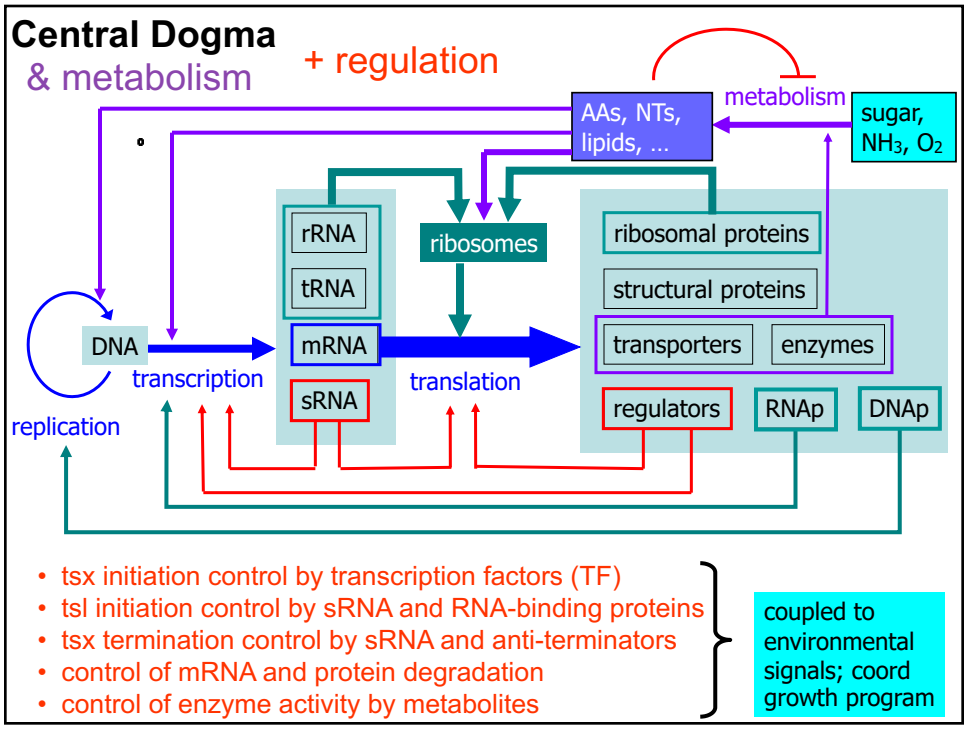
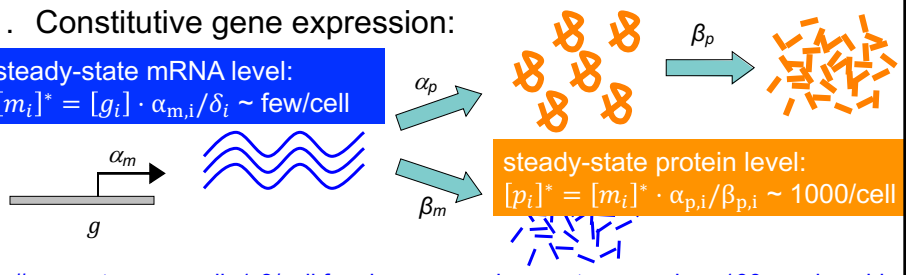


1

Integrated model of gene expression and regulation

1. Constitutive gene expression:

steady-state mRNA level:
$[m_i]^* = [g_i] \cdot \alpha_{m,i}/\delta_i$ ~ few/cell



