Bioinformatics: Network Analysis

Kinetics of Gene Regulation

COMP 572 (BIOS 572 / BIOE 564) - Fall 2013
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Regulation of Gene Expression

- The simplest model of gene expression involves only two steps:
  - the transcription of a gene into mRNA, and
  - the translation of the mRNA into protein.

Regulation of Gene Expression

- Consider the expression of a gene **x** that encodes protein **X** and is regulated by the promoter **P**.

- When each cell harbors n_A active promoters from which the mRNA of gene **x** is transcribed at an average rate k, the approximation of the rate of mRNA change gives the differential equation

$$\frac{\mathrm{d}n_m}{\mathrm{d}t} = n_A k - d_m n_m$$

where d_m is the rate constant associated with mRNA degradation.

Regulation of Gene Expression

- mRNA molecules are usually degraded rapidly, compared to other cellular processes, and it is often assumed that the concentration of mRNA rapidly reaches a pseudo-steady state, where $n_m = n_A k / d_m$, such that $\mathrm{d}n_m / \mathrm{d}t = 0$.

Regulation of Gene Expression

- The mRNA is translated into a protein by ribosomes, and it is assumed that each **x** mRNA molecule gives rise to $b_x = k_{tl,x}/d_m$ copies of the protein **X**, where $k_{tl,x}$ is the average translation rate.

- The equation that governs the evolution of the number of proteins, n_X, produced from n_m mRNA molecules is given by

$$\frac{\mathrm{d}n_X}{\mathrm{d}t} = k_{tl,x} n_m - k_X n_X$$

where k_X is the protein degradation rate constant.

Regulation of Gene Expression

- When a pseudo-steady state approximation is invoked for mRNA ($n_m=n_A k/d_m$), it is obtained that $k_{tl,x}n_m=k_{tl,x}n_A k/d_m=b_x n_A k$.

- The equation for the number of proteins takes the form

$$\frac{\mathrm{d}n_X}{\mathrm{d}t} = b_x n_A k - k_X n_X$$

where k_X is the rate of protein degradation.

Regulation of Gene Expression

- It is convenient to convert the equation for the evolution of the total number of proteins per cell into an equation for the evolution of cellular protein concentration, $X(t)=n_X(t)/v(t)$, where $v(t)$ is the cell volume.

- In this case, we have

$$\frac{\mathrm{d}X}{\mathrm{d}t} = \frac{\mathrm{d}(n_X(t)/v(t))}{\mathrm{d}t} = \frac{\frac{\mathrm{d}n_X(t)}{\mathrm{d}t}\cdot v(t) - n_X(t)\cdot\frac{\mathrm{d}v(t)}{\mathrm{d}t}}{v^2(t)}$$

$$= \frac{1}{v(t)}\left(\frac{\mathrm{d}n_X(t)}{\mathrm{d}t} - X\frac{\mathrm{d}v(t)}{\mathrm{d}t}\right)$$

$$= b_x\cdot k\cdot A(t) - (k_X + k_g)\cdot X$$

where $A(t)=n_A(t)/v(t)$ is the concentration of active promoters, and k_g is a constant associated with cell volume growth.

Regulation of Gene Expression

- *A(t)* depends on the concentration of the transcription factors that are bound to the promoter region at a given time.

- Consider the formation of a complex **PE** between the (unoccupied)promoter, **P**, and a transcriptional effector **E** of that promoter through the cooperative binding of β effector molecules to the unoccupied promoter.

- This scheme can be represented by the reversible chemical reaction of the Hill type with the equilibrium constant *K*:

$$\beta\mathbf{E} + \mathbf{P} \rightleftharpoons \mathbf{PE} \qquad K = \frac{PE}{E^{\beta} \cdot P}$$

Regulation of Gene Expression

- The total concentration of promoters is proportional to the concentration P_{tot} of the plasmid that carries the promoter.

- Simplifying assumption: It is assumed that the number of plasmids (and, hence, of promoters) per cell scales proportionally with the cell volume such that the plasmid concentration remains fairly constant throughout the cell division cycle, i.e., that $P_{tot}=P(t)+PE(t)$ is constant.

