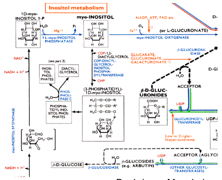
Networks in Cellular Biology

- *Dynamics*
- *Inference*
- *Evolution*

A. Metabolic Pathways

Enzyme catalyzed set of reactions controlling concentrations of metabolites



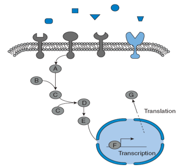
Boehringer-Mannheim

B. Regulatory Networks

Network of {Genes→RNA→Proteins}, that regulates each other transcription.

C. Signaling Pathways

Cascade of Protein reactions that sends signal from receptor on cell surface to regulation of genes.



Sreenath et al.(2008)

Networks → A Cell → A Human

- *A cell has ~10^{13} atoms.* — 10^{13}
- *Describing atomic behavior needs ~10^{15} time steps per second* — 10^{28}
- *A human has ~10^{13} cells.* — 10^{41}
- *Large descriptive networks have 10^{3}-10^{5} edges, nodes and labels* — 10^{5}
- *What happened to the missing 36 orders of magnitude???*
- *Which approximations have been made?*

A Spatial homogeneity → 10^{3}-10^{7} molecules can be represented by concentration ~10^{4}

B One molecule (10^{4}), one action per second (10^{15}) ~10^{19}

C Little explicit description beyond the cell ~10^{13}

A Compartmentalisation can be added, some models (ie Turing) create spatial heterogeneity

B Hopefully valid, but hard to test

C Techniques (ie medical imaging) gather beyond cell data

Systems Biology versus Integrative Genomics

Definitions:

***Systems Biology**: Predictive Modelling of Biological Systems based on biochemical, physiological and molecular biological knowledge*

***Integrative Genomics**: Statistical Inference based on observations of*

G - genetic variation
- *Within species – population genetics*
- *Between species – molecular evolution and comparative genomics*

T - transcript levels

P - protein concentrations

M - metabolite concentrations

F – phenotype/phenome

A few other data types available.

Little biological knowledge beyond "gene"

***Integrative Genomics** is more top-down and **Systems Biology** more bottom-up*

***Prediction:** Integrative Genomics and Systems Biology will converge!!*

A repertoire of Dynamic Network Models

To get to networks:

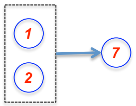
No space heterogeneity → molecules are represented by numbers/concentrations

Definition of Biochemical Network:

- *A set of k nodes (chemical species) labelled by kind and possibly concentrations, X_k.*

1 2 3 k

- *A set of reactions/conservation laws (edges/hyperedges) is a set of nodes. Nodes can be labelled by numbers in reactions. If directed reactions, then an inset and an outset.*



- *Description of dynamics for each rule.*

ODEs – ordinary differential equations $\frac{dX_7}{dt} = f(X_1, X_2)$

Mass Action $\frac{dX_7}{dt} = cX_1X_2$

Time Delay $\frac{d\bar{X}(t)}{dt} = f(\bar{X}(t-\tau))$

Discrete Deterministic – the reactions are applied.

Boolean – only 0/1 values.

Stochastic

Discrete: the reaction fires after exponential with some intensity $I(X_1,X_2)$ updating the number of molecules

Continuous: the concentrations fluctuate according to a diffusion process.

A. Metabolic Pathways

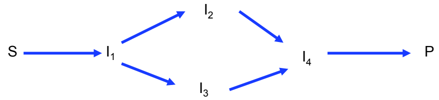
The parameters of reactions of metabolism is incompletely known and if if known, then the system becomes extremely complex. Thus a series of techniques have been evolved for analysis of metabolisms.

•Kinetic Modeling

Rarely undertaken since all reactions are sufficiently well known or parameters known under the different conditions (pH, temperature,..). This will change due to the rise of systems biology projects and the computational ability to model complete systems

•Flux Analysis

Conceptually easy analysis assume the system is in equilibrium and that organism has full control over which paths to send metabolites as long as stoichiometric constraints are obeyed.



Used to annotate new bacterial species by mapping the enzyme genes to a universal metabolism

•Metabolic Control Theory

Analysis the effect of change in concentration of enzymes/metabolites on flux and concentrations.

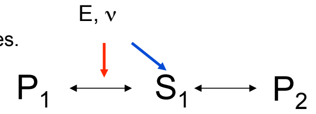
•Biochemical Systems Theory

Analysis based on ODEs of an especially simple form around observed equilibrium. Can address questions like stability and optimum control.

Control Coefficients

(Heinrich & Schuster: Regulation of Cellular Systems. 1996)

Flux J_j (edges) – Enzyme conc., E_k (edges), S – internal nodes.