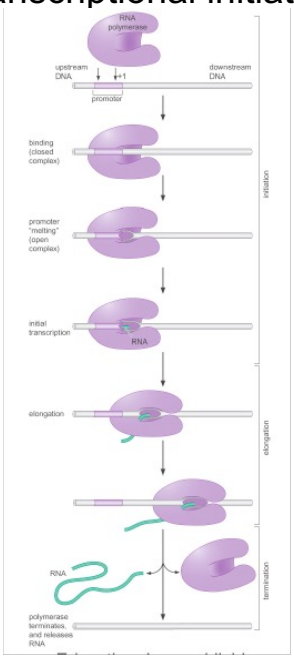
g = # promoters per cell; 1-8/cell for chromosomal promoters; can be >100 on plasmids
α_m = mRNA synthesis rate per promoter; max ~ 1/sec; typical ~ 1/min
β_m^{-1} = mRNA life-time; typical 1~2 min; max ~ doubling time
α_p = protein synthesis rate per mRNA; typical high ~ 10/min
β_p^{-1} = protein life-time; most ~ doubling time; ~ few min

mean-field description (rate eqn) for gene i
$[g_i]$ = conc of promoters
$[m_i]$ = conc of functional mRNA transcript
$[p_i]$ = conc of protein product

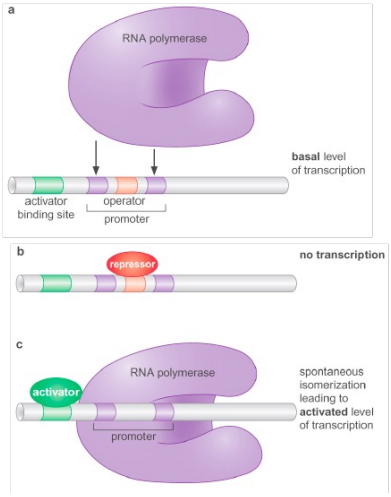
$$\begin{cases} \frac{d}{dt}[m_i] = \alpha_{m,i}[g_i] - \delta_{m,i}[m_i] \\ \frac{d}{dt}[p_i] = \alpha_{p,i}[m_i] - \beta_{p,i}[p_i] \end{cases}$$

2

transcriptional initiation and termination in bacteria



tsx init control by activators, repressors



4

Transcription regulation set molecularly by TF-TF and TF-RNAP interaction

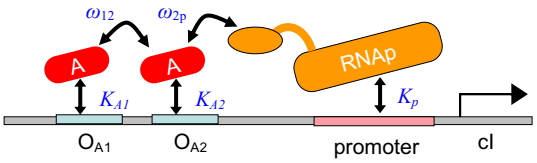
$$\frac{d}{dt}[m_i] = \alpha_{m,i}[g_i] - \delta[m_i]$$

$$\frac{d}{dt}[p_i] = \alpha_{p,i}[m_i] - \beta\,[p_i]$$

steady state (exponential growth):

$$[m]^* = \alpha_{m,i}[g_i]/\beta \qquad [p]^* = \frac{\alpha_{p,i}\alpha_{m,i}[g_i]}{\delta\,\beta}$$

growth rate

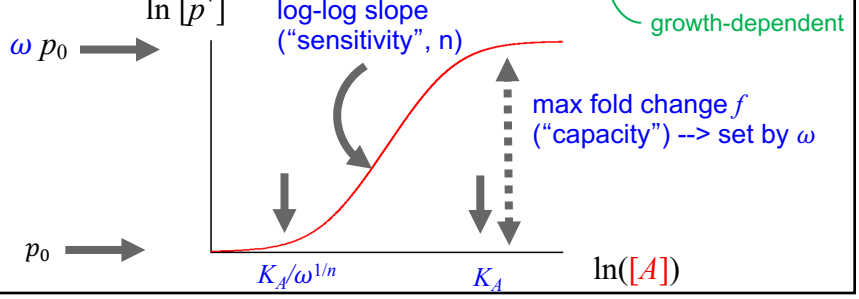


$$\alpha_{m,i} \propto \frac{1+\omega([A]/K_A)^n}{1+([A]/K_A)^n}$$

(Hill function)

