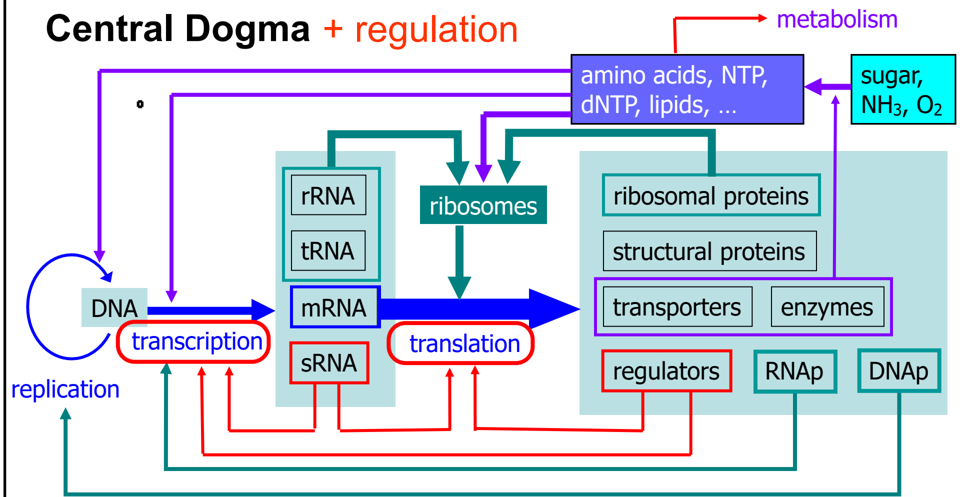
Central Dogma + regulation



- tsx initiation control by transcription factors (TF)
- tsl initiation control by sRNA and RNA-binding proteins
- tsx termination control by sRNA and anti-terminators
- control of mRNA and protein degradation
- control of enzyme activity by metabolites

coupled to environmental signals; coord growth program

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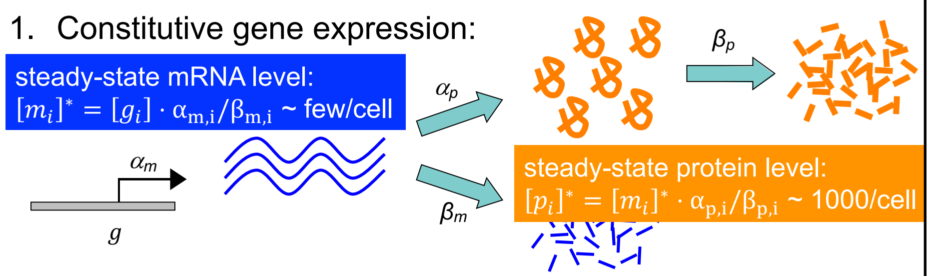
Integrated model of gene expression and regulation

1. Constitutive gene expression:



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

10-30 proteins/mRNA ("burstiness")

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

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

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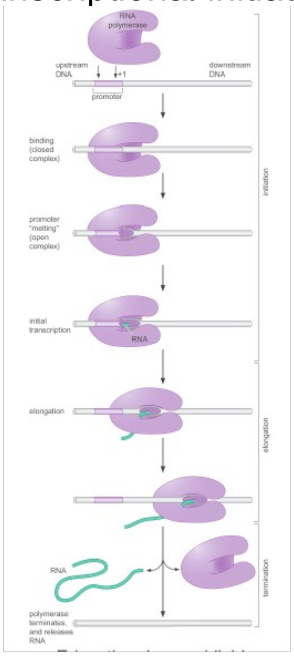
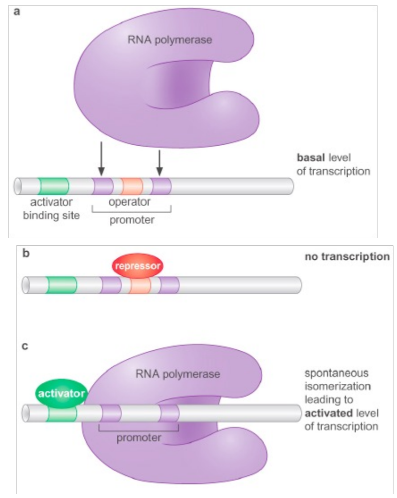
transcriptional initiation and termination in bacteria



tsx init control by activators, repressors



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

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

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

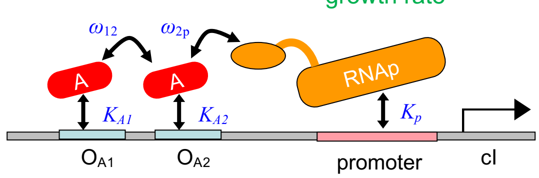
growth rate

steady state (exponential growth):