Flux Control Coeffecient – FCC:

$$C^{J_j}_{E_k} = \left(\frac{E_k}{J_j}\frac{\Delta J_j}{\Delta E_k}\right)_{\Delta E_k \to 0} = \frac{E_k}{J_j}\frac{\partial J_j}{\partial E_k} = \frac{\partial \ln(J_j)}{\partial \ln(E_k)}$$

Kacser & Burns, 73

$$C^{J_j}_{\nu_k} = \left(\frac{\nu_k}{J_j}\frac{\Delta J_j}{\Delta \nu_k}\right)_{\Delta \nu_k \to 0} = \frac{\nu_k}{J_j}\frac{\partial J_j}{\partial \nu_k} = \frac{\partial \ln(J_j)}{\partial \ln(\nu_k)}$$

Heinrich & Rapoport, 73-74

FCF: gluconeogenesis from lactate

Pyruvate transport	.01
Pyruvate carboxylase	.83
Oxaloacetate transport	.04
PEOCK	.08

Biochemical Systems Theory (Savageau)

(J.Theor.Biol.25.365-76 (1969) + 26.215-226 (1970))

$$X_0' = \alpha_0 X_0^{g00} X_1^{g01} - \beta_0 X_0^{h00} X_1^{h01}$$

$$X_1' = \alpha_1 X_0^{g10} X_1^{g11} - \beta_1 X_0^{h10} X_1^{h11}$$

Steady State Analysis.

Power-Law approximation around 1 steady state solution.

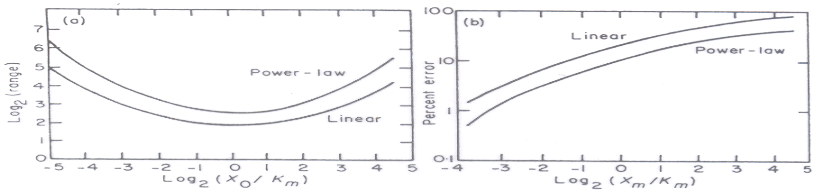
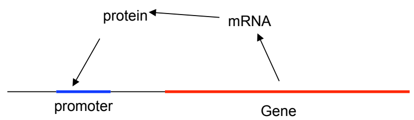


FIG. 1. A comparison of the power-law and linear approximations for the Michaelis rate law: $v/v_{max} = X/(K_m + X)$. (a) The maximum range in concentration (X_{max}/X_{min}) for which the approximation differs from the true rate by less than 5% as a function of the concentration at mid-range, X_0. (b) The average error for the best approximation in the range [0, X_m] as a function of X_m.

B. Regulatory Networks

Basic model of gene regulation proposed by Monod and Jacob in 1958:



Basic ODE model proposed and analyzed by Goodwin in 1964:

$$\frac{dX_{mRNA}}{dt} = f(X_{prot}) - c_{mRNA} X_{mRNA} \qquad \frac{dX_{prot}}{dt} = kX_{mRNA} - c_{prot} X_{prot}$$

Sign and shape of f describes activator/repressor and multimerisation properties.

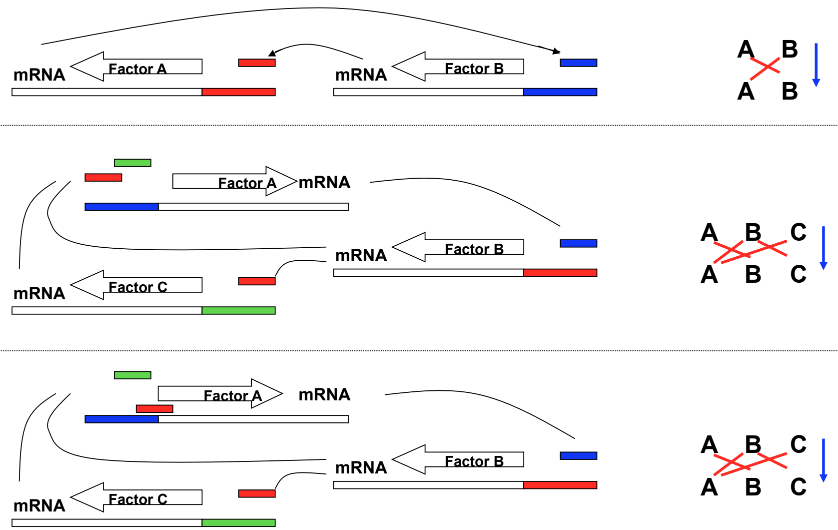
Extensions of this has been analyzed in great detail. It is often difficult to obtain biologically intuitive behavior.

Models of varying use have been developed:

Boolean Networks – genes (Gene+mRNA+protein) are turned/off according to some logical rules.

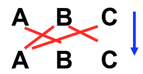
Stochastic models based on the small number of regulatory molecules.

