast	Gal3 → Gal4 →Gal3 Gal2 → Gal4 → Gal2	*B. subtilis* competence event	RoK ⊣ ComK ⊣ RoK ComK → ComK
Kallikrein-kinin system	PLAT → PLG → PLAT F12 → PLG → F12	Th1 and Th2 differentiation	STAT6 → GATA3 → STAT6 STAT4 ⊣ GATA3 ⊣ STAT4

- PP enhances bistability (Fig. A)
- PP induces a slower but amplified signal response (Fig. B & C)



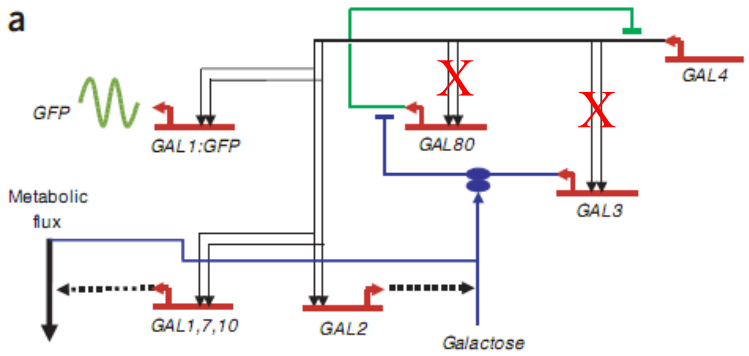
PP and Hysteretic Switching

- Hysteretic switching systems show different stimulus-response characteristics depending on the increasing or decreasing direction of stimulus profiles
- A hysteretic switching system with a wider range of safety zone can suppress the chattering over a wider range of stimuli and, as a result, can be more resistant to noises
- Hysteretic switch can be created using a single positive feedback circuit in engineering systems. However, various cellular signaling systems use coupled positive feedback circuits to implement the hysteretic switch. Why?
- The simulation study revealed that coupling of positive feedbacks extends (i) the safety zone and (ii) the parameter range for both reversible and irreversible hysteretic switching. In other words, hysteretic switching is substantially enhanced in coupled positive feedback circuits.
- Cellular systems with coupled positive feedback circuits can make a more reliable decision under noisy signaling.



Coupled Feedback: PN

- Transcriptional noise is known to be an important cause of cellular heterogeneity and phenotypic variation.
- The yeast genetic network regulating galactose metabolism involves two proteins, Gal3p and Gal80p, that feed back positively and negatively, respectively, on GAL gene expression.
- Dual feedback loops (PN) in the GAL regulon suppress cellular heterogeneity in yeast.



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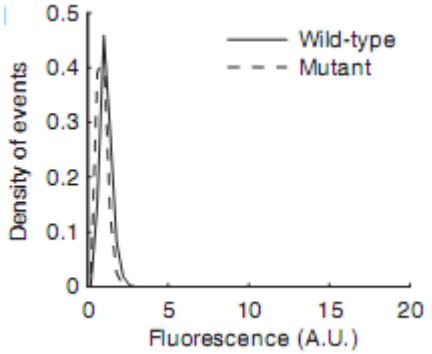
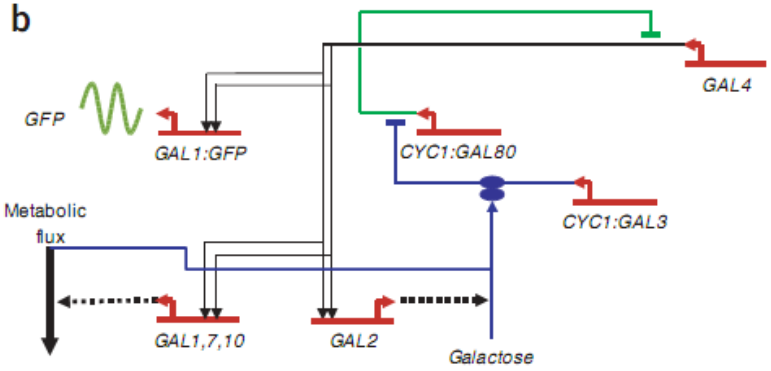


<0 hr after stimulation>



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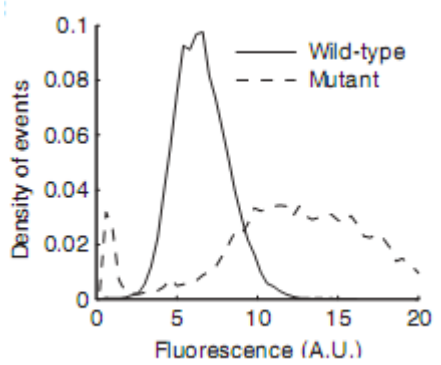