$$[p]^* = p_0\frac{1+\omega([A]/K_A)^n}{1+([A]/K_A)^n}$$

growth-dependent

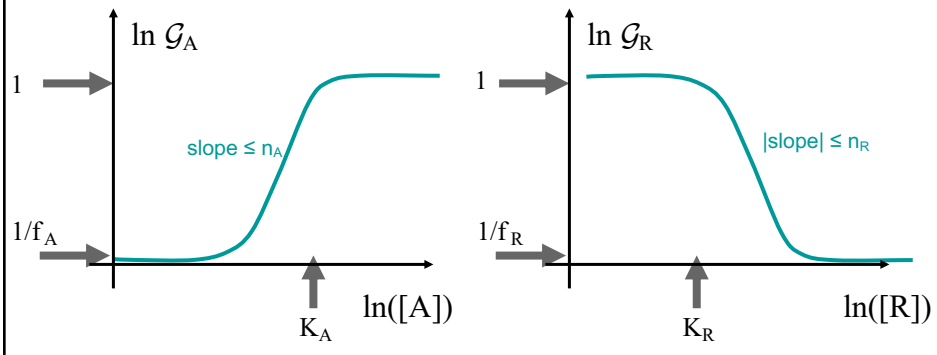


8

Simple circuit using transcriptional control

consider tsx init control only (for simplicity)

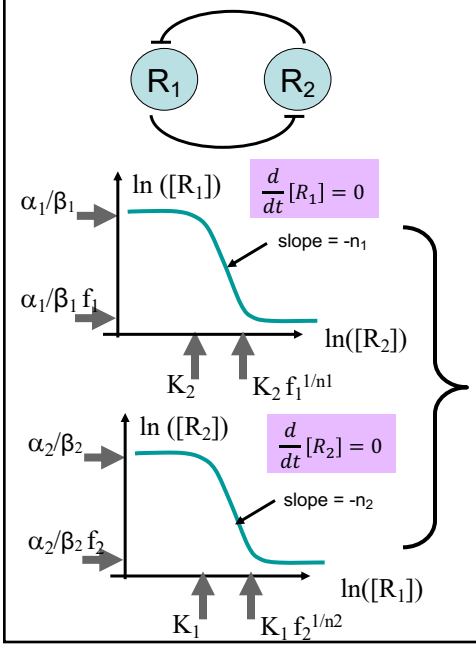
$$\frac{d}{dt}[p_i] = \alpha_0 \cdot \mathcal{G} - \beta\,[p_i]$$



$$\mathcal{G}_A = \frac{f_A^{-1} + ([A]/K_A)^{n_A}}{1 + ([A]/K_A)^{n_A}} \qquad \mathcal{G}_R = \frac{1 + f_R^{-1}([R]/K_R)^{n_R}}{1 + ([R]/K_R)^{n_R}}$$

15

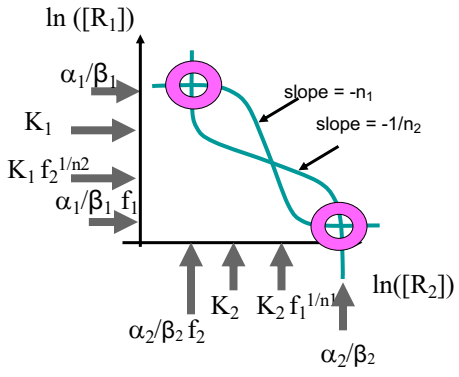
3. Toggle switch



- qualitatively, two stable states:
  - -- R1 on and R2 off
  - -- R1 off and R1 on
- quantitatively:

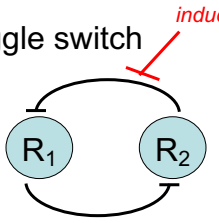
$$\frac{d}{dt}[R_1] = \alpha_1 \mathcal{G}_{R1}\left(\frac{[R_2]}{K_1}\right) - \beta_1[R_1]$$

$$\frac{d}{dt}[R_2] = \alpha_2 \mathcal{G}_{R2}\left(\frac{[R_1]}{K_2}\right) - \beta_2[R_2]$$



