Computational Systems Biology

Kinetic models of gene regulation

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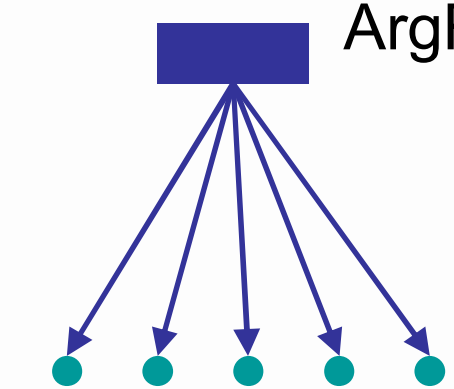
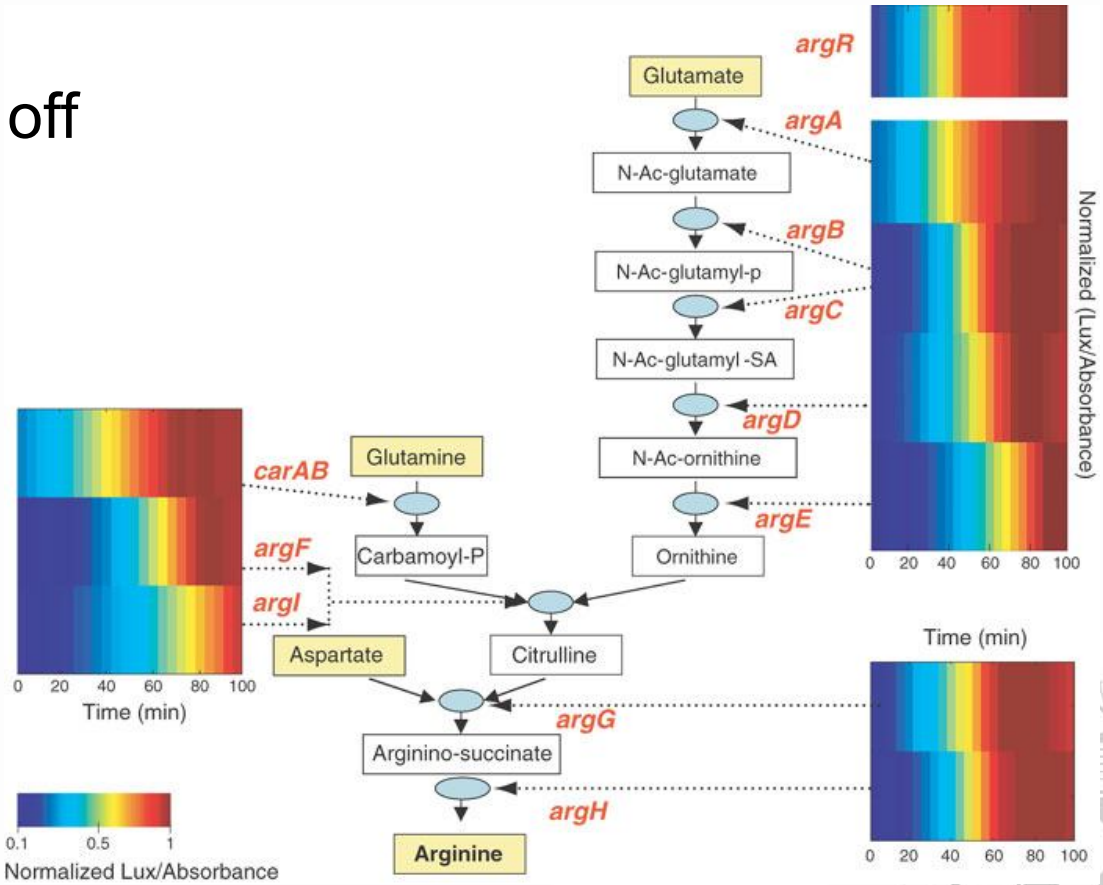
From static network to dynamic behavior

