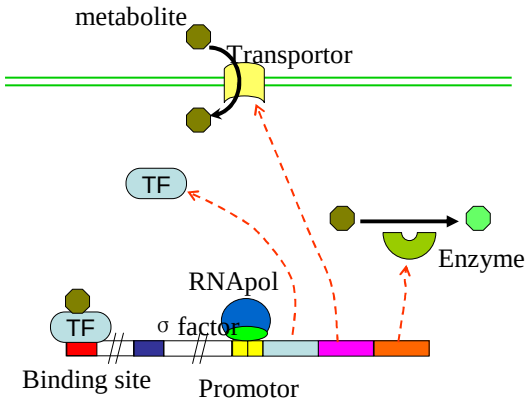
Cellular processes



Transport

Metabolite-protein binding

DNA-protein binding

Transcription and translation

Enzyme catalyzed metabolic reaction

Protein degradation

Two component signal transduction

……

Represent processes as reactions

- Transport: m_{out} → m_{in}
- M-P binding: m+TF→mTF
- Transcription: mTF+DNA→mTF+mRNA (?)
- Translation: mRNA→mRNA+protein (?)
- Metabolic reaction: m1→m2
- Degradation: protein→null, mRNA→null(?)

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

Kinetic equations

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

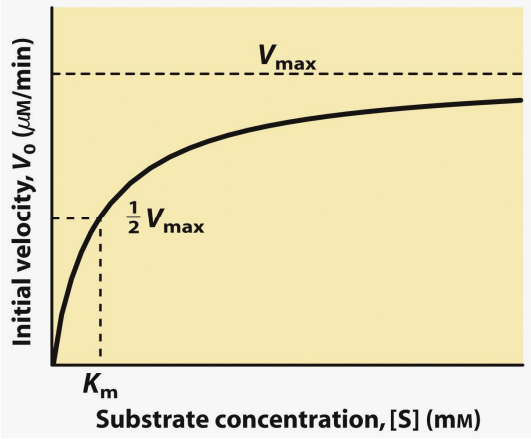
Michaelis-Menten Kinetics $v = \frac{v_m S}{\mathrm{K_s} + S}$

Enzyme kinetics

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

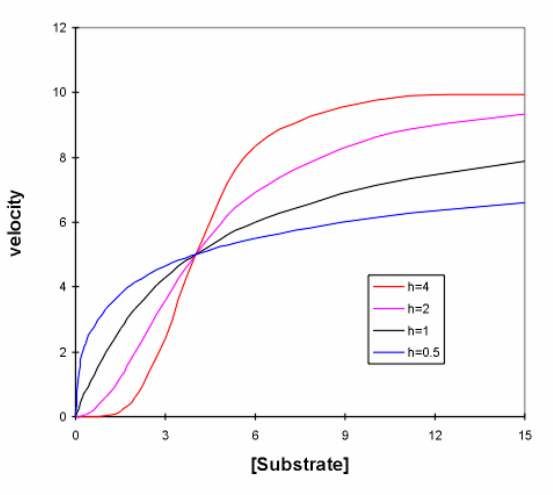
h: Hill coefficient

Michaelis-Menten



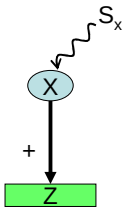
Saturated kinetics

Hill equation



Sigmoid function, a switch mechanism

A simple gene regulation 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
- Degradation: $v = \alpha_z Z$

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

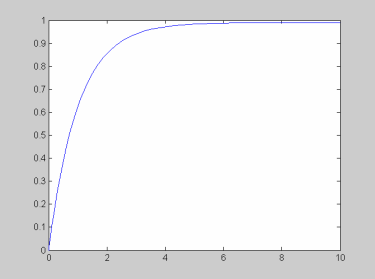
Simulation

- Further simplification: X is not controlled by other TFs, therefore assume X constant: X=1
- No basal transcription: Bz=0
- When swithch on (Sx present)

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

V_m=1, K=0.1, h=2, a_z=1

Z_0=0



other models

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

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

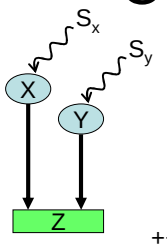
- X bind to DNA to repress transcription while XSx not (ArsR, lac operon, inducer)