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

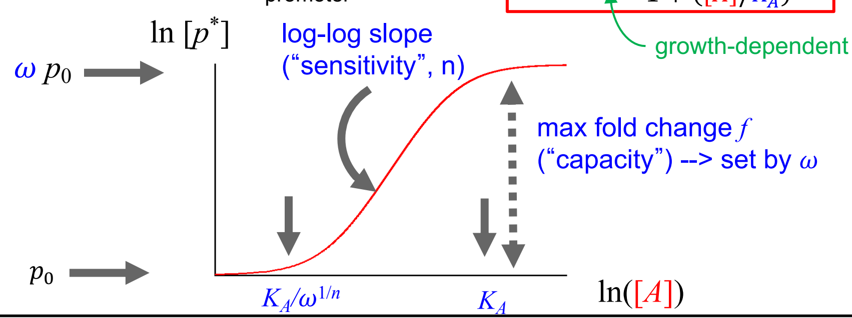
$$\alpha_{m,i} \propto \frac{1+\omega([A]/K_A)^n}{1+([A]/K_A)^n}$$

(Hill function)



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

growth-dependent



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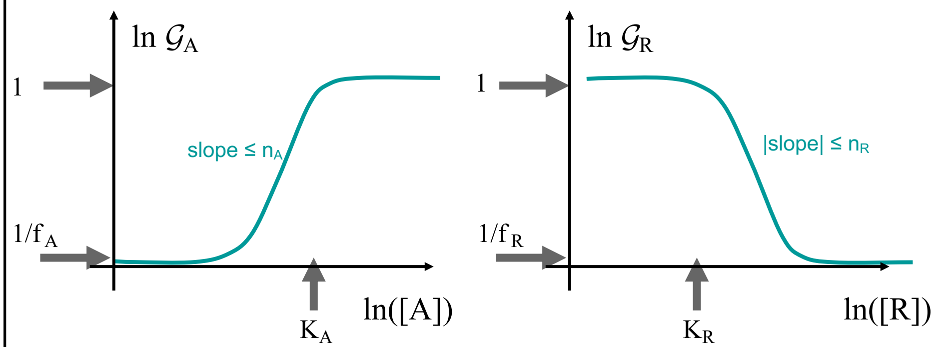
Simple circuit using transcriptional control

consider tsx init control only (for simplicity)

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



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

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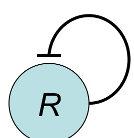
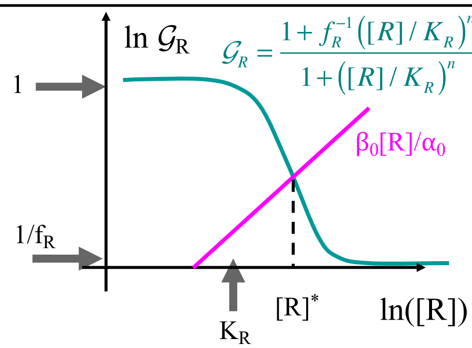
1. Negative autoregulation

(a very common network motif)



$$\frac{d}{dt}[R] = \alpha_o \mathcal{G}_R\left(\frac{[R]}{K_R}\right) - \beta_0[R]$$



assume circuit 'properly' biased: $K_R > [R]^* > f_R^{1/n} K_R$ or $K_R < \alpha_0/\beta_0 < K_R f_R^{1/n}$

steady-state solution: $\frac{[R]^*}{K_R} \approx \left(\frac{\alpha_0}{\beta_0 K_R}\right)^{1/(n+1)}$