- Combining this assumption with the equilibrium relation (on the previous slide), the conservation of plasmid concentration can be used to derive the concentration of the active promoter A.

Regulation of Gene Expression

- We have to deal with two cases:
  - Case 1: The effector **E** is a transcriptional repressor.
  - Case 2: The effector **E** is a transcriptional activator.

Regulation of Gene Expression

- Case 1: The effector **E** is a transcriptional repressor:
  - The unoccupied promoters are supposed to be active, and $A^R=P$ (the superscript R stands for the repression case).
- Here, we have $P_{tot}=P+PE=P+K\cdot E^{\beta}\cdot P=A^R+K\cdot E^{\beta}\cdot A^R$.
- Then, in this case, we have

$$A^R = \frac{P_{tot}}{1 + K \cdot E^{\beta}}$$

Regulation of Gene Expression

- Case 2: The effector **E** is a transcriptional activator:
  - The unoccupied promoters are assumed to be passive, and $A^A = PE$ (the superscript R stands for the activation case).
- Here, we have $P_{tot} = P + PE = A^A / K \cdot E^{\beta} + A^A$.
- Then, in this case, we have

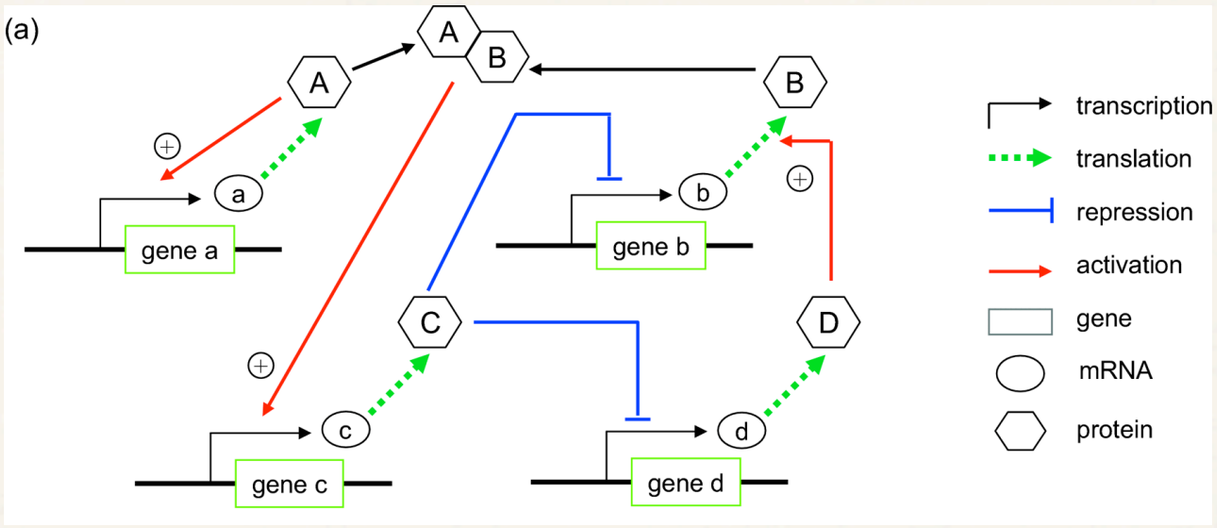
$$A^A = \frac{P_{tot} \cdot K \cdot E^{\beta}}{1 + K \cdot E^{\beta}}$$

Regulation of Gene Expression

- The two cases can be combined by introducing an exponent *a* that takes the value 0 in the repression case and 1 in the activation case:

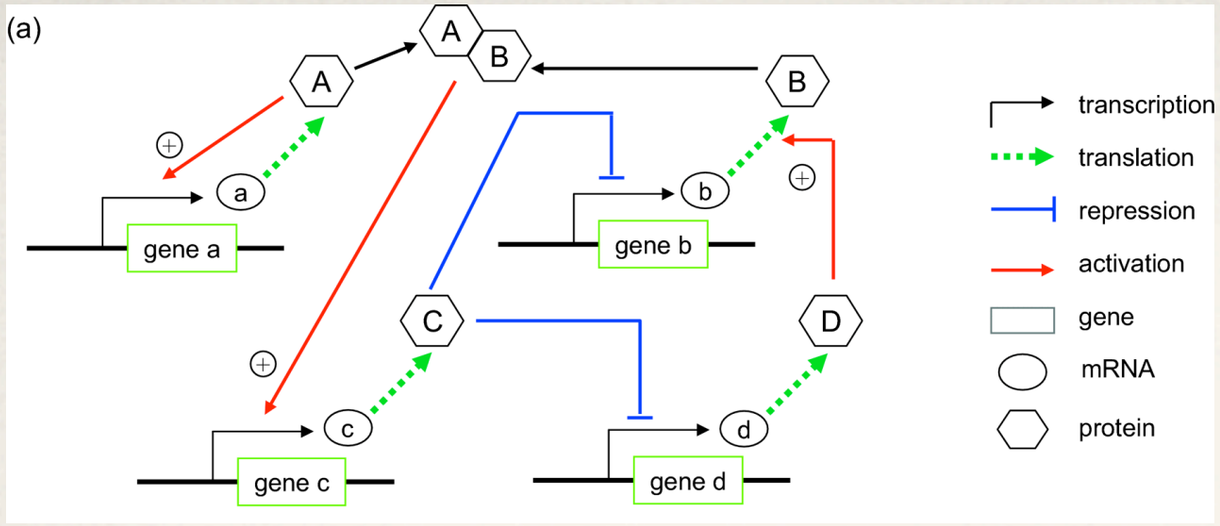
$$A = \frac{P_{tot} \cdot (K \cdot E^{\beta})^{a}}{1 + K \cdot E^{\beta}}$$

Describing GRN Dynamics with ODEs



$$\frac{\mathrm{d}a}{\mathrm{d}t} = f_a(a) \qquad \frac{\mathrm{d}b}{\mathrm{d}t} = f_b(b, c, d)$$

$$\frac{\mathrm{d}c}{\mathrm{d}t} = f_c(a, b, c) \qquad \frac{\mathrm{d}d}{\mathrm{d}t} = f_d(c, d)$$