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

- 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 (both TFs are required)

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

OR relationship (both TFs are required)

++

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

+-

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

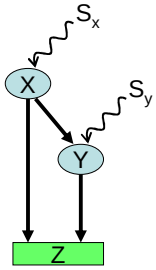
-+

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

--

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

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

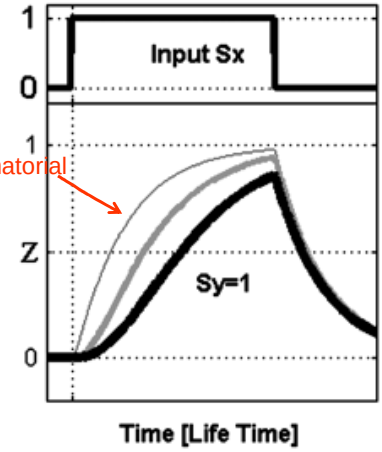
$$\frac{dZ}{dt} = \frac{v_m * XS_x^h * YS_y^h}{\left(K_{xz}^h + XS_x^h\right)\left(K_{yz}^h + YS_y^h\right)} - \alpha_z Z$$

OR

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

Easily simulated with the Matlab ODE solver!

Function of FFL



Simple combinatorial regulation

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

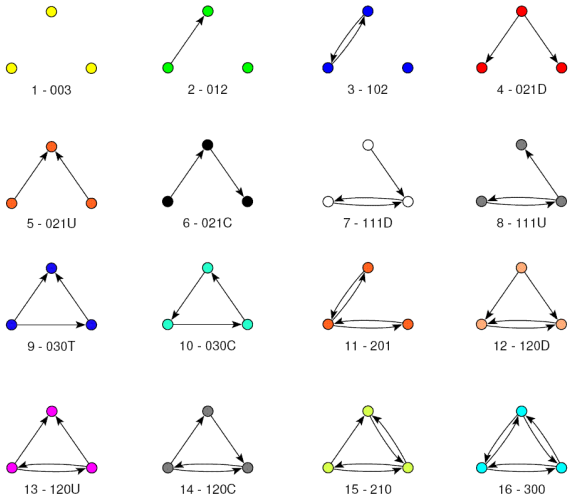
Why we study FFL

FFL is one of the most important network motifs in the transcriptional regulatory network of E. coli (Shen-Oorr et al., Nature Genetics, 31:64).

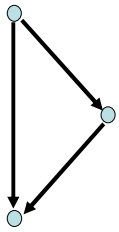
Network motif: Subgraphs that appear in the network at frequencies much higher than those found in randomized networks. They are the elementary building blocks of network

Milo et al. ***Network motifs: simple building blocks of complex networks.***
Science. 2002, 298(5594):824-7.

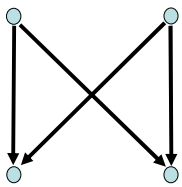
Three node subsets



Network motifs in regulatory network



Feed forward loops

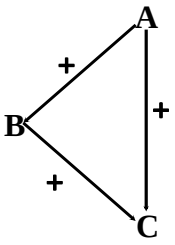


Bi-fan motif

Different types of FFLs

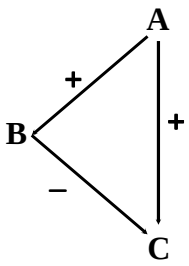
Mangan and Alon, (2003) PNAS, 100:11980

Coherent FFLs



Direct effect of the upper regulator *A* on the target gene *C* is consistent with its indirect effect through *B*.

Incoherent FFL



Direct effect is inconsistent with the indirect effect.