➔ general dependence of parameters on cellular physiology:
- β_0 = dilution due to cell growth; can vary ~10x
- α_0 > 2-fold change thru cell cycle (gene dosage, Rb conc, etc) also strongly dependent on growth rate

➔ complex circuits usually cannot tolerate wildly floating operation points

➔ expect $[R]^*/K_R$ to be insensitive to parameters if n is large
[= homeostatic control]

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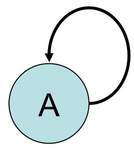
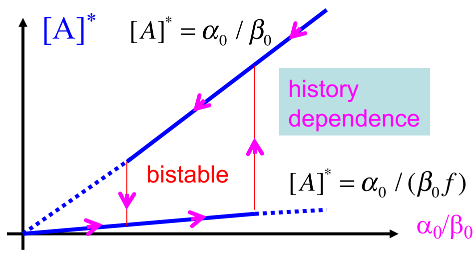
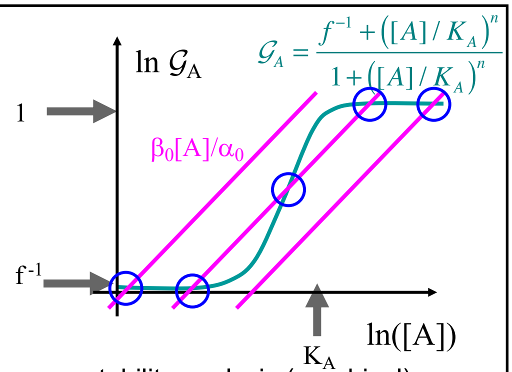
2. Positive autoregulation



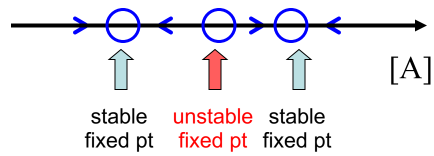
$$\frac{d}{dt}[A] = \alpha_o \mathcal{G}_A\left(\frac{[A]}{K_A}\right) - \beta_0 [A]$$

- large β_0/α_0, $[A]^*$ ≈ basal level
- small β_0/α_0, $[A]^*$ ≈ saturated level
- intermediate β_0/α_0, $[A]^*$ has 3 soln



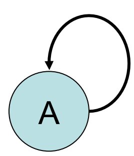


stability analysis (graphical):



➔ regime of bistability from the existence of unstable fixed point

2. Positive autoregulation



$$\frac{d}{dt}[A] = \alpha_o \mathcal{G}_A\left(\frac{[A]}{K_A}\right) - \beta_0 [A]$$

stability analysis (analytic):

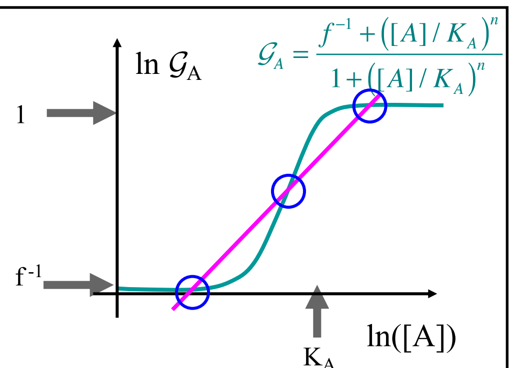
small perturbation: $\delta A \equiv [A] - [A]^*$

$$\frac{d}{dt}\delta A = \alpha_o \left.\frac{\partial \mathcal{G}_A}{\partial [A]}\right|_{[A]^*} \cdot \delta A - \beta_0 \cdot \delta A$$

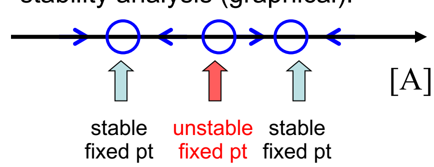
$$= \left(s^* - 1\right) \cdot \beta_0 \cdot \delta A$$

where $s^* \equiv \left.\frac{\partial \ln \mathcal{G}_A}{\partial \ln [A]}\right|_{[A]^*}$ is "sensitivity".

