Computational Systems Biology

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目录

1 Michaelis-Menten Kinetics

1.1 Law of Mass Action

Basic chemical reaction: $A \xrightarrow{k} B$.

Law of Mass Action: $\frac{d[A]}{dt} = -k[A], \frac{d[B]}{dt} = k[A]$. k: rate constant.

With back reaction: $A \underset{k_-}{\overset{k_+}{\rightleftharpoons}} B$. k_+: forward rate constant, k_-: backward rate constant.

If $k_+ >> k_-$, ignore k_-.

At steady state, $0 = \frac{d[A]}{dt} = -k_+[A] + k_-[B] = -\frac{d[B]}{dt} \Rightarrow \frac{k_-}{k_+} = \frac{[A]}{[B]}$.

If no other reaction involving $A\&B$, then $[A]_{eq} = A_0\frac{k_-}{k_++k_-}, [B]_{eq} = A_0\frac{k_+}{k_++k_-}$.

Biomolecular Chemical Reaction: $A + B \underset{k_-}{\overset{k_+}{\rightleftharpoons}} C$. $\frac{d[A]}{dt} = k_-[C] - k_+[A][B] = -\frac{d[C]}{dt}$.

At steady state, $k_{eq} = \frac{k_-}{k_+} = \frac{[A]_{eq}[B]_{eq}}{[C]_{eq}}$. Assume $[A] + [C] = A_0, [A]_{eq} = A_0\frac{k_{eq}}{k_{eq}+[B]_{eq}}, [C]_{eq} = A_0\frac{[B]_{eq}}{k_{eq}+[B]_{eq}}$.

When $[B]_{eq} = k_{eq}$, half of A is in the bound state at steady state.

$A + A \underset{k_-}{\overset{k_+}{\rightleftharpoons}} C$. Q: Which one is conseverd? A: $[A] + 2[C]$.

$\frac{d[A]}{dt} = 2k_-[C] - 2k_+[A]^2, \frac{d[C]}{dt} = k_+[A]^2 - k_-[C] \Rightarrow \frac{d[A]+2[C]}{dt} = 0$.

Remark: Law of mass action is only valid for elementary reaction.

1.2 MM Kinetics

S: substrate, 底物. E: enzyme, 酶. $E + S \underset{k_-}{\overset{k_+}{\rightleftharpoons}} ES, k_+ = k_1[E][S], k_- = k_{-1}[ES]$.

Dissociation constant: $k_d = \frac{k_{-1}}{k_1}$. Q: unit of k_d? A: concentration.

Fraction E-bond $f_B = \frac{[ES]}{[E]+[ES]}$.

$[S]_T \to 0 \Rightarrow f_B \to 0; [S]_T \to \infty \Rightarrow f_B \to 1; [E]_T \to \infty \Rightarrow f_B \to 0; [E]_T \to 0 \Rightarrow 0 < f_B < 1$. [$\frac{d[ES]}{dt} = k_1[E][S] - k_{-1}[ES] = 0 \Rightarrow \frac{k_{-1}}{k_1} = \frac{[E][S]}{[ES]} \Rightarrow f_B = \frac{[S]}{k_d+[S]} \in (0,1)$].

$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} E + P$. Transition State Theory.

$\frac{d[S]}{dt} = -k_1[E][S] + k_{-1}[ES], \frac{d[E]}{dt} = -k_1[E][S] + (k_{-1} + k_2)[ES], \frac{d[ES]}{dt} = k_1[E][S] - (k_{-1} + k_2)[ES], \frac{d[P]}{dt} = k_2[ES] \equiv v$ (turnover rate).

Initial Condition: $[S]|_{t=0} = S_0, [E]|_{t=0} = E_0, [ES]|_{t=0} = 0, [P]|_{t=0} = 0$.

Q: v v.s. $[S]$? A: Nonlinear. But $\frac{1}{v}$ v.s. $\frac{1}{[S]}$ may be linear for some time.

$[E] + [ES] = E_0$, so $\frac{d[E]}{dt}$ can be neglected.

Pseudo-steady state (quasi-equilibrium assumption): substrate-enzyme binding >> turnover into product $\Rightarrow \frac{d[ES]}{dt} = 0 \Rightarrow [ES] = \frac{k_1[S]E_0}{k_1[S]+k_{-1}+k_2} \Rightarrow v = \frac{d[P]}{dt} = \frac{k_2[S]E_0}{\frac{k_{-1}+k_2}{k_1}+[S]} = \frac{v_{\max}[S]}{k_m+[S]}$ where $k_m = \frac{k_{-1}+k_2}{k_1}$ (Michaelis Constant).

Q: Relation between $S_0\&E_0$ for pseudo-steady state? A: $S_0 >> E_0$.

$\frac{d[S]}{dt} = -k_1E_0[S] + (k_1[S] + k_{-1})[ES], \frac{d[ES]}{dt} = k_1E_0[S] - (k_1[S] + k_{-1} + k_2)[ES], \frac{d[P]}{dt} = k_2[ES]$.