FFL distribution in E. coli regulatory network

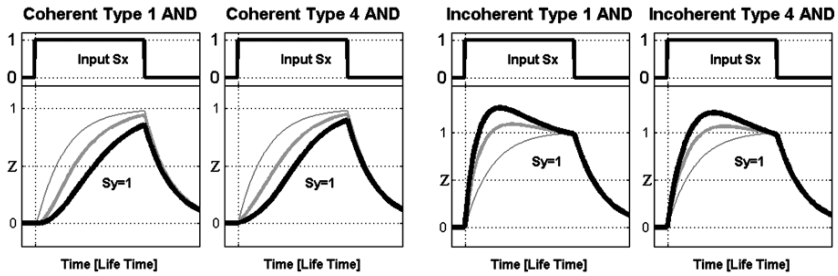
Coherent FFLs: 330 **Incoherent FFLs: 152**

type								
number	265	28	7	30	119	9	8	16
examples	*flhC-fliA-fliGH*	*cpxR-csgD-csgA*	*fis-hns-cysG*	*fnr-narL-dcuB*	*crp-nagC-manXYZ*	*arcA-betI-betAB*	*ihf-flhD-nrfA*	*fnr-narL-moeAB*

Some types of FFLs are dominated!

Different behavior

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



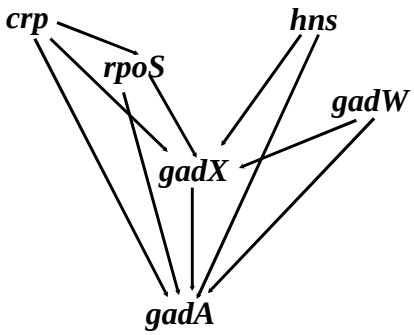
Delay the responses of the target gene

speed up the responses of the target gene

only 56 genes are solely regulated by one FFL.

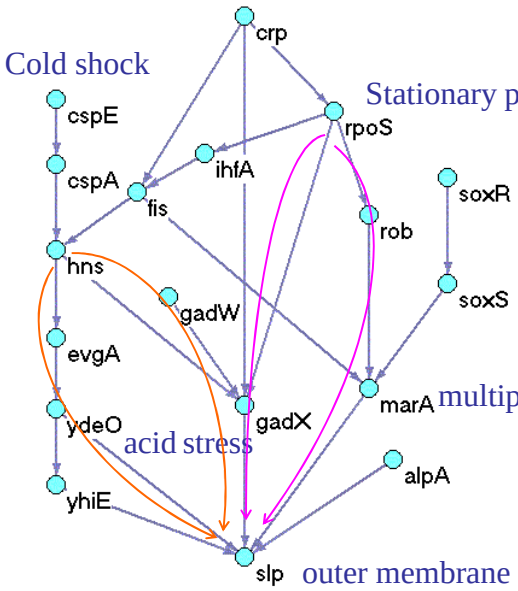
How the dynamic behavior will be changed when there are more FFLs or other regulators control the target gene?

A complex regulatory circuit



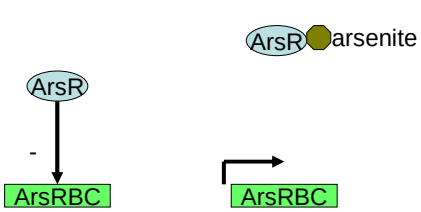
gadA: glutamate decarboxylase (in aminobutarate pathway, a by path of TCA cycle), important in oxidative stress and acid stress response

A more complex one



Multi-node feed forward loops

Fortunately Arsenic regulatory is simple



ArsB: arsenate transport

ArsC: arsenate reductase

Plasmid contain ArsRDABC

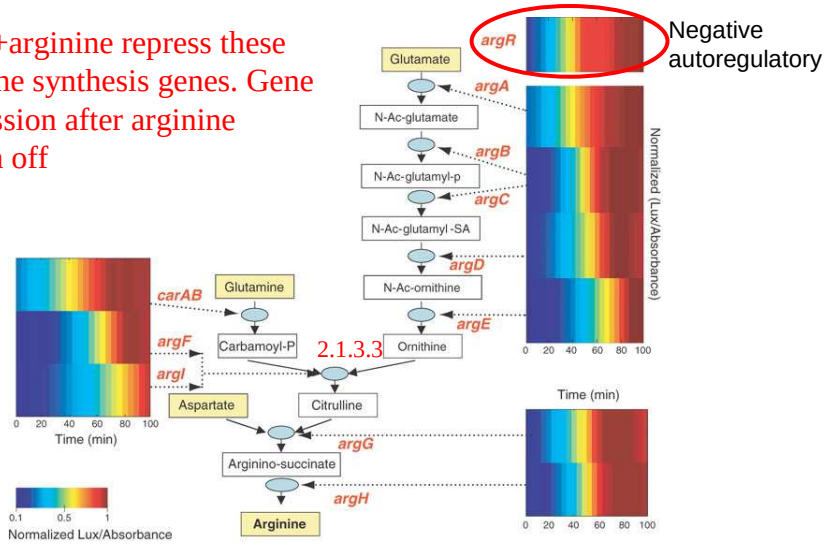
Something not in the previous model: Negative autoregulatory of arsR!