Boolean Networks



Remade from Somogyi & Sniegoski,96. F2

Boolean functions, Wiring Diagrams and Trajectories

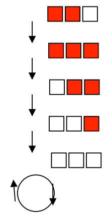


Inputs	2	1	1
Rule	4	2	2

A activates B
B activates C
A is activated by B, inhibited by (B>C)

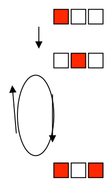
Point Attractor

A	B	C
1	1	0
1	1	1
0	1	1
0	0	1
0	0	0
0	0	0



2 State Attractor

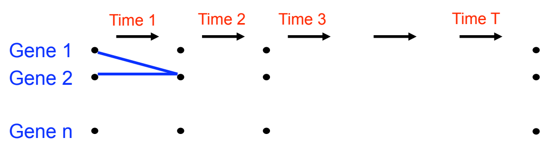
A	B	C
1	0	0
0	1	0
1	0	1
0	1	0



Remade from Somogyi & Sniegoski,96. F4

Boolean Networks

R.Somogyi & CA Sniegoski (1996) Modelling the Complexity of Genetic Networks Complexity 1.6.45-64.



k=1: 4 output

0 0 or 1

input

1

k=2: 16 output

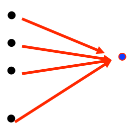
0,0

input 0,1

1,0 0 or 1

1,1

A single function: **The whole set:**



2^k 2^{k^k}

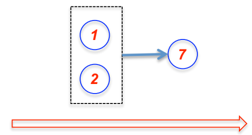
For each gene dependent on i genes: $\binom{k}{i}$ choices of dependent genes. Number of Boolean Rules $(\binom{k}{i} 2^i)^k$

Contradiction: Always turned off (biological meaningless) Tautology: Always turned on (household genes)

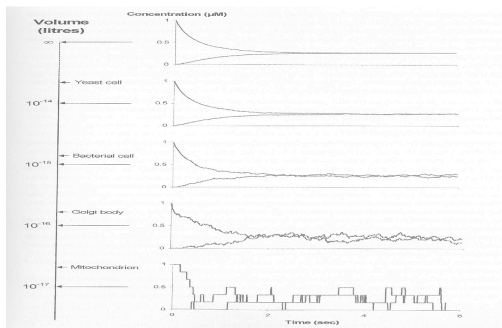
Stochasticity & Regulation

ODEs can be converting to continuous time Markov Chains by letting rules fire after exponential waiting times with intensity of the corresponging equation of the ODE

$$\frac{dX_7}{dt} = cX_1X_2$$



Expo[#A#B k_1] distributed



60000

6000

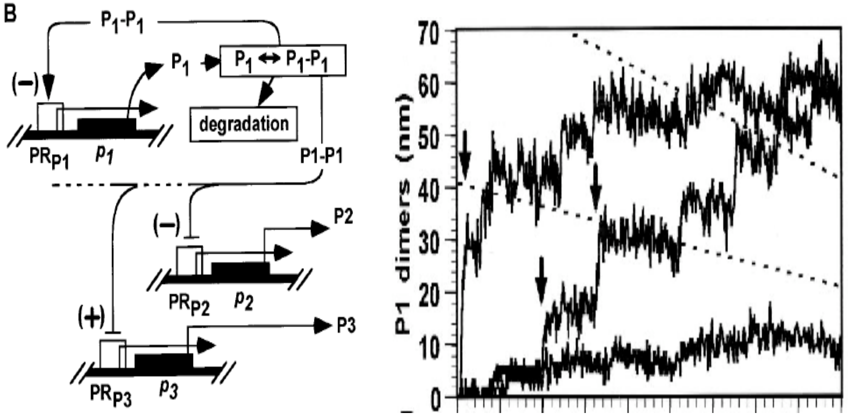
600

60

6

Regulatory Decisions

McAdams & Arkin (1997) Stochastic mechanisms in Gene Expression. PNAS 94.814-819.



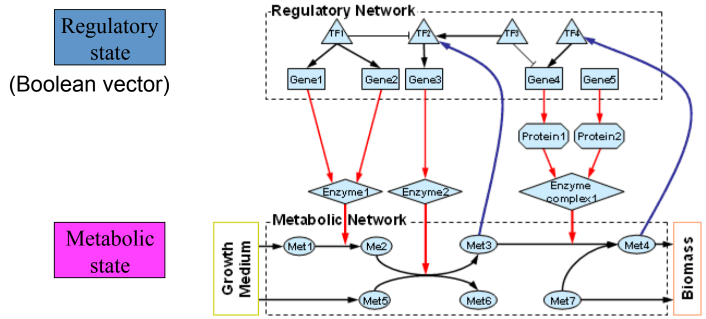
Network Integration

Genome-scale integrated model for E. coli (Covert 2004)

1010 genes (104 TFs, 906 genes)

817 proteins

1083 reactions



A genome scale computational study of the interplay between transcriptional regulation and metabolism.
(T. Shlomi, Y. Eisenberg, R. Sharan, E. Ruppin)
Molecular Systems Biology (MSB), 3:101, doi:10.1038/msb4100141, 2007

Chen-Hsiang Yeang and Martin **Vingron**, "A **joint model** of regulatory and metabolic networks" (2006). **BMC** Bioinformatics. 7, pp. 332-33.

Modified from Ruppin

Summary

Biological System and Network Models

A. Metabolic Pathways

- *Kinetic Modelling*
- *Flux Analysis*
- *Metabolic Control Theory*
- *Biochemical Systems Analysis*

B. Regulatory Networks

- *The Natural ODE model*
- *Boolean Netwoks*
- *Stochastic Models*

C. Signaling Pathways