Enzyme expression
dynamics after arginine off



Arg synthesis genes

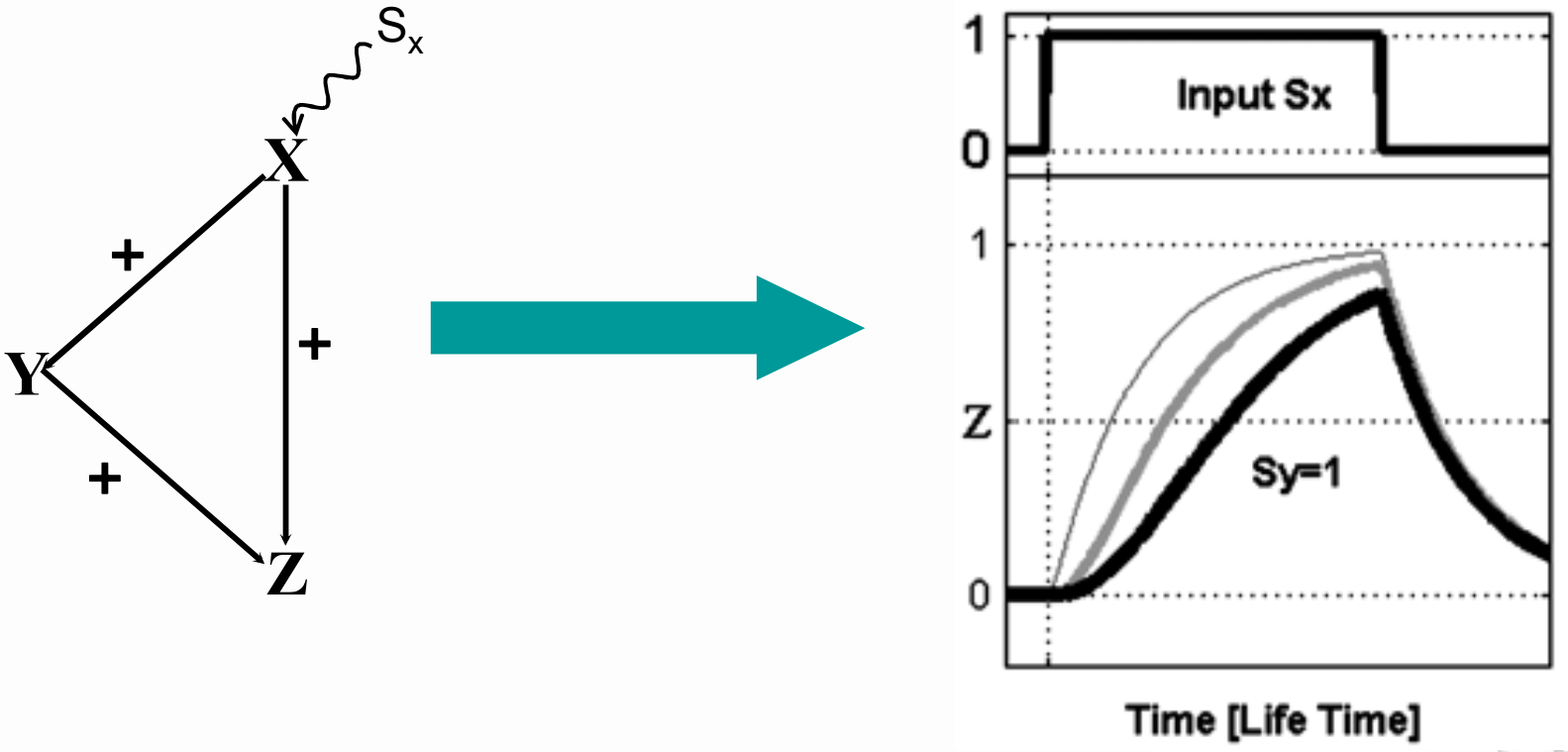


Also has a nice model to explain why.

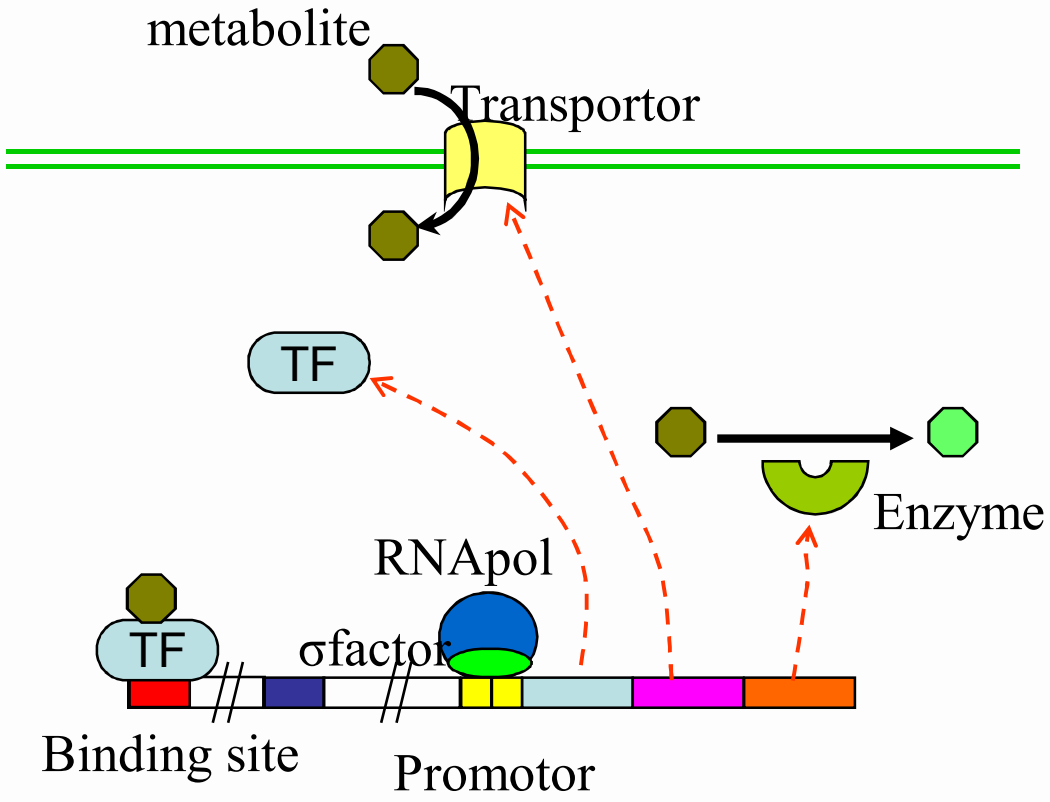
Zaslaver et al, Nature Genetics, 36-486 (2004)

Expression dynamics can not be described by network model!

Dynamic models are needed



From Interactions to Processes



Transport

Metabolite-protein binding

DNA-protein binding

Transcription and translation

Enzyme catalyzed metabolic reaction

Protein degradation

Two component signal transduction

.....

Kinetic models needed to describe the processes!

First step: Represent processes as reactions

Not as interactions as in the static picture of the graph analysis

- Transport: $m_{out} \rightarrow m_{in}$
- M-P binding: m+TF→mTF
- Transcription: $NA \xrightarrow{\text{mTF}} \text{mRNA}$
- Translation: $\text{AA} \xrightarrow{\text{mRNA}} \text{protein}$
- Metabolic reaction: m1→m2
- Degradation: protein→null, mRNA→null(?)

In gene regulation process the mass balance is not important

Most important: determine the rate of these reactions?

$v = f(x)$ Which factors affect reaction rate? In which function?