<6 hr after stimulation>

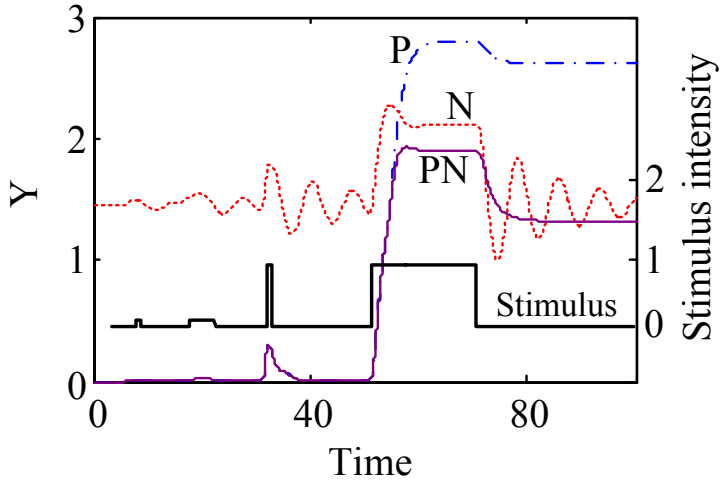
(Nature Genetics 38:1082 - 1087 (2006))

Coupled Feedbacks: PN

❑ **Example circuits of PN.**

Related network	Coupled feedback loops	Related network	Coupled feedback loops
Mitotic trigger in *Xenopus*	APC ⊣ Cdc2 → APC Cdc25 → Cdc2 → Cdc25	Galactose-signaling network in yeast	Gal80 ⊣ Gal4 → Gal80 Gal3 → Gal4 →Gal3
Ca2+ spikes /oscillations	SERCA ⊣ Ca^{2+}_{cyt} → SERCA IP3R → Ca^{2+}_{cyt} → IP3R	Receptor Signals by ß-Arrestins	c-Src ⊣ GRK → c-Src G → GRK → G
Ca2+ spikes /oscillations	SERCA ⊣ Ca^{2+}_{cyt} → SERCA RYR → Ca^{2+}_{cyt} → RYR	*B. subtilis* competence event	ComS → ComK ⊣ ComS ComK → ComK
Circadian oscillation in *Drosophila*	Per/Tim ⊣ Clk/Cyc → Per/Tim PDP1 → Clk/Cyc → PDP1	Mitotic trigger in *Xenopus*	APC ⊣ Cdc2 → APC Weel ⊣ Cdc2 ⊣ Weel
Circadian oscillation in *Drosophila*	Vri ⊣ Clk/Cyc → Vri PDP1 → Clk/Cyc → PDP1	Mitotic trigger in *Xenopus*	APC ⊣ Cdc2 → APC Myt1 ⊣ Cdc2 ⊣ Myt1
Circadian oscillation in Mammalia	Per/Cry ⊣ Clock/Bmal1 → Per/Cry Rorα → Clock/Bmal1 → Rorα	Circadian oscillation in Mammalia	Rev-erbα ⊣ Clock/Bmal1 → Rev-erbα Rorα → Clock/Bmal1 → Rorα

❑ **PN enables reliable decision by properly modulating signal responses and effectively dealing with noises**

