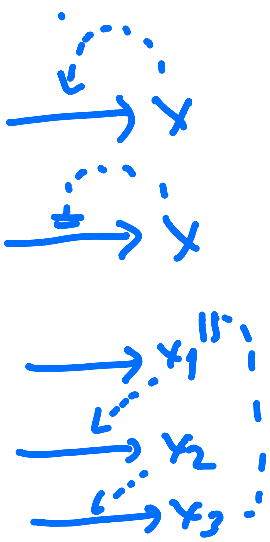
W11- Feedback control in biological Interactions

} Nelson chp 9
Gonze, Tyson write-ups

Feedback loops: gene regulation*
RNA, mb, synthesis*
protein phosphorylation
catalysis *
cell cycle and circadian rhythms



activation --- regulatory

inhibition

chemical reactions

feedback loops occur in chemical reaction

$$A + B \xrightarrow{k} C + D$$

$$\eta(A) \quad \eta(B) \quad \eta(C) \quad \eta(D)$$

$$-1 \quad -1 \quad + \quad +$$

$$A + B \xrightarrow{\kappa} C + D$$

$$W(A, B, C, D) = \kappa A B$$

$$\frac{dA}{dt} = -\eta_A W = \kappa A B$$

$$\frac{dB}{dt} = -\eta_B W = \kappa A B$$

$$\frac{dC}{dt} = -\eta_c W = -\kappa A B$$

$$\frac{dD}{dt} = -\eta_d W = -\kappa A B$$

where does this come from?

a Markov process

$$t \longrightarrow t + \Delta t$$

$$\begin{pmatrix} A \\ B \\ C \\ D \end{pmatrix} \xrightarrow{\Delta t\, \kappa A B} \begin{pmatrix} A-1 \\ B-1 \\ C+1 \\ D+1 \end{pmatrix}$$

$$\begin{pmatrix} A \\ B \\ C \\ D \end{pmatrix} \xrightarrow{1 - \kappa A B \Delta t} \begin{pmatrix} A \\ B \\ C \\ D \end{pmatrix}$$

$$P(A\,B\,C\,D \mid t + \Delta t) = \Delta t\, \kappa (A+1)(B+1)\, P(A+1, B+1, C-1, D-1 \mid t)$$

$$+ (1 - \Delta t\, \kappa A B)\, P(A, B, C, D \mid t)$$

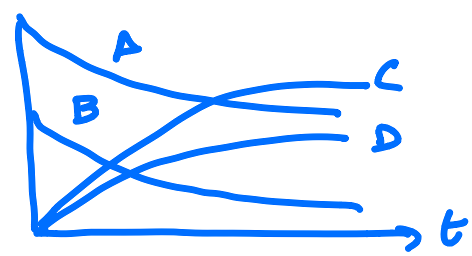
$$\frac{dP(ABCD|t)}{dt} = K(A+1)(B+1)P(A+1, B+1, C-1, D-1|t) - KAB\,P(ABCD|t)$$

$$\sum_{C,D}\sum_{B}\sum_{A} A\frac{dP}{dt} = K\sum_{\substack{A\\BCD}} A(A+1)(B+1)\,P(A+1, B+1\,C-1\,D-1|t) - K\sum A^2B\,P(A, B, C, D|t)$$

$$\frac{d\langle A\rangle_t}{dt} = K\sum(A-1)AB\;P(ABCD|t) - K\sum A^2B\,P(ABCD|t)$$

$$= -K\sum AB\,P(ABCD|t)$$

$$= -K\langle AB\rangle_t$$



General reaction

$$n_1 X_1 + \ldots + n_N X_N \xrightarrow{\kappa} p_1 X_1 + \ldots + p_N X_N$$

$$\nu(x) = \kappa\, x_1^{n_1} \cdots x_N^{n_N}$$ mass action

averages of propensities

$$\eta(x_i) = p_i - n_i$$ stoichiometry

$$\boxed{\frac{dx_i}{dt} = \eta(x_i)\, \nu(\bar{x})}$$

Again, this is the $\Delta t \to 0$ evolution of

averages $\quad \langle x_i \rangle_t = \sum_{x_1 \ldots x_N} x_i\, P(x_1 \ldots x_N | t)$