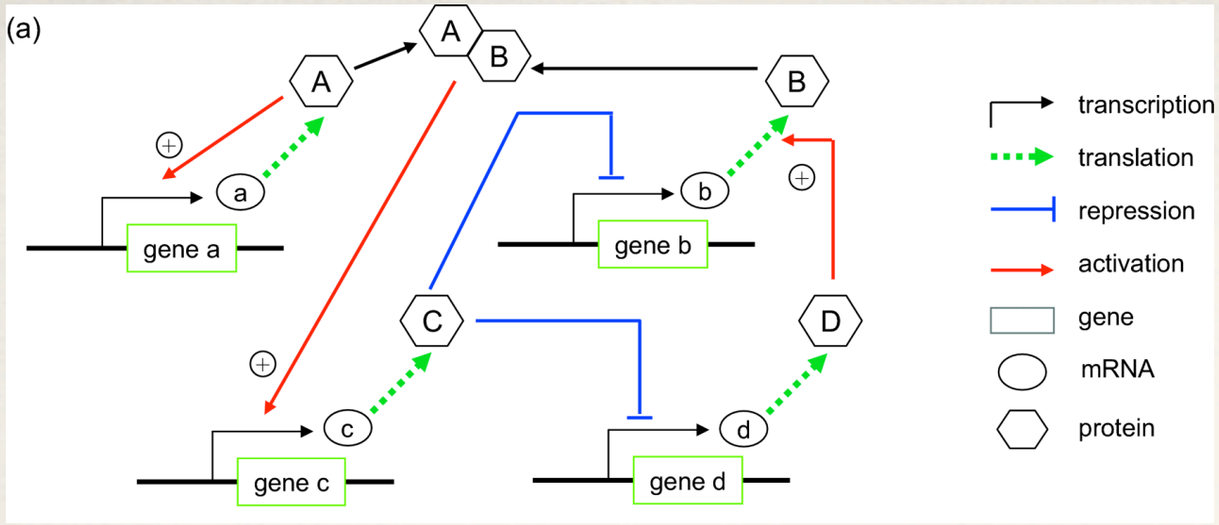


$$\frac{\mathrm{d}a}{\mathrm{d}t} = f_a(a)$$

$$f_a(a) = v_a - k_a \cdot a$$

constant rate of expression of gene **a**

rate constant of degradation of mRNA **a**

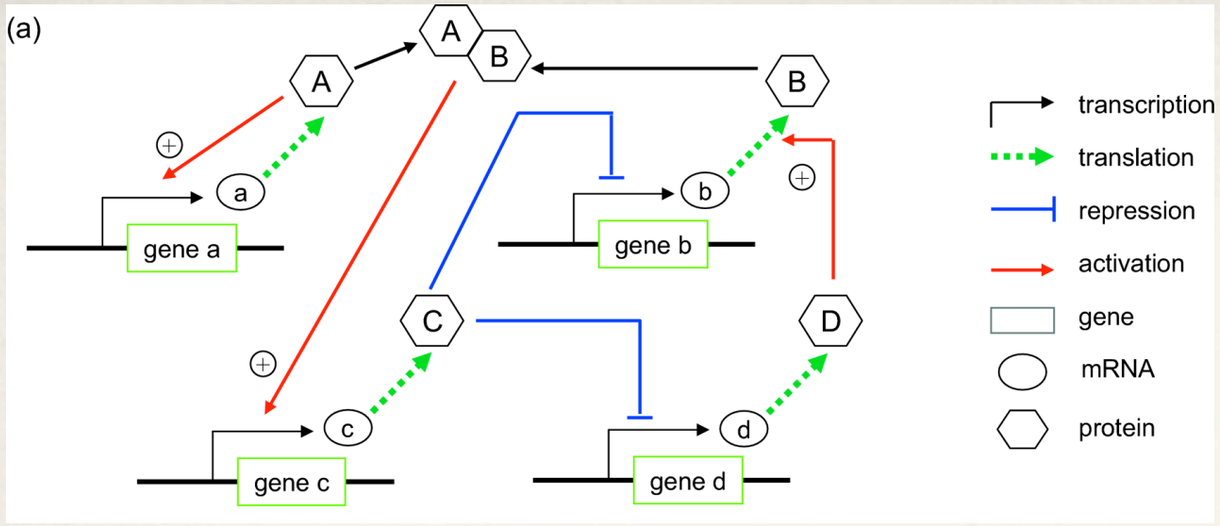


$$\frac{\mathrm{d}b}{\mathrm{d}t} = f_b(b, c, d)$$

$$f_b(b, c, d) = \frac{V_b \cdot d^{n_d}}{K_b + d^{n_d}} \frac{1}{K_{Ic} + c^{n_c}} - k_b \cdot b$$

Hill term that describes the formation of **b** activated by **d** with maximal rate V_b, dissociation constant K_b, and Hill coefficient n_d