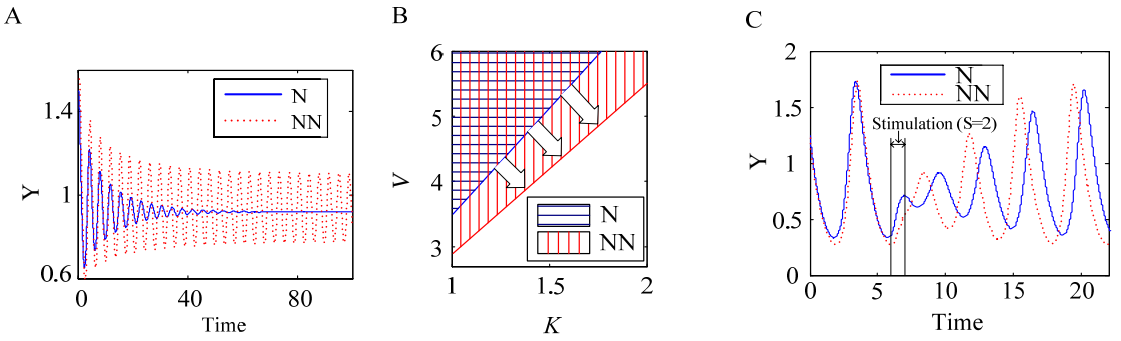


Coupled Feedbacks: NN

❑ **Example circuits of NN.**

Related network	Coupled feedback loops
Circadian oscillation in *Drosophila*	Per/Tim ⊣ Clk/Cyc → Per/Tim Vri ⊣ Clk/Cyc → Vri
Circadian oscillation in Mammalia	Per/Tim ⊣ Clk/Cyc → Per/Tim Vri ⊣ Clk/Cyc → Vri
TSH-cAMP signaling pathway in thyrocytes	RGS2 ⊣ AC → RGS2 GRK ⊣ AC → GRK
Chemotactic signaling in Ameba	ERK2 → PKA⊣ ERK2 ACA→ PKA ⊣ ACA
Plant circadian clock	TOC1 → CCA1/LHY ⊣ TOC1 CCA1/LHY ⊣ CCA1/LHY
p53 network	p38MAPK → p53 ⊣ p38MAPK Mdm2 ⊣ p53 → Mdm2

- ❑ **NN enforces the sustained oscillation (Fig. A)**
- ❑ **NN enhances oscillations (Fig. B)**
- ❑ **NN induces robust oscillation to noises (Fig. C)**



Coupled Feedbacks and Circadian Clocks

- The plant circadian rhythm is quickly entrained to the change of a light stimulus but the mammalian circadian rhythm shows a relatively slow entrainment. Where does a different entrainment feature of plants and mammals originate?

- **The core circadian regulatory network (CCRN)**
  - **Plants** : coupled negative feedback loops
  - **Animals**: coupled negative and positive feedback loops

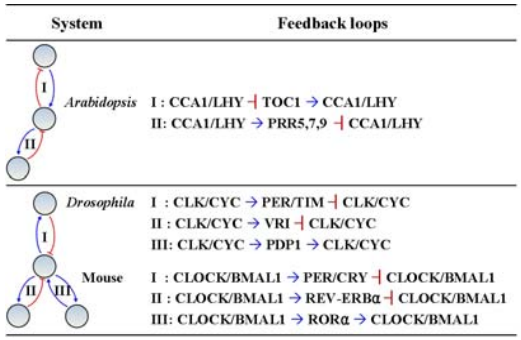
- **The way of regulation induced by a light stimulus**
  - **Plants and mammals** : gene transcription
  - ***Drosophila***: protein degradation

- **Mathematical Simulations**
  - How does the topological difference of CCRNs affect the different feature of entrainments? → the additional positive feedback induced much longer time to entrain (Fig. C).
  - How does the different role of light stimulus determine the entrainment time? → the protein degradation induced by light expedites the entrainment compared to the gene transcription (Fig. D).

- The topological structure of a CCRN, the regulatory mechanism induced by light, and the interacting point of light are important factors determining entrainment features.

(Biophysical Journal 93:L01-L03 (2007))

A



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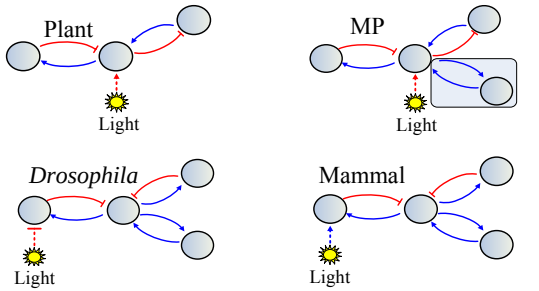

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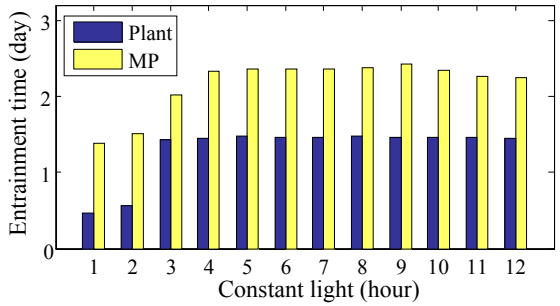

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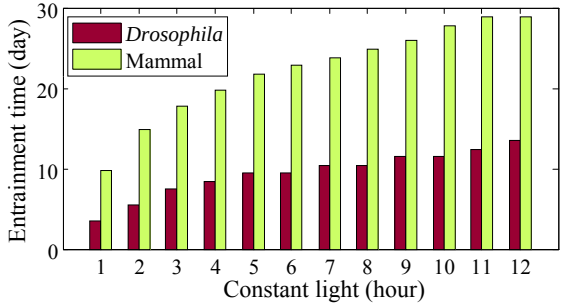

Coupled Feedbacks: Summary

PP

- PP with different feedback reaction speeds can effectively reduce the signal noises (Science 310:496-498).
- PP can enhance signal amplification and bistability.
  - PP is found in the muscle cell fate specification networks , T-cell differentiation network, the cell cycle start system whose switching mechanisms require strong bistability.
  - These network systems might have evolutionarily acquired PP.