Kinetic equations

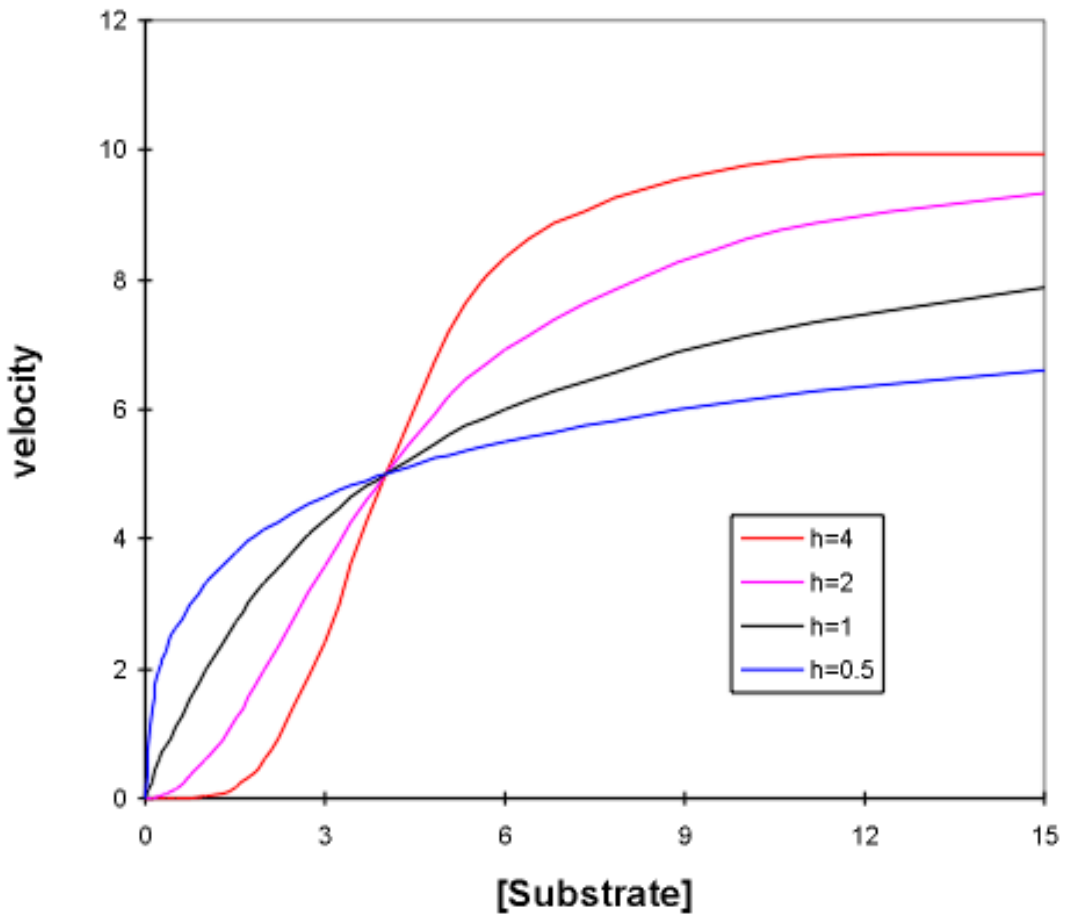
Mass action kinetics $$v = k * S_1 * S_2 * \cdots * S_n$$

Michaelis-Menten Kinetics $$v = \frac{v_m S}{\mathrm{K_s} + S}$$

Hill equation $$v = \frac{v_m S^h}{\mathrm{K}^{\mathrm{h}} + S^h} = v_m \frac{\left(\frac{S}{K}\right)^h}{1 + \left(\frac{S}{K}\right)^h}$$

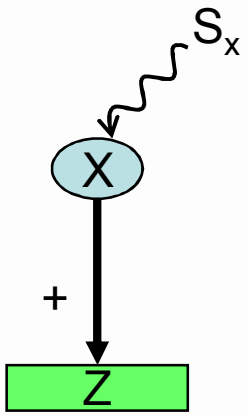
h: Hill coefficient

Hill equation



Sigmoid function, a switch mechanism

Start from a simple model



- M-TF binding: Sx+X→XSx
- Transcription: XSx +DNA→ XSx +$mRNA_z$
- Translation: $mRNA_z$→$mRNA_z$+Z
- Degradation: Z→null

Simplification

- M-TF binding is a switch process:

$$XS_x = \begin{cases} 0 \text{ if } S_x = 0 \\ X \text{ if } S_x = 1 \end{cases}$$

- Transcription and Translation combined:
  XSx +DNA→ XSx +Z

$$v = B_z + \frac{v_m * XS_x^h}{K^h + XS_x^h}$$

Bz=0

- Degradation:

$$v = \alpha_z Z$$

Simulation (switch on Sx=1)

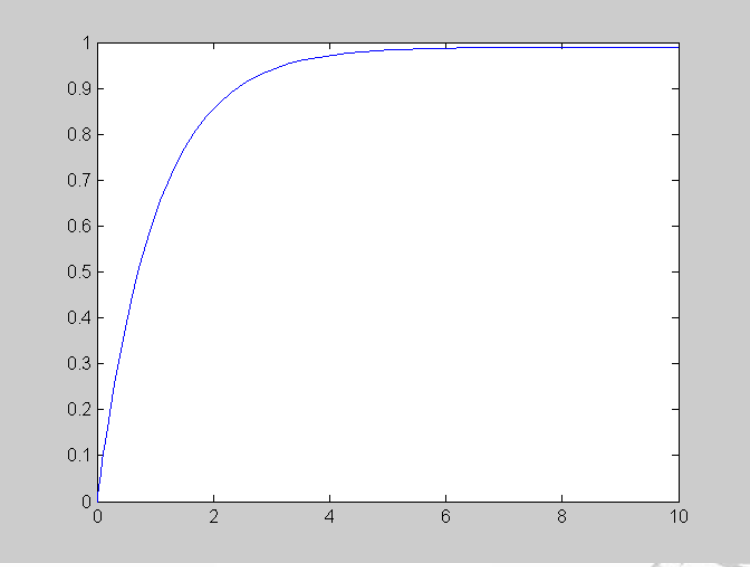
- Which are the variables in the system?
- regulator X is not controlled by other TFs, therefore assume X constant: X=1
- Only one variable Z

$$\frac{dZ}{dt} = \frac{v_m * XS_x^h}{K^h + XS_x^h} - \alpha_z Z = \frac{v_m}{K^h + 1} - \alpha_z Z$$