时间尺度分离: Let $\tau = k_1E_0t, \overline{ES} = \frac{[ES]}{E_0}, \overline{S} = \frac{[S]}{S_0}, \frac{d[S]}{dt} \Rightarrow \frac{d\overline{S}}{d\tau} = -\overline{S} + (\overline{S} + k - \lambda)\overline{ES}$ where $k = \frac{k_{-1}+k_2}{k_1S_0}, \lambda = \frac{k_2}{k_1S_0}$. $\epsilon\frac{d\overline{ES}}{d\tau} = \overline{S} - (\overline{S} + k)\overline{ES} = 0$ where $\epsilon = \frac{E_0}{S_0}$.

2 Equilibrium Binding and Cooperativity

Consider that a protein has n binding stes. $S + P_{j-1} \underset{k_{-j}}{\overset{k_{+j}}{\rightleftharpoons}} P_j, j = 1, 2, \cdots, n.$

$\frac{d[P_0]}{dt} = -k_{+1}[P_0][S] + k_{-1}[P_1]$. Def associate constant $k_a = k_{+1}/k_{-1}, k_d = k_{-1}/k_{+1} = 1/k_a$.

At steady state, $k_1 = \frac{[P_1]}{[P_0][S]}, k_j = \frac{[P_j]}{[P_{j-1}][S]}, j = 1, 2, \cdots, n.$

Average # r of substrates bound to proteins, $r = \frac{[P_1]+2[P_2]+\cdots+n[P_n]}{[P_0]+[P_1]+\cdots+[P_n]} = \frac{k_1[P_0][S]+2k_1k_2[P_0][S]^2+\cdots}{[P_0]+k_1[P_0][S]+k_1k_2[P_0][S]^2+\cdots} = \frac{k_1[S]+2k_1k_2[S]^2+\cdots+nk_1k_2\cdots k_n[S]^n}{1+k_1[S]+k_1k_2[S]^2+\cdots+k_1k_2\cdots k_n[S]^n} \in (0, n)$. Saturation function: $Y = r/n \in (0, 1)$.

2.1 Identical and Independent Binding Sites

$P_0 + S \underset{k_-}{\overset{k_+}{\rightleftharpoons}} P_1 \Rightarrow -nk_+[P_0][S] + k_-[P_1] = 0.$

$P_1 + S \underset{k_-}{\overset{k_+}{\rightleftharpoons}} P_2 \Rightarrow -(n-1)k_+[P_1][S] + 2k_-[P_2] = 0.$

Intrinsic association constant $k = k_+/k_-, \Rightarrow k_j = \frac{(n-j+1)k}{j}, j = 1, 2, \cdots, n \Rightarrow r = \frac{nk[S]}{1+k[S]}$.

2.2 Identical and Interacting Binding Sites

$P_0 \underset{k_-}{\overset{k_+}{\rightleftharpoons}} P_1 \underset{k_-^*}{\overset{k_+^*}{\rightleftharpoons}} P_2, \Rightarrow k_1 = 2k, k_2 = \frac{1}{2}k^*.r = \frac{2k[S]+2kk^*[S]^2}{1+2k[S]+kk^*[S]^2}, Y = \frac{r}{2} = \frac{k[S]+kk^*[S]^2}{1+2k[S]+kk^*[S]^2}.$

$k = k^*$ (independent case), $Y^* = \frac{k[S]}{1+k[S]}.k \neq k^*$, $Y - Y^* = \frac{(k^*-k)k[S]^2}{(1+k[S])(1+2k[S]+kk^*[S]^2)}$.

Positive cooperativity: $Y - Y^* > 0 \Rightarrow k^* > k$. Negative cooperativity: $Y - Y^* < 0 \Rightarrow k^* < k$.

Another definition for cooperativity is sigmoidality. $\beta = k^*/k, x = k[S] \Rightarrow Y = \frac{x(1+\beta x)}{1+2x+\beta x^2}, \frac{dY}{dx} = \frac{1+2x\beta+\beta x^2}{(1+2x+\beta x^2)^2}, \frac{d^2Y}{dx^2} = 2\frac{\beta-2-\beta x(3+3x\beta+\beta x^2)}{(1+2x+\beta x^2)^3}$. $\beta > 2$ (second derivative can change sign).

Consider the limit (P_1 can be neglected). $P_0 + 2S \underset{k_-}{\overset{k_+}{\rightleftharpoons}} P_2, k = k_+/k_-$. $k_+[P_0][S]^2 = K_-[P_2] \Rightarrow k = k_+/k_- = [P_2]/[P_0][S]^2 \Rightarrow Y = \frac{[P_2]}{[P_0]+[P_2]} = \frac{k[S]^2}{1+k[S]^2}$ (Hill function) $\Rightarrow \frac{\ln\frac{Y}{1-Y}}{\ln[S]} = 2.$

Assumption: no intermediate states! With inter states, $Y = \frac{x(1+\beta x)}{1+2x+\beta x^2}, n_H = \frac{d\ln\frac{Y}{1-Y}}{d\ln[S]} = 1 + \frac{(\beta-1)x}{(1+x)(1+\beta x)}$. Q: when $n_H \to 2$? A: $x \to 0, \beta \to \infty$.