PN

- PN can have the properties of both positive feedback loops and negative feedback loops
- PN is considered as a regulatory motif that can efficiently deal with signal noises while achieving proper response time
  - PN can reduce noises
  - PN suppresses cellular heterogeneity in the yeast GAL regulon network (Nat. Genet. 38:1082-1087)
  - The response time of PN is shorter than that of positive feedback loops while longer than that of negative feedback loops
  - PN is most ubiquitous (compared to PP and NN)

NN

- NN suppresses signal amplitudes resulting in noise reduction.
- NN accelerates the response time.
- NN enforces sustained oscillation which is robust to noises.
  - Many circadian networks and the chemotactic signaling network in ameba, both showing sustained oscillations, contain NN.

Mathematics to Biology?

- Data analysis => Bioinformatics
  - Clustering
  - Classification
- Mathematical modeling
  - ODE
  - PDE
- Dynamics analysis
  - Simulation analysis
  - Bifurcation analysis
- Data to Network => Reverse engineering
  - ODE
  - Boolean network
  - Statistic models
- Network topology analysis
  - Graph theory
  - Motif analysis
- Topology ⇔ Dynamics
  - Network reduction

Acknowledgements

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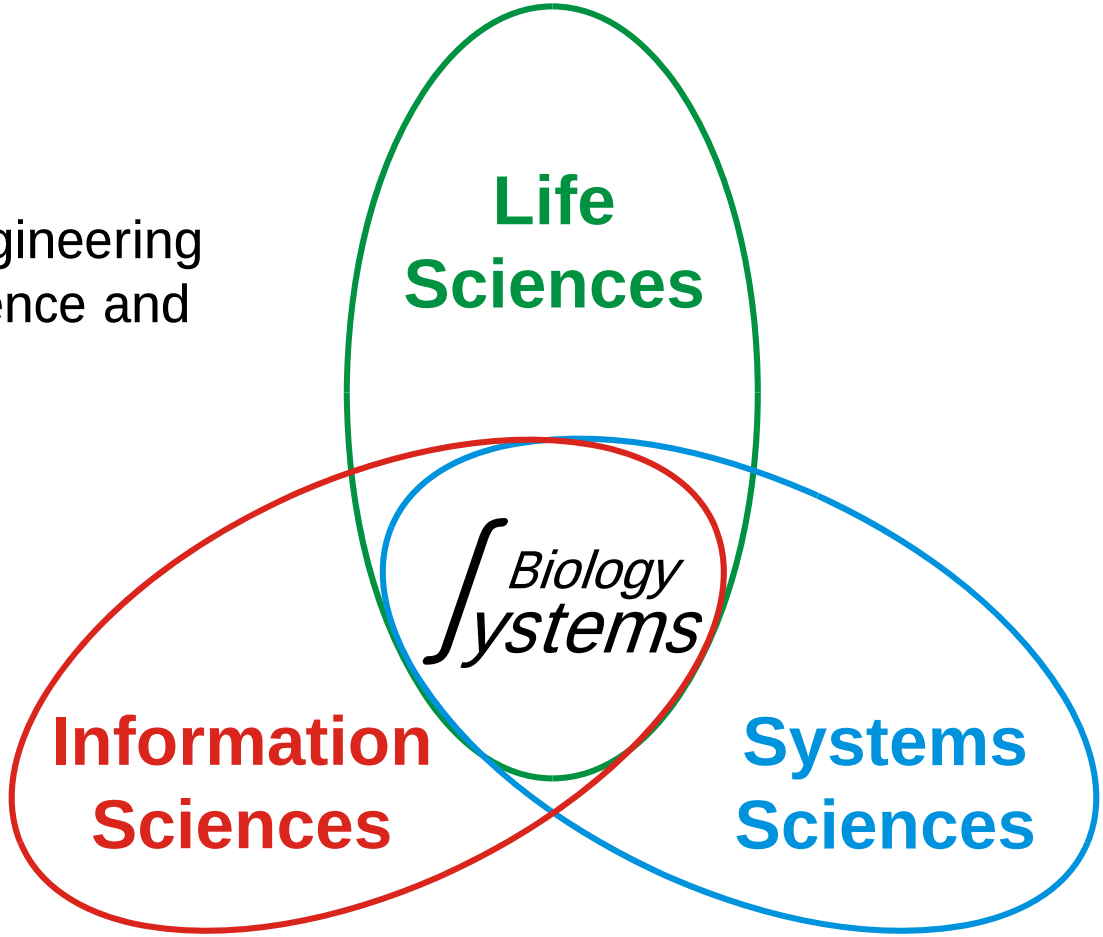

Thank you!