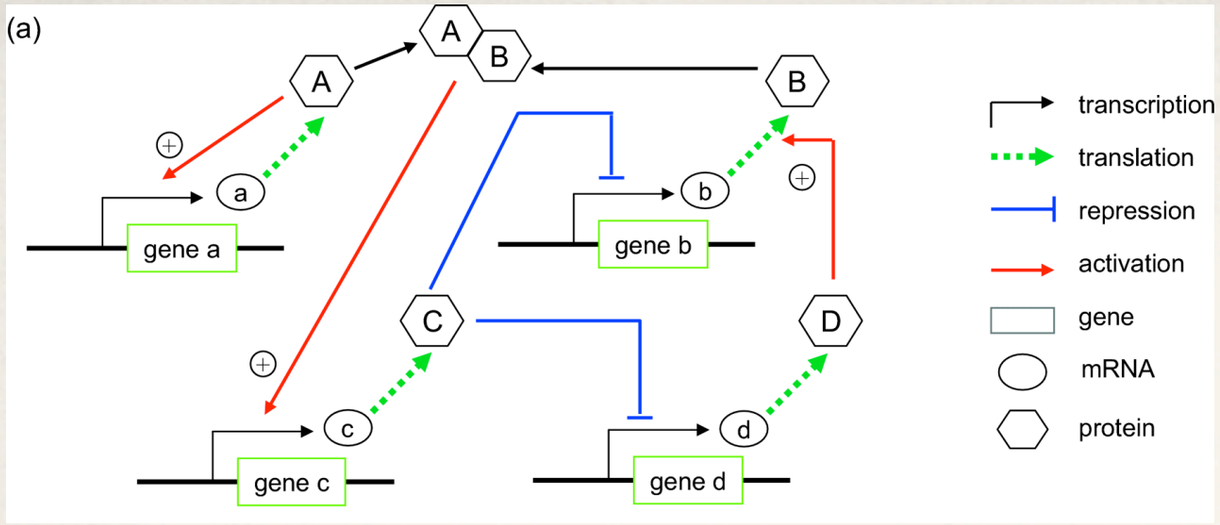
Inhibition of **b** by **c**



$$\frac{\mathrm{d}c}{\mathrm{d}t} = f_c(a, b, c)$$

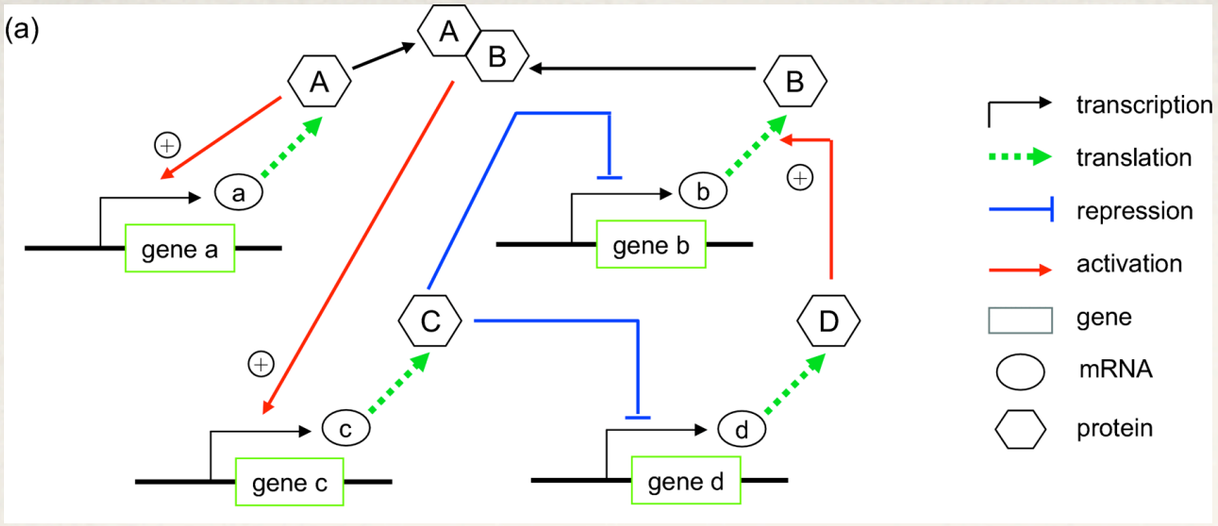
$$f_c(a, b, c) = \frac{V_c \cdot (a \cdot b)^{n_{ab}}}{K_c + (a \cdot b)^{n_{ab}}} - k_c \cdot c$$

Hill term that describes the formation of **c**



$$\frac{\mathrm{d}d}{\mathrm{d}t} = f_d(c,d)$$

$$f_d(c,d) = \frac{V_d}{K_{Ic} + c^{n_c}} - k_d \cdot d$$



$$\frac{\mathrm{d}a}{\mathrm{d}t} = f_a(a) \qquad \frac{\mathrm{d}b}{\mathrm{d}t} = f_b(b,c,d)$$

$$\frac{\mathrm{d}c}{\mathrm{d}t} = f_c(a,b,c) \qquad \frac{\mathrm{d}d}{\mathrm{d}t} = f_d(c,d)$$

$$f_a(a) = v_a - k_a \cdot a$$

$$f_b(b,c,d) = \frac{V_b \cdot d^{n_d}}{K_b + d^{n_d}} \frac{1}{K_{Ic} + c^{n_c}} - k_b \cdot b$$