2.3 Non-Identical and Interacting Binding Sites

$P_0 \underset{k_{1-}}{\overset{k_{1+}}{\rightleftharpoons}} P_1, P_0 \underset{k_{2-}}{\overset{k_{2+}}{\rightleftharpoons}} P_1', P_1 \underset{k_{3-}}{\overset{k_{3+}}{\rightleftharpoons}} P_2, P_1' \underset{k_{4-}}{\overset{k_{4+}}{\rightleftharpoons}} P_2$. $k_j = k_{j+}/k_{j-}$.

Principal of detailed balance: $k_1 = \frac{[P_1]}{[P_0][S]}, k_2 = \frac{[P_1']}{[P_0][S]}, k_3 = \frac{[P_2]}{[P_1][S]}, k_4 = \frac{[P_2]}{[P_1'][S]} \Rightarrow k_1k_3 = k_2k_4$.

不同配体别构合作效应: if $k_3 > k_2 \Rightarrow k_4 > k_1$. (Kim, *et al.* Probing Allostery through DNA, Science 2013).

$Y = \frac{1}{2}\frac{[P_1']+[P_1]+2[P_2]}{[P_0]+[P_1']+[P_1]+[P_2]} = \frac{k_1[S]+k_2[S]+2k_1k_2[S]^2}{1+k_1[S]+k_2[S]+k_1k_2[S]^2}$. $J = \frac{1}{2}(k_1 + k_2), J^* = \frac{2k_1k_3}{(k_1+k_2)}, x' = J[S], \beta' = \frac{J^*}{J} \Rightarrow Y = \frac{x'(1+x'\beta')}{1+2x'+\beta' x'^2}$.

3 Transcription Networks

3.1 Basic Models

Signal $\to$ protein $X \to$ Gene, Environment $\to$ Transcription Factors $\to$ Genes $\to$ Environment.

$X \xrightarrow{S_X} X^* \to$ bound activator/regressor $\to Y$/ No Transcription.

Timescales: Transcription & Translation of target genes: activation of T.F.(faster), binding(fast), Trans & Trans(slow), Protein synthesis(slower). For Ecoli: $\sim$ 1msec, $\sim$ 1sec, $\sim$ 5min, $\sim$ 1h.

Q: Can a T.F. be an activator for some genes and regressor for others? A: Yes.

Input function: rate of product of $Y = f(X^*)$ – monotonic. For example,

Hill function: for activator, $f(X^*) = \beta X^{*n}/(K^n + X^{*n}) + \beta_0$; for regressor, $f(X^*) = \frac{\beta}{1+(\frac{X^*}{K})^n}$.

Logic input function: for activator, $f(X^*) = \beta I(X^* > K)$; for regressor, $f(X^*) = \beta I(X^* < K)$.

Dynamics: response time: $T_{\frac{1}{2}}$: the time to reach halfway between the initial and final levels.

$\frac{dY}{dt} = f(X^*) - \alpha Y$. Decay rate: $\alpha = \alpha_{\text{degradation}} + \alpha_{\text{dilution}}$.

Q: response time for activation compares to for decay? Increase β, response time for activation? A: same, =.

Activation: $\frac{dY}{dt} = \beta - \alpha Y = 0 \Rightarrow Y_{st} = \beta/\alpha$. $T = 0, Y(0) = 0 \Rightarrow Y(t) = Y_{st}(1 - e^{-\alpha t})$. $T_{\frac{1}{2}} = \ln 2/\alpha$.

Decay: $\frac{dY}{dt} = -\alpha Y \Rightarrow Y(t) = Y_{st}e^{-\alpha t}$. $T_{\frac{1}{2}}$: $Y(t) = \frac{Y_{st}}{2} \Rightarrow T_{\frac{1}{2}} = \ln 2/\alpha$. large $\alpha \to$ rapid change in concentration. $\beta \to$ only affects steady state level.

At early time, when $\alpha t << 1, Y(t) = \frac{\beta}{\alpha}(1 - e^{-\alpha t}) \sim \beta t$.

Response time for stable protein: $\alpha_{\text{deg}} = 0, \alpha = \alpha_{\text{dil}} \Rightarrow T_{\frac{1}{2}} = \ln 2/\alpha_{\text{dil}} := \tau$ – one cell generation time.

3.2 Ultrasensitivity

Titration: $T + I \underset{k_-}{\overset{k_+}{\rightleftharpoons}} TI$. T: transcription factor, I: inhibitor. $[T][I] = k[TI], [T] + [TI] = T_t, [I] + [TI] = I_t$, k: dissociation constant. $[T]^2 - [T](T_t - I_t - k) - kT_t = 0 \Rightarrow [T] = \frac{T_t - I_t - K + \sqrt{(T_t - I_t - k)^2 + 4kT_t}}{2}$. Let $T = \frac{[T]}{k}, T_t = \frac{T_t}{k}, I_t = \frac{I_t}{k} \Rightarrow T = \frac{T_t - I_t - 1 + \sqrt{(T_t - I_t - 1)^2 + 4T_t}}{2}$.