Production Degradation

Initial concentration Z_0=0

Vm=1, K=0.1, h=2, az=1



Metabolite-TF interactions

- bind to active an activator: 20
- bind to deactive a repressor: 14
- Bind to deactive an activator: 5
- Bind to active a repressor: 11

other models

- X bind to DNA to active transcription while XSx not: X +DNA→ X +mRNAz

$$X = \begin{cases} 0 \text{ if } S_x = 1 \\ X \text{ if } S_x = 0 \end{cases} \qquad v = \frac{v_m * X^h}{K^h + X^h}$$

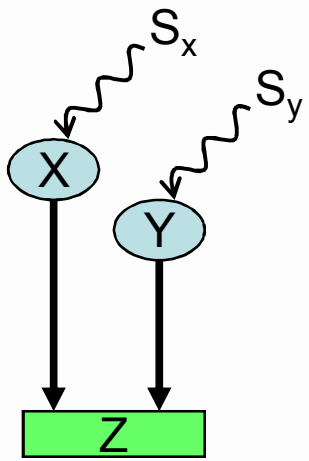
- X bind to DNA to repress transcription while XSx not (ArsR, lac operon, inducer)

$$v = \frac{v_m K^h}{K^h + X^h}$$

- XSx bind to DNA to repress transcription (ArgR+arginine, corepressor)

$$v = \frac{v_m K^h}{K^h + XS_x^h}$$

Combinatorial regulation



AND relationship

$$v = f(X) * f(Y)$$

OR relationship

++

$$v = \frac{v_m\left(\left(X/Kx\right)^h + \left(Y/Ky\right)^h\right)}{1 + \left(X/Kx\right)^h + \left(Y/Ky\right)^h}$$

+-

$$v = \frac{v_m\left(\left(X/Kx\right)^h + 1\right)}{1 + \left(X/Kx\right)^h + \left(Y/Ky\right)^h}$$

-+

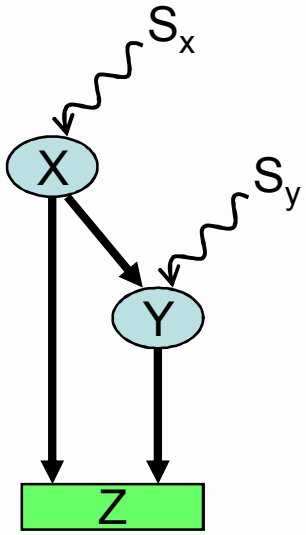
$$v = \frac{v_m\left(1 + \left(Y/Ky\right)^h\right)}{1 + \left(X/Kx\right)^h + \left(Y/Ky\right)^h}$$

--

$$v = \frac{v_m}{1 + \left(X/Kx\right)^h + \left(Y/Ky\right)^h}$$

Mangan and Alon, (2003) PNAS, 100:11980

Feed forward loop



The regulator Y is also regulated by X, therefore the concentration of Y is also changed but not constant

$$\frac{dY}{dt} = \frac{v_{my} * XS_x^h}{K_{XY}^h + XS_x^h} - \alpha_y Y$$

AND

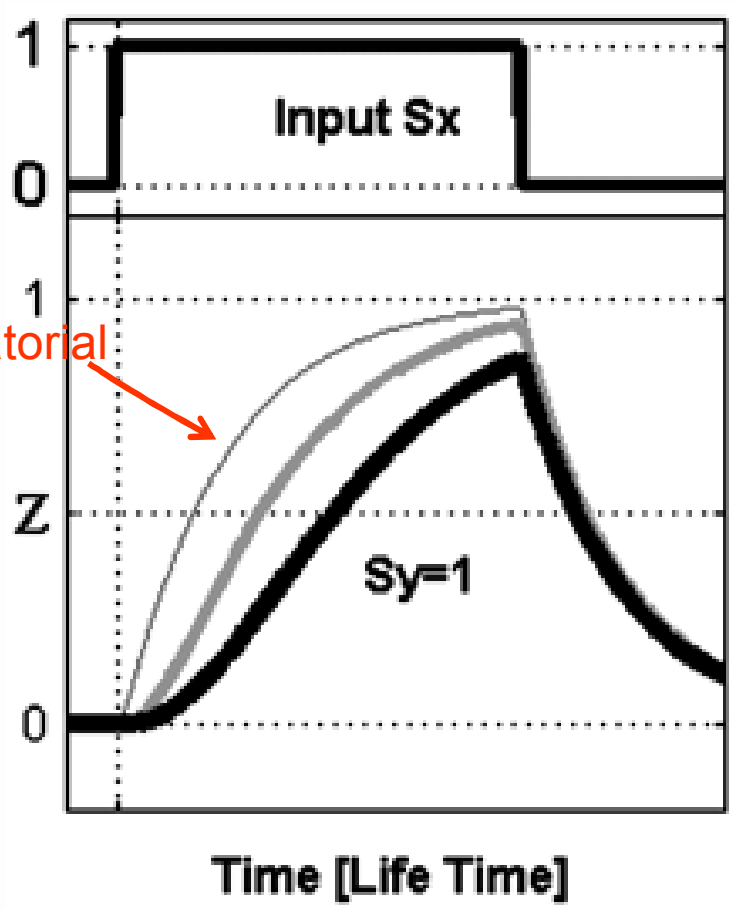
$$\frac{dZ}{dt} = \frac{v_m * XS_x^h * YS_y^h}{\left(K_{xz}^h + XS_x^h\right)\left(K_{yz}^h + YS_y^h\right)} - \alpha_z Z$$

OR

$$\frac{dZ}{dt} = \frac{v_m\left(\left(XS_x/Kxz\right)^h + \left(YS_y/Kyz\right)^h\right)}{1 + \left(XS_x/Kxz\right)^h + \left(YS_y/Kyz\right)^h} - \alpha_z Z$$

Easily simulated with the Matlab ODE solver or in Copasi!