$$f_c(a,b,c) = \frac{V_c \cdot (a \cdot b)^{n_{ab}}}{K_c + (a \cdot b)^{n_{ab}}} - k_c \cdot c$$

$$f_d(c,d) = \frac{V_d}{K_{Ic} + c^{n_c}} - k_d \cdot d$$

v_a=1, k_a=1,

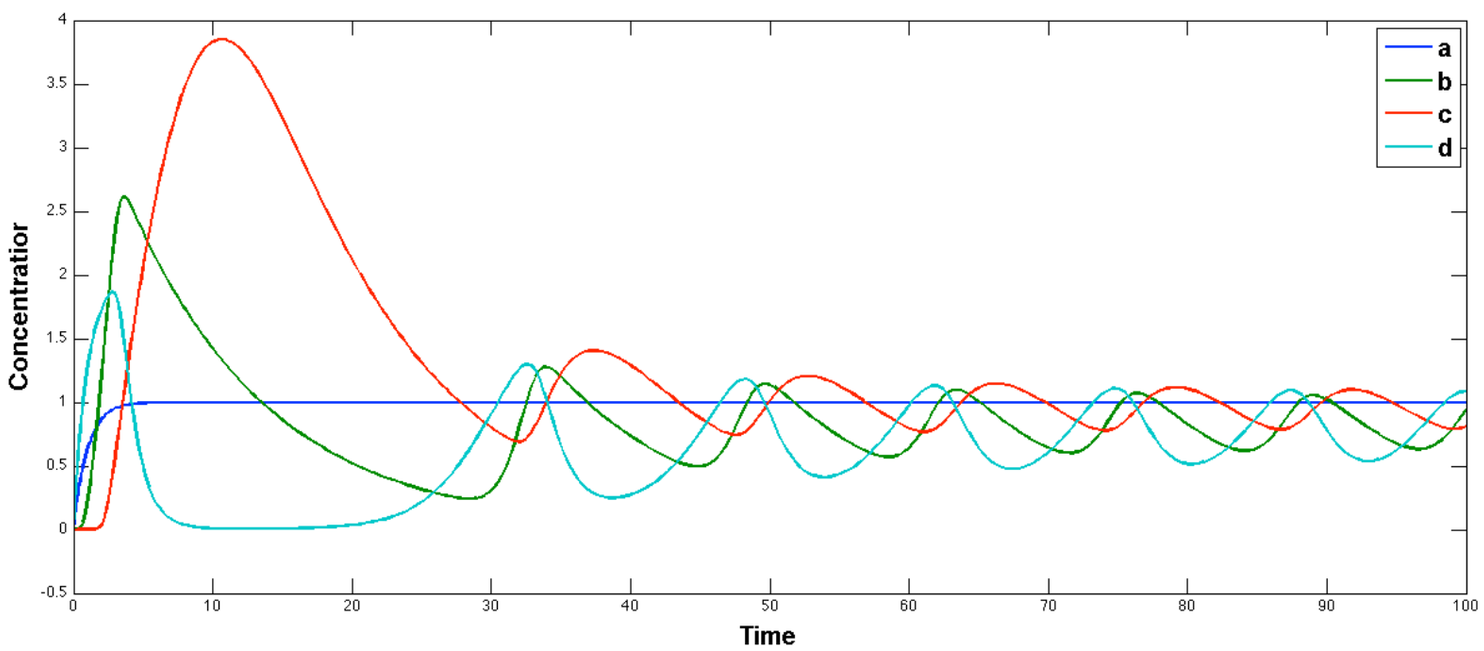
V_b=1, K_b=5, K_{Ic}=0.5, k_b=0.1,

V_c=1, K_c=5, k_c=0.1,

V_d=1, k_d=1,

n_{ab}=4, n_c=4, n_d=4.

a(0)=b(0)=c(0)=d(0)=0.



Acknowledgments

- *"Synchrony in a population of hysteresis-based genetic oscillators"*, Kuznetsov *et al.*, SIAM J. Appl. Math., 65(2): 392-425, 2004.