Take limit: 1. $T_t << I_t + 1 \Rightarrow T = \frac{T_t}{I_t + 1}$, buffering agent.

2. $T_t >> I_t + 1 \Rightarrow T = T_t - (I_t + 1)$, saturated region.

3. $T_t \sim I_t + 1$, transition region.

3.3 Autoregulation

Network motif: a way to detect building block patterns.

Ecoli: $N = 420$ Nodes, $E = 520$ edges.

Randomized network: $E_{\max} = \frac{1}{2}N(N-1) \cdot 2 + N = N^2, P = E/N^2$. $\langle N_{\text{self}} \rangle_{\text{rand}} = N \times P = E/N \approx 1.2$, but in Ecoli, $N_{\text{self}} = 40$ with 34 negative and 6 positive $\Rightarrow$ Negatively autoregulated genes are a network motif.

Q: Does it have useful functions?

1. Response time.

Single regulated genes: $T_{\frac{1}{2}} = \frac{\ln 2}{\alpha}$.

Q: NAR response time? A: $\downarrow$.

Q: NAR off response time? A: =.

$\frac{dx}{dt} = f(x) - \alpha x$ where $f(x) = \frac{\beta}{1+(\frac{x}{k})^n}$(decreasing Hill function). When n is large enough, $x_{st} = k$, and simplify $f(x)$ by logic approximation $f(x) = \beta I(x < k)$. $\frac{dx}{dt} = \beta - \alpha x$ while $x < k$. At eartly times, $x(t) \sim \beta t$. NAR: strong promotion β can give rapid product.

2. Robustness

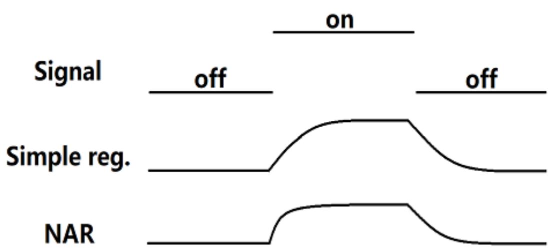
X_{eq}^{NAR} robust to small changes on α and β, i.e. fluctuation in prod rate and deg rate.

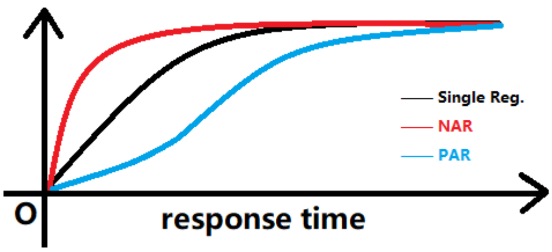
4 Positive Feedback and Multistability

PAR: $\frac{dx}{dt} = \beta_1 \frac{x^n}{k^n+x^n} - \alpha x + \beta_0$. At early time, prod rate of $x = \beta_0$.

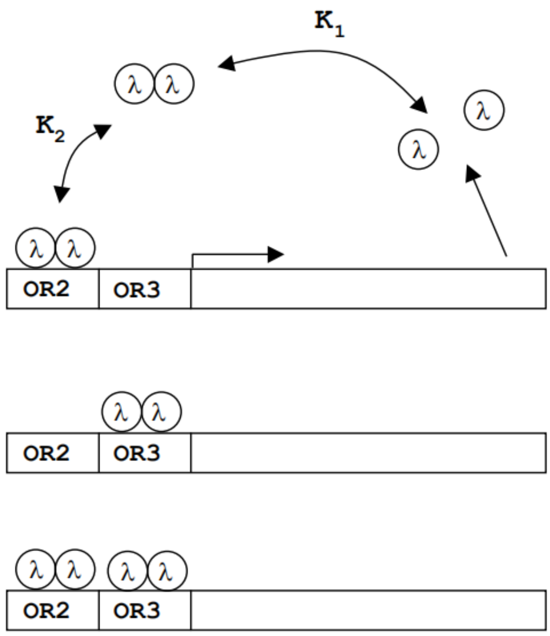
1. slow response time: development process, relatively long time process; prolonged delay.

2. bistability: $\frac{dx}{dt} = 0$ has $1-3$ solutions for x.





Consider the following reactions:



Def $X : \lambda, X_2 : \lambda\lambda, D :$ DNA promotor site, $P :$ RNA polymerase.

$2X \xleftrightarrow{k_1} X_2, D + X_2 \xleftrightarrow{k_2} DX_2, D + X_2 \xleftrightarrow{k_3} DX_2^*, DX_2 + DX_2 \xleftrightarrow{k_4} DX_2X_2^*, DX_2 + P \xleftrightarrow{k_t} DX_2 + P + nX, X \xrightarrow{k_d} \emptyset$.