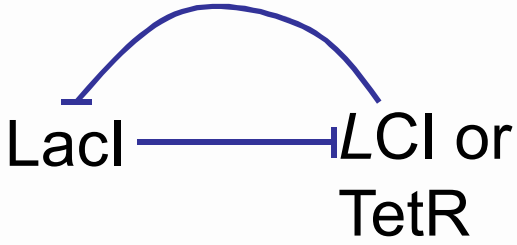
Dynamics of FFL



The response to Sx switch on is delayed for FFL controlled genes. The target gene only respond to persistent signal but not noise

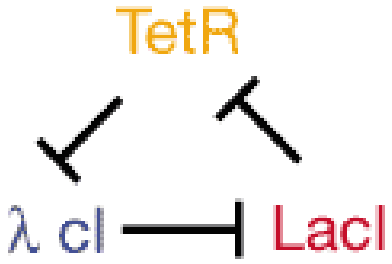
Mangan and Alon, (2003) PNAS, 100:11980

Other gene circuit models



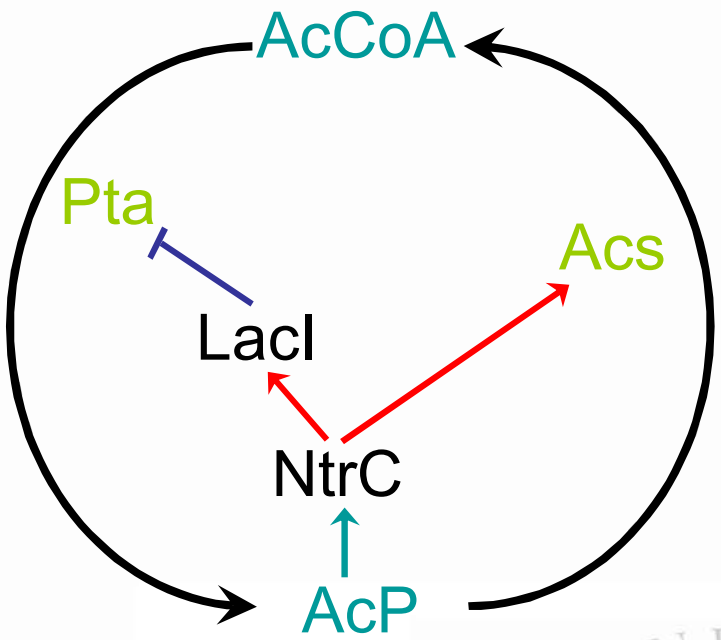
Toggle switch

Gardner et al, Nature, *403-339, 2000*



Repressilator

Elwitz et al, Nature, 403-335, 2000



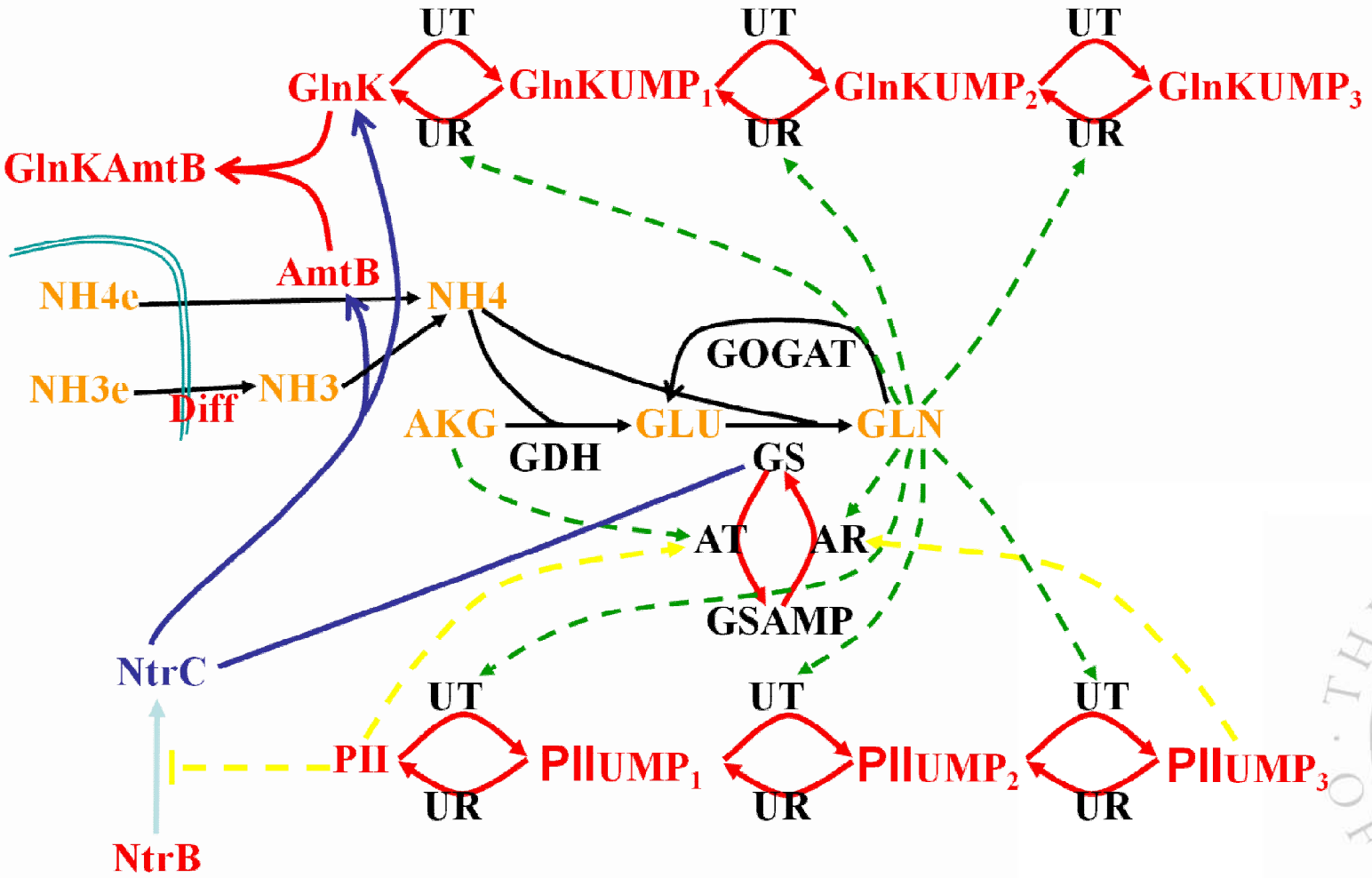
Metabolator

Fung et al, Nature, 435-118, 2005

Network motif and gene circuit

- Network motif: statistically highly represented substructures in a large network
- Gene circuit: A functionally independent regulatory unit involving different types of interactions
- Synthetic Biology: design and build of an artificial biological circuit with a novel function
- Experimental Design always needs guidance from computational modelling

A real world example: ammonium assimilation model



Reactions

Transport & Metabolite