for $P(x_1 .. x_N | t)$ describing the underlying

Markov process

$$t \xrightarrow{\Delta t} t + \Delta t$$

$$x_i \xrightarrow{\kappa \Delta t\, w(x)} x_i + \eta_i$$

$$x_i \xrightarrow{1 - \kappa \Delta t\, w(x)} x_i$$

$$P(x_1 \ldots x_N | t + \Delta t) = \kappa \Delta t\, w(\bar{x} + \eta)\, P(\bar{x} - \eta | t) + [1 - \kappa \Delta t\, w(x)]\, P(\bar{x} | t)$$

$$\frac{dP}{dt} = \kappa\, w(\bar{x} - \eta)\, P(x - \eta | t) - \kappa\, w(x)\, P(x | t)$$

Examples.

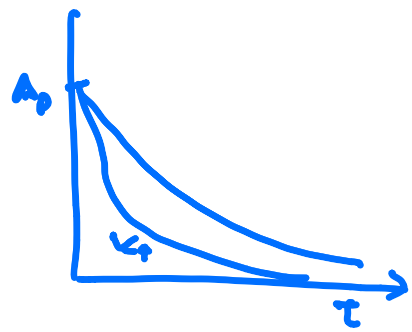
$A \rightarrow \phi$ degradation

$A \xrightarrow{k} A^*$ change

$A \xrightarrow{k} B + C$ dissociation.

$$\frac{dA}{dt} = -kA$$

$$\frac{dB}{dt} = kA = \frac{dC}{dt}$$



$$A(t) = A_0 e^{-kt}$$

• Cooperative

		$\eta(A)$	$\eta(C)$
$3A \xrightarrow{k} C + A$		-2	$+1$

$$W = kA^3$$

$$\frac{dA}{dt} = -2kA^3$$

• Serial reactions

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

	$\eta_1(A)$	$\eta_1(B)$	$\eta_1(C)$	W
r_1: $A \xrightarrow{k_1} B$	-1	$+1$	0	$k_1 A$
r_2 $B \xrightarrow{k_2} C$	0	-1	$+1$	$k_2 B$