Q: which are fast processes? A: reaction 1,2,3,4 $\sim$ sec, reaction 5,6 $\sim$ min – hour.

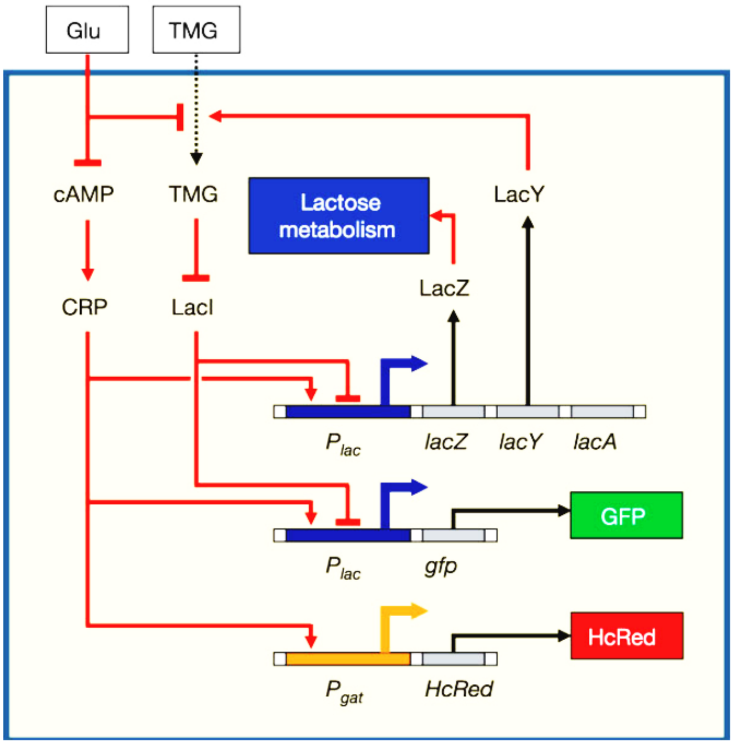
$k_3 = \sigma_1 k_2, k_4 = \sigma_2 k_2$, define $y = [X_2], d = [D], u = [DX_2], v = [DX_2^*], z = [DX_2X_2^*]$.

$y = k_1[X]^2, u = k_2 dy = k_1 k_2 d[X]^2, v = \sigma_1 k_2 dy = \sigma_1 k_1 k_2 d[X]^2, z = \sigma_2 k_2 uy = \sigma_2 (k_1 k_2)^2 d[X]^4$.

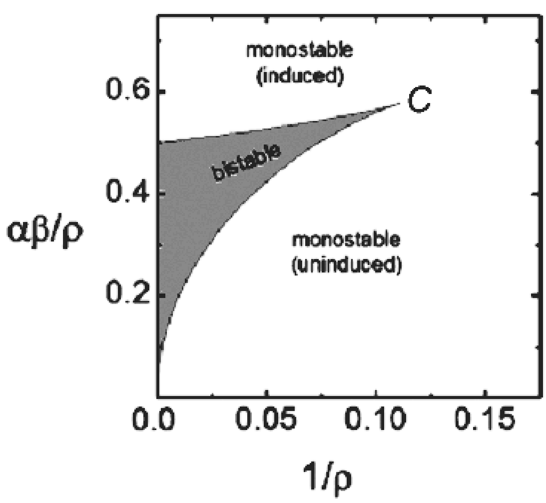
$\frac{d[X]}{dt} = nk_tP_0u - k_d[X] + r$ (r : basal rate). $d_T = d + u + v + z \Rightarrow d_T = d[1 + (1+\sigma_1)k_1k_2[X]^2 + \sigma_2 k_1^2 k_2^2 [X]^4] \Rightarrow \frac{d[X]}{dt} = \frac{nk_tP_0k_1k_2d_T[X]^2}{1+(1+\sigma_1)k_1k_2[X]^2+\sigma_2k_1^2k_2^2[X]^4}$.

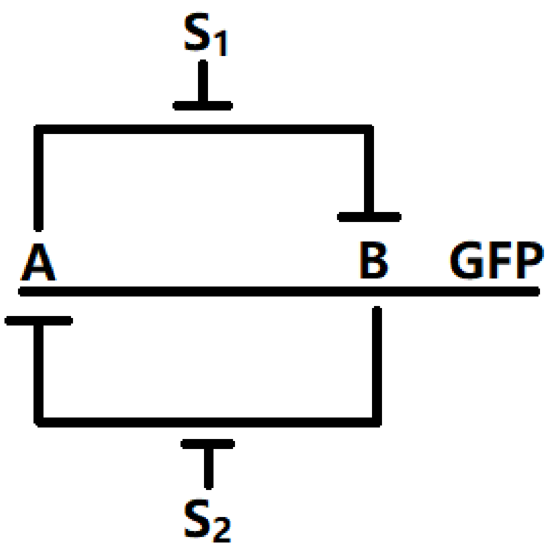
Def $\overline{X} = \sqrt{k_1k_2}[X], \overline{t} = t(r\sqrt{k_1k_2})$, $\frac{d\overline{X}}{d\overline{t}} = \frac{\sqrt{nk_tP_0d_T}\overline{X}^2/r}{1+(1+\sigma_1)\overline{X}^2+\sigma_2\overline{X}^2} - \frac{k_d/r}{\sqrt{k_1k_2}}\overline{X} = \frac{\alpha\overline{X}^2}{1+(1+\sigma_1)\overline{X}^2+(1+\sigma_2)\overline{X}^4} - \gamma\overline{X}$.