➔ $s^* > 1$ for bistability

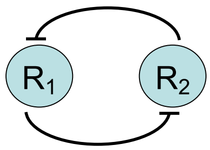


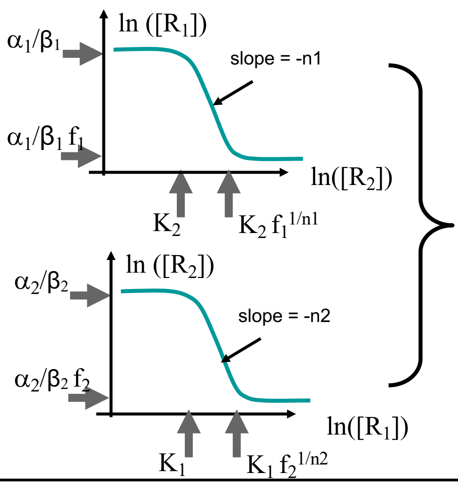
stability analysis (graphical):



➔ regime of bistability from the existence of unstable fixed point

3. Toggle switch

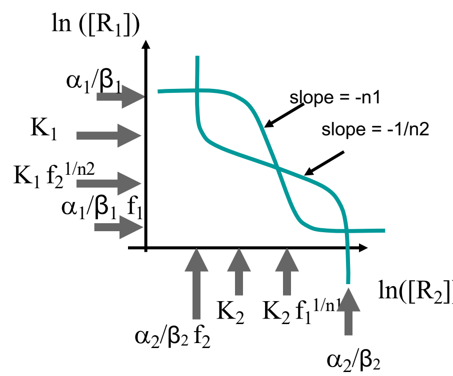




- qualitatively, two stable states:
  - -- R1 on and R2 off
  - -- R1 off and R1 on
- quantitatively:

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

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



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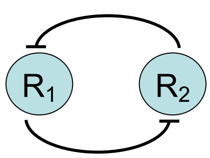
3. Toggle switch

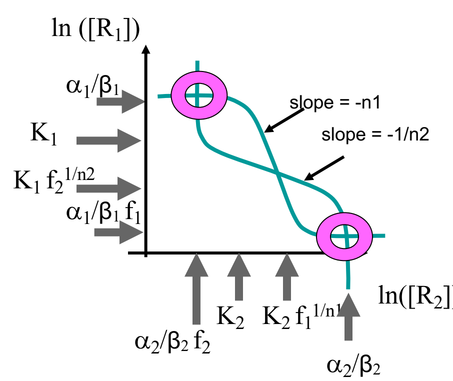


- bistability favored by
  - -- $n_1 \cdot n_2 \gg 1$
  - -- large f_1 and f_2
  - -- appropriate ranges of K, α, β
- defining feature of bistability:
  - ➔ remain in a state for a "long" time after initialized to it
- initialization by changing
  - -- K (via inducer)
  - -- α (via activator/repressor)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

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

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

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



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

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

more generally, Hill form

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

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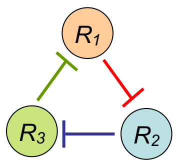
4. Oscillators

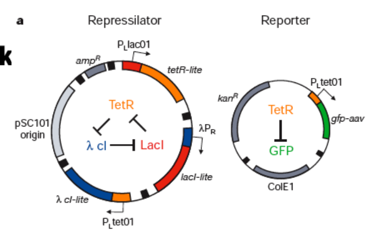


"Repressilator"

A synthetic oscillatory network of transcriptional regulators

Michael B. Elowitz & Stanislas Leibler

NATURE | VOL 403 | 20 JANUARY 2000 |

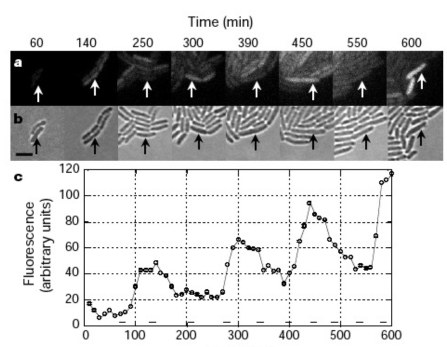


- a.k.a. ring-oscillator
- uses only transcriptional repressors (with protein degradation tags)
- modeling gives oscillation for sufficiently cooperative repression

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

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

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



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