$$\frac{dA}{dt} = -k_1 A, \quad \frac{dB}{dt} = k_1 A - k_2 B$$

$$\frac{dc}{dt} = +k_2 B$$

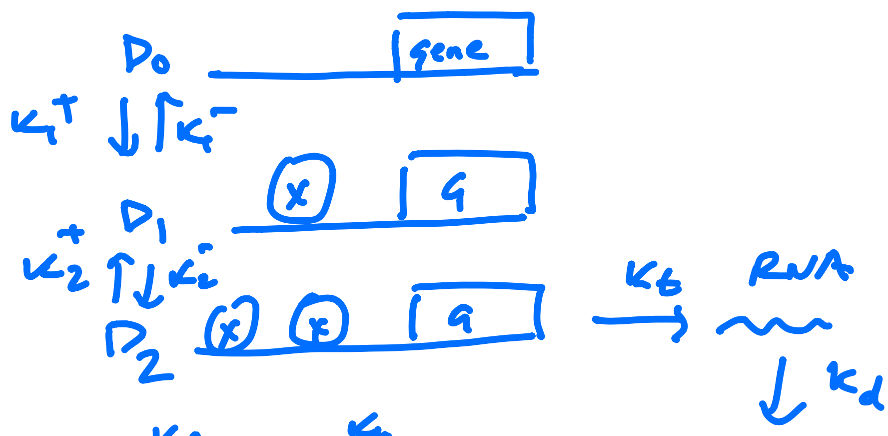
Multiple reactions

$$n_1^1 X_1 + \quad + n_N^1 X_N \to p_1^1 X_1 + \ldots + p_N^1 X_N$$

$$n_1^r X_1 + \quad + n_N^r X_N \to p_1^r X_1 + \quad + p_N^r X_N$$

$$\frac{dX_i}{dt} = \sum_r \eta_r(X_i)\, w_r(\bar{X})$$

Transcriptional activation



$$\phi \xrightarrow{k_a} X \xrightarrow{k_b} \phi$$

assume: $k^+_{1,2} \approx k^-_{1,2} \gg k_t$

ν_r

r	reaction	w_r	X	D_0	D_1	D_2	R
1	$\phi \xrightarrow{k_a} X$	k_a	+1	0	0	0	0
2	$X \xrightarrow{k_b} \phi$	$k_b \cdot X$	-1	0	0	0	0
3	$X + D_0 \xrightarrow{k_1^+} D_1$	$k_1^+ X D_0$	-1	-1	+1	0	0
4	$D_1 \xrightarrow{k_1^-} D_0 + X$	$k_1^- D_1$	+1	+1	-1	0	0
5	$X + D_1 \xrightarrow{k_2^+} D_2$	$k_2^+ X D_1$	-1	0	-1	+1	0
6	$D_2 \xrightarrow{k_2^-} D_1 + X$	$k_2^- D$	1	0	1	-1	0
7	$D_2 \xrightarrow{k_t} D_2 + RNA$	$k_t D_2$	0	0	0	0	+1
8	$RNA \xrightarrow{k_d} \phi$	$k_d R$	0	0	0	0	-1

$$\frac{dX}{dt} = K_a - K_b X - K_1^+ X D_0 + K_1^- D_1$$

$$\frac{dD_1}{dt} = -\frac{dD_0}{dt} = K_1^+ X D_0 - K_1^- D_1$$

$$\frac{dR}{dt} = K_1 D_1 - K_2 R$$

$$K_1^+, K_1^- \gg K_b \rightarrow K_1^+ X D_0 = K_1^- D_1$$

$$D_1 = \frac{K_1^+}{K_1^-} X \cdot (D_T - D_1)$$

$$D_1 = D_T \frac{X K_1^+ / K_1^-}{1 + \frac{K_1^+}{K_1^-} X}$$

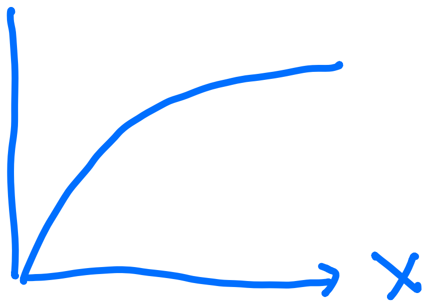
$$D_1 = D_T \frac{X}{\frac{K_1^-}{K_1^+} + X} \qquad K_1 \equiv \frac{K_1^-}{K_1^+}$$

$$D_1 = D_T \frac{X}{K_1 + X}$$

$$\frac{dx}{dt} = x_a - k_b x$$

$$\frac{dR}{dt} = \underbrace{k_t D_T}_{v} \frac{x}{k_1 + x} - k_d R$$

$$k_1 \sim k \frac{x}{k_1 + x}$$



Multiple binding sites

$$\phi \xrightarrow{k_a} X$$
$$X \xrightarrow{k_b} \phi$$
$$X + D_0 \xrightarrow{k_1^+} D_1$$
$$D_1 \xrightarrow{k_1^-} D_0 + X$$
$$D_1 + X \xrightarrow{k_2^+} D_2$$
$$D_2 \xrightarrow{k_2^-} D_1 + X$$
$$D_2 \xrightarrow{k_b} D_2 + R$$
$$R \xrightarrow{k_d} \phi$$

$$\frac{dX}{dt} = k_a - k_b X - k_1^+ X D_0 + k_1^- D_1 - k_2^+ X D_1 + k_2^- D_2$$