Consider the following reactions:



Denote TMG as X, LacI as R and LacY as Y, andconsider $X \dashv R \dashv Y \to X$. Model: $\frac{R}{R_T} = \frac{1}{1+(x/x_0)^n}, n \approx 2, \tau_y\frac{dy}{dt} = \alpha\frac{1}{1+R/R_0} - y, \tau_x\frac{dx}{dt} = \beta y - x \Rightarrow y_{st} = \frac{\alpha}{1+R/R_0}, x_{st} = \beta y_{st} \Rightarrow y_{st} = \alpha\frac{1+(\beta y)^2}{\rho+(\beta y)^2}(\rho = 1 + R_T/R_0) \Rightarrow y^3 - \alpha y^2 + \frac{\rho}{\beta^2}y - \frac{\alpha}{\beta^2} = 0$. Let it $= (y-a)(y-a)(y-\theta a) = 0$(bistable), we get $\rho = (1+2\theta)(1+2/\theta), \alpha\beta = (2+\theta)^{\frac{3}{2}}/\theta^{\frac{1}{2}}$.





Toggle switch: $A \dashv B, B \dashv A$. Boolean approximation: 0 for low and 1 for high.

Q: possible steady state? A: $A1B0$ or $A0B1$.

Q: to switch off GFP? A: S_2.

Toggele model (Dimensionless Equations): $\frac{du}{dt} = \frac{\alpha_1}{1+v^\beta} - u$, $\frac{dv}{dt} = \frac{\alpha_2}{1+u^\gamma} - v$.

Good: Essential math; Bad: Lose connection to experiment.

Q: effective liefetime of u vs v? A: $\tau_u = \tau_v$.

Q: If degration rates go up, what parameters change? A: α_1 and α_2, $\downarrow$.

Equilibrium reactions: $P_1 + R_2^\beta \xleftrightarrow{k_1} P_1R_2^\beta, P_2 + R_1^\gamma \xleftrightarrow{k_2} P_2R_1^\gamma, \gamma R_1 \xleftrightarrow{k_3} R_1^\gamma, \beta R_2 \xleftrightarrow{k_4} R_2^\beta$. $[P^T] = [P_1^T] = [P_1] + [P_1R_2^\beta] = [P_2^T] = [P_2] + [P_2R_1^\gamma]$.

$R_{\text{gen1}} = a_1[P_1] = a_1[P^T]\frac{[P_1]}{[P_1]+[P_1R_2^\beta]} = a_1[P^T]\frac{1}{1+k_1[R_2^\beta]} = \frac{a_1[P^T]}{1+k_1k_4[R_2]^\beta}$.

$R_{\text{gen2}} = a_2[P_2] = a_2[P^T]\frac{[P_2]}{[P_2]+[P_2R_1^\gamma]} = a_2[P^T]\frac{1}{1+k_2[R_1^\gamma]} = \frac{a_2[P^T]}{1+k_2k_3[R_1]^\gamma}$.

$\frac{d[R_1]}{dt} = \frac{a_1[P^T]}{1+k_1k_4[R_2]^\beta} - \delta[R_1]$, $\frac{d[R_2]}{dt} = \frac{a_2[P^T]}{1+k_2k_3[R_1]^\gamma} - \delta[R_2]$($\delta$: decay rate).

Def $\widetilde{t} = t\delta, u = [R_1](k_2k_3)^{1/\gamma}, v = [R_2](k_1k_4)^{1/\beta}$, then

$\frac{du}{d\widetilde{t}} = \frac{a_1[P^T](k_2k_3)^{1/\gamma}}{\delta}\frac{1}{1+v^\beta} - u = \frac{\alpha_1}{1+v^\beta}$, $\frac{dv}{d\widetilde{t}} = \frac{a_2[P^T](k_1k_4)^{1/\beta}}{\delta}\frac{1}{1+u^\gamma} - v = \frac{\alpha_2}{1+u^\gamma}$. $u_{st} = \frac{\alpha_1}{1+v^\beta}, v_{st} = \frac{\alpha_2}{1+u^\gamma}$.

5 Stability and Oscillation

5.1 Stability Analysis

1D case: $\dot{x} = ax \Rightarrow x^* = 0$ stable iff $a < 0$.