Transport reactions

$NH_3ex = NH_3in$
$AmtB + NH_4ex = AmtBNH_4$
$AmtBNH_4 = AmtBNH_3 + Hex$
$AmtBNH_3 = AmtB + NH_3in$
$NH_3in + Hin = NH_4in$

Metabolic reactions

$NH_4in + GLU + ATP = GLN + ADP$
$AKG + GLN + NADPH = 2\ GLU + NADP$
$NH_4in + AKG + NADPH = GLU + NADP$

Exchange reactions

GLU → protein
GLN → protein
GLU → AKG
GLN → GLU

Protein level regulation

PII (GlnK, GlnB) modification

PII+UTP → PIIUMP

PIIUMP+UTP → PIIUMP2

PIIUMP2+UTP → PIIUMP3

PIIUMP3 →PIIUMP2 +UMP

PIIUMP2 → PIIUMP +UMP

PIIUMP → PII +UMP

GS modification

GS+ATP → GSAMP

GSAMP → GS +ADP

AmtB binding

AmtB+GlnK = AmtBGlnK

Gene level regulation

NtrC phosphorylation

NtrBP+NtrC=NtrCP+NtrB; PII

GS regulation

→GS; NtrCP

GS →

GSAMP →

AmtB, GlnK regulation

→AmtB; NtrCP

→GlnK; NtrCP

AmtB →

GlnK →

AmtBGlnK →

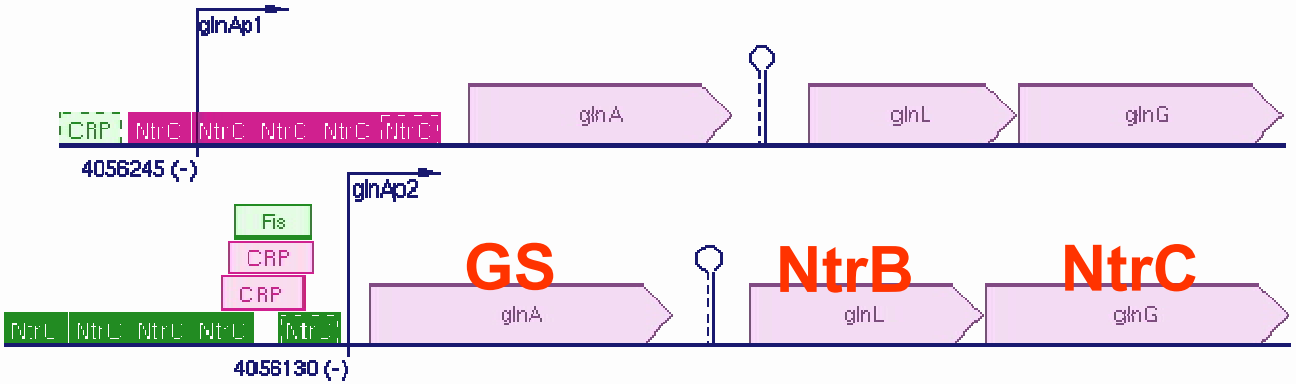
AmtBNH3 →

AmtBNH4 →

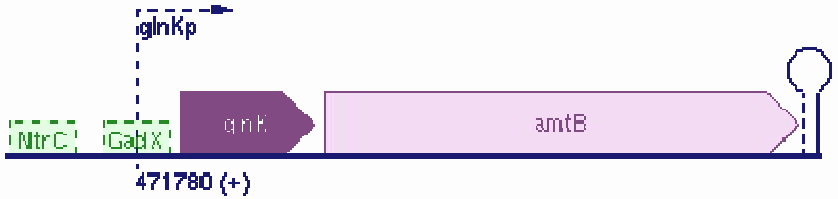
GlnKUMP(1-3) →

Gene regulation

NtrBC two component system: dual regulator. GS gene regulation through two promoters