$$\frac{dD_0}{dt} = -k_1^+ X D_0 + k_1^- D_1$$

$$\frac{dD_1}{dt} = k_1^+ X D_0 - k_1^- D_1 + k_2^+ X D_1 - k_2^- D_2$$

$$\frac{dD_2}{dt} = k_2^- D_2 - k_2^+ X D_1$$

$$\frac{dR}{dt} = k_b D_2 - k_d R$$

$$\frac{dD_0}{dt} = \frac{dD_1}{dt} = \frac{dD_2}{dt} = 0$$

$$k_2^- D_2 = k_2^+ X D_1$$
$$k_1^- D_1 = k_1^+ X D_0$$

$$K_1 = \frac{k_1^-}{k_1^+} \quad K_2 = \frac{k_2^-}{k_2^+}$$

$$K_2 D_2 = X D_1$$
$$K_1 D_1 = X D_0$$

$$D_1 = \frac{X D_0}{K_1}$$

$$D_2 = \frac{X D_1}{K_2} = \frac{X^2}{K_2} \frac{D_0}{K_1}$$

$$D_T = D_0 + D_1 2 + D_2 = D_0 + 2\frac{x D_0}{K_1} + \frac{x^2}{K_1 K_2} D_0$$

$$= \left(1 + 2\frac{x}{K_1} + \frac{x^2}{K_1 K_2}\right) D_0$$

$$D_0 = \frac{D_T}{1 + 2\frac{x}{K_1} + \frac{x^2}{K_1 K_2}}$$

$$\frac{dR}{dt} = k_t D_2 = k_t \frac{x^2}{K_1 K_2} \cdot \frac{D_T}{1 + 2\frac{x}{K_1} + \frac{x^2}{K_1 K_2}}$$

$$\frac{dR}{dt} = k_t \frac{\frac{x^2}{K_1 K_2} D_T}{1 + 2\frac{x}{K_1} + \frac{x}{K_1}\frac{x}{K_2}}$$

① non cooperative binding.

$$K_1 = K_2 = K$$

$$\frac{dR}{dt} = k_t \cdot \frac{(x/K)^2 D_T}{(1 + x/K)^2} = k_t D_T \left(\frac{x/K}{1 + x/K}\right)^2$$

② Cooperative binding

$K_2 << K_1$

$$\frac{dR}{dt} = k_t D_T \frac{\frac{x^2}{K_1 K_2}}{1+2\frac{x}{K_1}+\frac{x^2}{K_1 K_2}}$$

$K^2 = K_1 K_2$

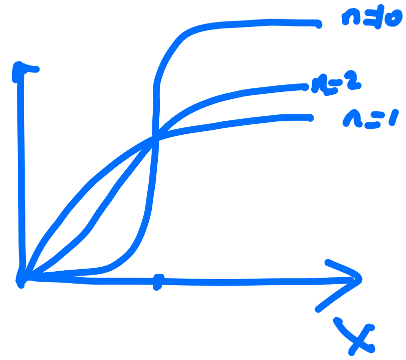
$K_2 \to 0$ K is finite $\to$ $$\frac{dR}{dt} = k_t D_T \frac{x^2/K^2}{1+2\frac{x}{K_1}+\left(\frac{x}{K}\right)^2}$$

$K_1 \to \infty$

$K_1 >> K$

$$\frac{dR}{dt} \simeq k_t D_T \frac{x^2/K^2}{1+x^2/K^2}$$

$$= v \frac{x^2}{K^2+x^2}$$



In general $$\frac{dR}{dt} = v \frac{K^n}{K^n+x^n}$$

Transcriptional inhibition

$$\phi \to X \to \phi$$

$$\frac{dX}{dt} = k_a - k_d X - k_1^- X D_0 + k_1^- D_1$$

$$X + D_0 \underset{k_1^-}{\overset{k_1^+}{\rightleftharpoons}} D_1$$

$$D_0 \xrightarrow{k_t} D_0 + R$$

$$\frac{dD_0}{dt} = -k_1^+ X D_0 + k_1^- D_1$$

$$\frac{dD_1}{dt} = k_1^+ X D_0 - k_1^- D_1$$

$$k_1^+ X D_0 = k_1^- D_1$$

$$K_1 = k_1^- / k_1^+ \qquad X D_0 = K_1 D_1$$

$$D_0 = K_1 \frac{D_1}{X} = K_1 \frac{(D_T - D_0)}{X}$$

$$D_0 = \frac{K_1/X \, D_T}{1 + K_1/X}$$

$$\frac{dR}{dt} = k_t D_T \frac{K_1/X}{1 + K_1/X}$$

$$= k_T D_T \frac{K_1}{X + K_1} \to \frac{K_1^n}{X^n + K_1^n}$$