2D case: $\dot{x} = f(x,y), \dot{y} = g(x,y) \Rightarrow f(x_0,y_0) = 0, g(x_0,y_0) = 0$. Let $\Delta x = x - x_0, \Delta y = y - y_0 \Rightarrow \dot{x} \approx f(x_0,y_0) + \delta x\frac{\partial f}{\partial x}|_{(x_0,y_0)} + \delta\frac{\partial f}{\partial y}|_{(x_0,y_0)}, \dot{y} \approx g(x_0,y_0) + \delta x\frac{\partial g}{\partial x}|_{(x_0,y_0)} + \delta\frac{\partial g}{\partial y}|_{(x_0,y_0)} \Rightarrow \dot{x} = a\Delta x + b\Delta y, \dot{y} = c\Delta x + d\Delta y$ or $\dot{\overrightarrow{X}} = A\overrightarrow{X}$. $A = \begin{pmatrix} a & b \\ c & d \end{pmatrix}$, $\text{tr}(A) = a + d$, $\det(A) = ad - bc$. (x_0, y_0) stable iff $\text{tr}(A) < 0$, $\det(A) > 0$.

Example: Toggle Switch: $\dot{u} = f(u,v) = \frac{\alpha_1}{1+v^\beta} - u, \dot{v} = g(u,v) = \frac{\alpha_2}{1+u^\gamma} - v \Rightarrow u = \frac{\alpha_1}{1+v^\beta}, v = \frac{\alpha_2}{1+u^\gamma}$.

$A = \begin{pmatrix} -1 & \frac{-\alpha_1\beta v^{\beta-1}}{(1+v^\beta)^2} \\ \frac{-\alpha_2\gamma u^{\gamma-1}}{(1+u^\gamma)^2} & -1 \end{pmatrix}$. $\text{tr}(A) = -2$, $\det(A) = 1 - \frac{\alpha_1\beta v^{\beta-1}\alpha_2\gamma u^{\gamma-1}}{(1+v^\beta)^2(1+u^\gamma)^2} > 0 \Leftrightarrow \beta\gamma v^{\beta+1}u^{\gamma+1} > \alpha_1\alpha_2$.

Assumption: 1. large α_1, α_2; 2. ratio between on or off is large (either $u/v >> 1$ or $v/u >> 1$).

In the case when $u >> v$, $u \approx \alpha_1, v \approx \frac{\alpha_2}{\alpha_1^\gamma} \Leftrightarrow \log(\alpha_1) \approx \frac{1}{\gamma}\log(\alpha_2)$. When $v << u$, $\log(\alpha_2) = \frac{1}{\beta}\log(\alpha_1)$. When $\frac{1}{\gamma} < \frac{\log(\alpha_1)}{\log(\alpha_2)} < \beta$, bistability occurs.

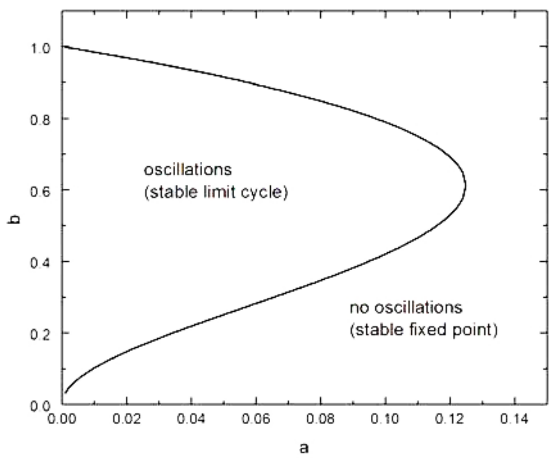
5.2 Biological Oscillations

1D case: $\dot{x} = f(x) = \frac{\alpha}{1+x^n} - x$. Q: possible oscillation? A: No, becase $\dot{x}(t)$ should be the same for the same x.

2D case: $\dot{m} = \frac{\alpha}{1+p^n} - m, \dot{p} = -\beta(p - m)$ where m: mRNA, p: protein, β: lifetime of mRNA. $\beta << 1$. Q: possible oscillation? A: No. $A = \begin{pmatrix} -1 & -\frac{\alpha n p^{n-1}}{(1+p^n)^2} \\ \beta & -\beta \end{pmatrix} \Rightarrow \text{tr}(A) < 0, \det(A) > 0 \Rightarrow \lambda_{1,2} < 0 \Rightarrow$ stable.

$\dot{x} = -x + ay + x^2y, \dot{y} = b - ay - x^2y$. Nullclines: $y = \frac{x}{a+x^2}, y = \frac{b}{a+x^2} \Rightarrow x^* = a, y^* = \frac{b}{a+b^2}$.

$A = \begin{pmatrix} -1+2x^*y^* & a+x^{*2} \\ -2x^*y^* & -a-x^{*2} \end{pmatrix}$. $\mathrm{tr}(A) = -\frac{b^4+(2a-1)b^2+(a+a^2)}{a+b^2}$, $\det(A) = a + b^2 > 0$. When $\mathrm{tr}(A) < 0$, stable fixed point; when $\mathrm{tr}(A) > 0$, unstable $\Rightarrow$ stable limit cycle.