Weak glnAp1 is rpoD dependent while strong glnAp2 is rpoN dependent

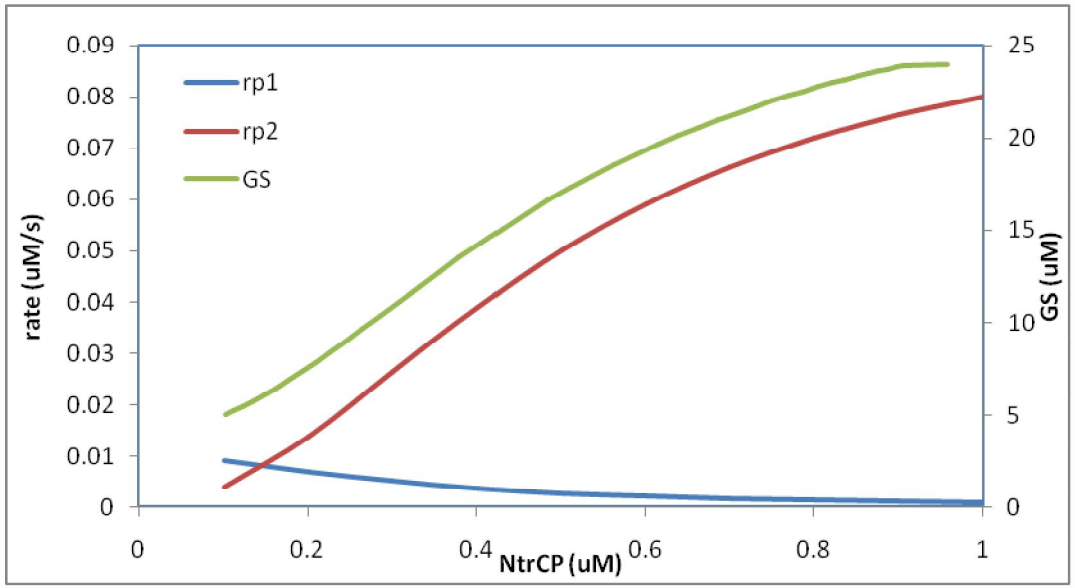


GS gene regulation

GS production: -> GS; NtrCP

$$r = \frac{vp_1}{1+\left(\frac{NtrCP}{Kp_1}\right)^h} + \frac{vp_2}{1+\left(\frac{Kp_2}{NtrCP}\right)^h}$$

Promoter 1 is weak (low vp1), repressed by NtrCP
Promoter 2 is strong (high vp1), activated by NtrCP

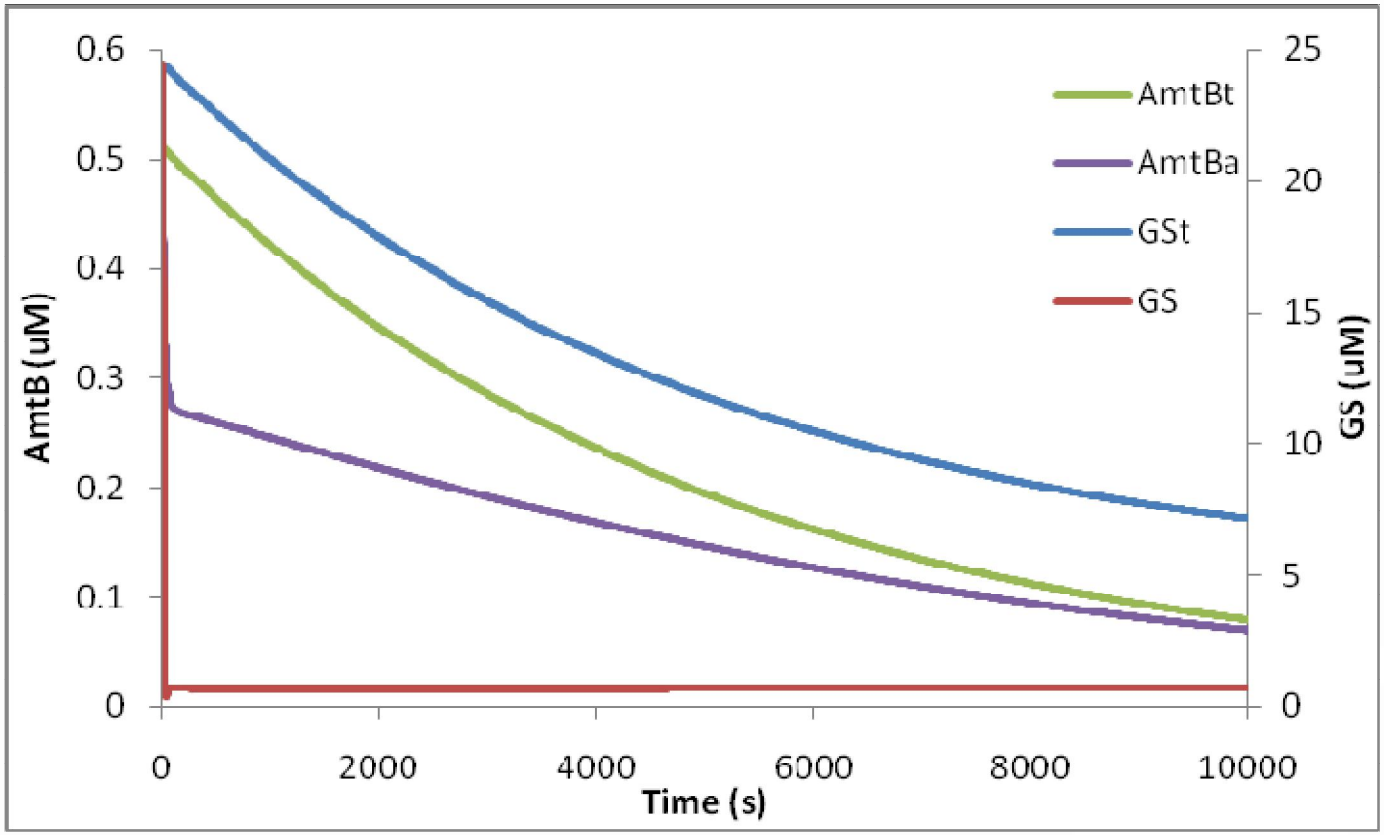


Steady state GS concentration change around six times, 25 uM at very low NH4ex

Model analysis

- Steady state fluxes and concentrations at various NH4/NH3 concentrations and various pHs (fit experimental data)
- Cellular dynamic responses to suddenly changed environment
- Effect of gene knock out
- Parameter sensitivity analysis and contribution from different regulation mechanisms (like MCA for metabolic pathway model)