More than half of regulators in E. coli are autoregulated!

Autoregulatory model: PNAS,100:7714, 2003.

ArsR is highly expressed when arsenite present, but what is its function?

ArgR+arginine repress these arginine synthesis genes. Gene expression after arginine switch off



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

ArgR highly expressed but useless? Quick switch off!

Using model to answer the question!

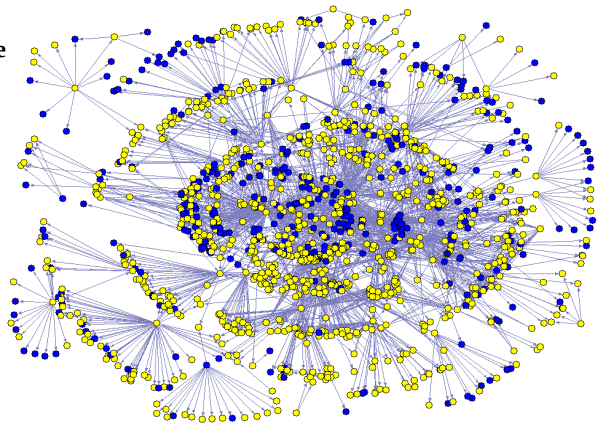
Where to find the data

- Ecocyc (ecocyc.org)
- RegulonDB (http://www.cifn.unam.mx/Computational_Genomics/regulondb/)
- Literature

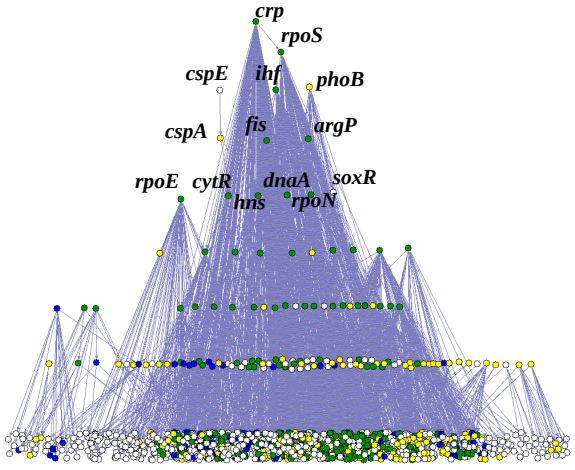
G o o o o o o o o o o gle

The whole regulatory network

1278 genes
2724 interactions
157 genes for TFs
382 metabolic enzyme genes (Blue)

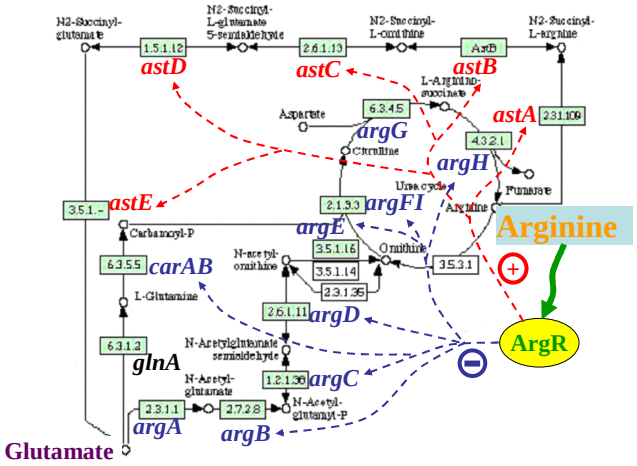


Acyclic structure: one way information flow



Where is the feed back?

Feedback through metabolites



The whole picture