19

3. Toggle switch

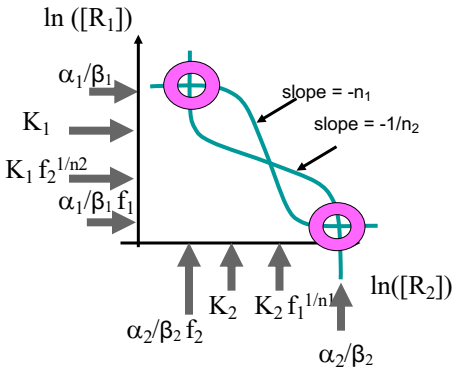


- bistability favored by
  - -- $n_1 \cdot n_2 \gg 1$
  - -- large f_1 and f_2
  - -- appropriate ranges of K,α,β
- defining feature of bistability:
  - ➔ remain in a state for a "long" time after initialized to it
- initialization by changing
  - -- K (via inducer)
  - -- α (via activator/repressor)
  - -- β (via proteolysis, temperature)

- qualitatively, two stable states:
  - -- R1 on and R2 off
  - -- R1 off and R1 on
- quantitatively:

$$\frac{d}{dt}[R_1] = \alpha_1 \mathcal{G}_{R1}\left(\frac{[R_2]}{K_1}\right) - \beta_1[R_1]$$

$$\frac{d}{dt}[R_2] = \alpha_2 \mathcal{G}_{R2}\left(\frac{[R_1]}{K_2}\right) - \beta_2[R_2]$$



20

Induction of TF

$$X + I \underset{k_-}{\overset{k_+}{\rightleftharpoons}} XI$$

dissociation constant $K_I \equiv \frac{[X]\cdot[I]}{[XI]} = \frac{k_-}{k_+}$

$[X]_{tot} = [X] + [XI]$

$$[XI] = [X]_{tot}\frac{[I]}{[I]+K_I} \approx [X]_{tot}\frac{[I]_{tot}}{[I]_{tot}+K_I}$$

usually $[I]_{tot} \gg [X]_{tot}$, so $[I] \approx [I]_{tot}$

will drop the subscript "tot" from here on

"activated TF" X^* = form of TF able to bind specifically to DNA or able to activate RNAp

if $X^* = XI$, then $[X^*] = [X]_{tot}\frac{[I]}{[I]+K_I}$

if $X^* = X$, then $[X^*] = [X]_{tot}\frac{K_I}{[I]+K_I}$

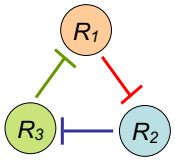
more generally, Hill form

$$[X^*] = [X]_{tot}\Big/\left(1 + \left(\frac{[I]}{K_I}\right)^{\pm n}\right)$$

or $[X^*] = [X]_{tot}\Big/\left(1 + \left(\frac{[I]}{K_I}\right)^{\pm 1}\right)$

21

4. Oscillators

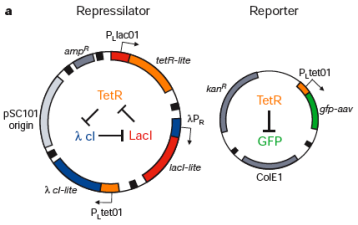


"Repressilator"

A synthetic oscillatory network of transcriptional regulators

Michael B. Elowitz & Stanislas Leibler

NATURE | VOL 403 | 20 JANUARY 2000



- a.k.a. ring-oscillator
- uses only transcriptional repressors (with protein degradation tags)
- modeling gives oscillation for sufficiently cooperative repression

$$\frac{d[R_1]}{dt} = \alpha_1 \cdot \mathcal{G}_{R1}\left([R_3]\right) - \beta_1 \cdot [R_1]$$

$$\frac{d[R_2]}{dt} = \alpha_2 \cdot \mathcal{G}_{R2}\left([R_1]\right) - \beta_2 \cdot [R_2]$$

$$\frac{d[R_3]}{dt} = \alpha_3 \cdot \mathcal{G}_{R3}\left([R_2]\right) - \beta_3 \cdot [R_3]$$