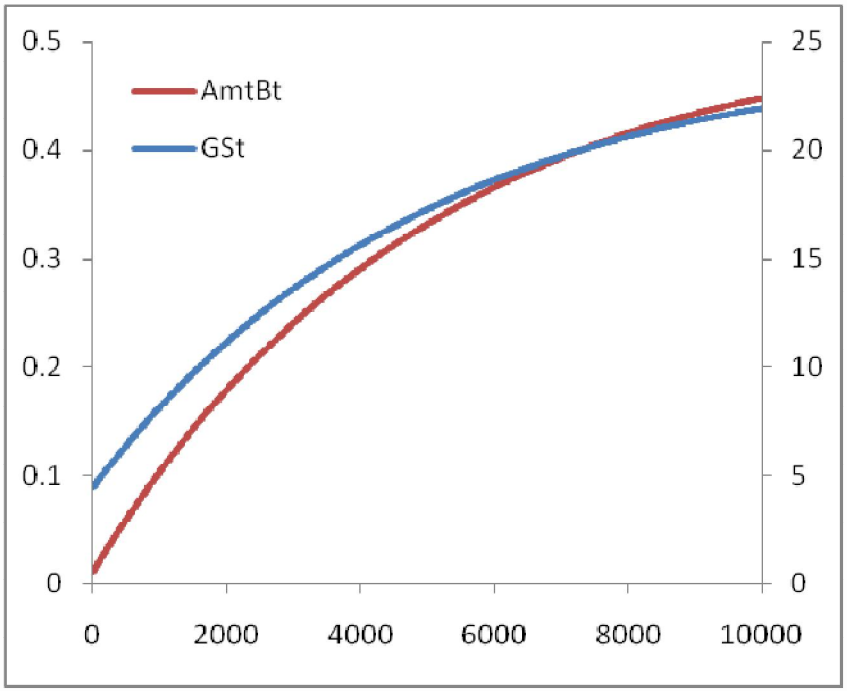
Dynamic simulation: 5 to 500 µM

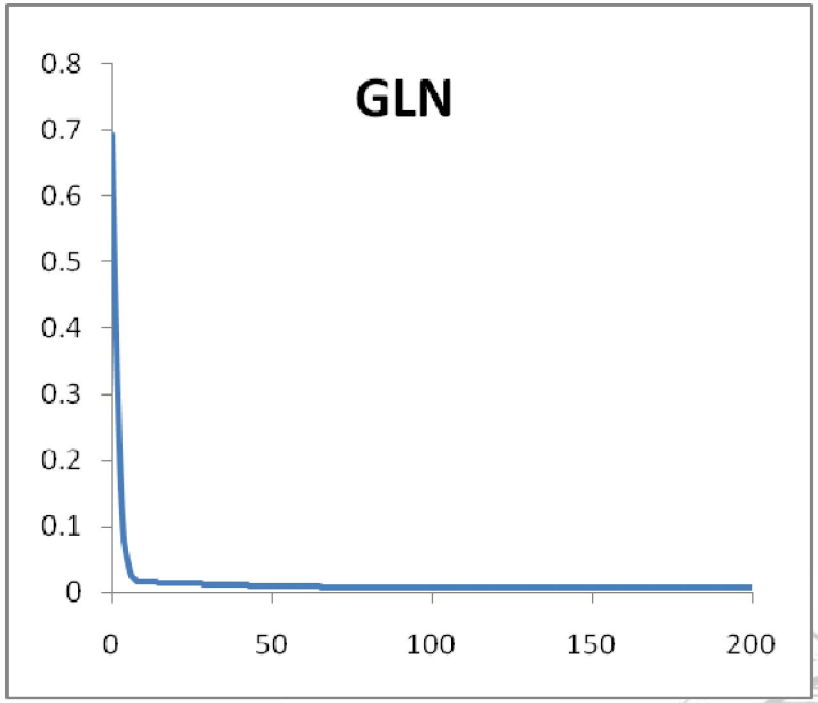


Gene regulation takes a very long time, but in consistence with the protein half life at about 1 hour.

Protein level regulation is much fast! Active protein reduced quickly.

Dynamic simulation: 500 to 5 µM





Slow gene regulation response leads to very low GLN concentration (less than 0.01mM), very low N assimilation rate (0.01mM/s) and negative GDH flux (nearly 50s).

May use a FFL to speed up the response

Softwares for modelling

- Copasi: www.copasi.org, very good software for kinetic model analysis but not for visualization
- Jdesigner/Jarnec: sys-bio.org, diagram+simulation
- CellDesigner: automatic layout+simulation
- Simbiology: by mathworks, powerful and expensive, only tool to deal with the currency metabolites in visualization

Alves, et al: Tools for kinetic modeling of biochemical networks, Nature Biotechnology, v24:667, 2006

Desired features

- SBML import and export
- Built-in kinetic laws to select and user-defined kinetic laws for easy reuse
- Give the parameter values and initial concentrations of variables (species such as ATP can be set at constant)
- Run the simulation and see the results in graph or data

Databases on models

- Biomodels database http://www.ebi.ac.uk/biomodels/
- over 200 Curated models from literature on metabolic pathways, gene regulatory circuits and signal transduction pathways
- SBML files can be directly imported by many software for simulation (http://sbml.org)
- Graph visualization for easy checking

Other model Databases

- Kitano Model repository (http://www.systems-biology.org/001/): KEGG pathway models
- CellML repository: more than 100 models from literature but not curated, some may not have parameter values. CellML is not supported by many software