5.3 Ruling out Closed Orbits

1. Gradient system: $\dot{x} = -\nabla V(x)$.

Thm: Closed orbits are impossible in gradient systems.

Proof: Suppose there were a closed orbit. ΔV: change of V after one circuit. So $0 = \Delta V = \int_0^T \frac{dV}{dt} dt = \int_0^T \nabla V \cdot \dot{x} dt = -\int_0^T ||\nabla V||^2 dt < 0$, which is contradictory.

2. Lyapunov functions.

$\dot{x} = f(x)$ with a fixed point at x^*. Suppose we can find a Lyapunov function i.e. a continuous differentiable, real-valued function $V(x)$ with (1) $V(x) > 0$ for all $x \neq x^*$ and $V(x^*) = 0$; (2) $\dot{V}(x) < 0$ for all $x \neq x^*$ (all trajectories follow "downhill" to x^*). Then x^* is globally asymptotically stable, no closed orbit.

3. Poincare-Bendixson thm.

(1) R is a closed bounded subset of the plane;

(2) $\dot{x} = f(x)$ is a continuous, differentiable vector field on an open set containing R;

(3) R does not contain any fixed point;

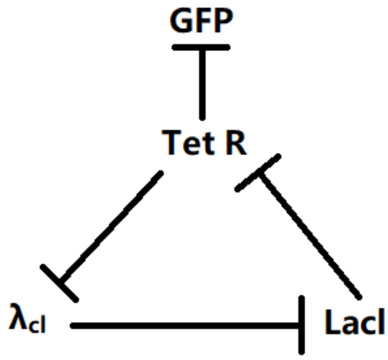
(4) There exists a trajectory C that is confined in R.

Theen either C is a closed orbit or it spirals toward a closed orbit as $t \to \infty$.

5.4 Synthetic Genetic Oscillators

Example 1: $\begin{cases} \frac{dm_i}{dt} = -m_i + \frac{\alpha}{1+p_j^n} + \alpha_0 \\ \frac{dp_i}{dt} = -\beta(p_i - m_i) \end{cases}$ where $i =$ [lacl, tetR, cl], $j =$ [cl, lacl, tetR].

Let us assume that we can ignore the intermediate step of mRNA synthesis. $\frac{dp_1}{dt} = -p_1 + \frac{\alpha}{1+p_3^n} + \alpha_0$, $\frac{dp_2}{dt} = \frac{\alpha}{1+p_1^n} - p_2 + \alpha_0$, $\frac{dp_3}{dt} = \frac{\alpha}{1+p_2^n} - p_3 + \alpha_0 \Rightarrow p_1 = p_2 = p_3 = p$, steady when $p = \frac{\alpha}{1+p^n} + \alpha_0$.

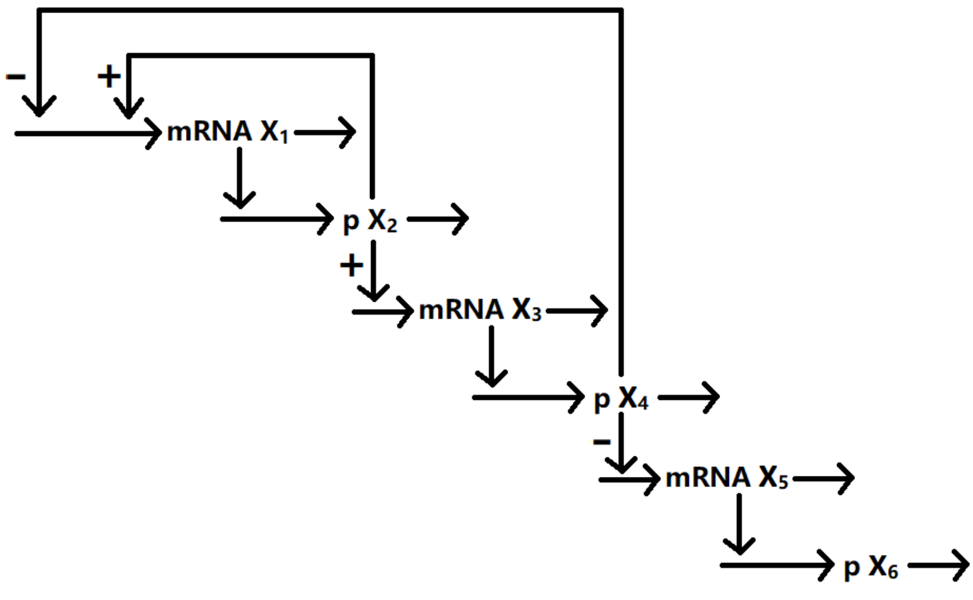


$A = \begin{pmatrix} -1 & 0 & X \\ X & -1 & 0 \\ 0 & X & -1 \end{pmatrix}$ where $X = -\frac{\alpha n p^{n-1}}{(1+p^n)^2}$. Eigenvalue $\lambda_1 = X - 1, \lambda_2 = -1 - \frac{1}{2}X + i\frac{\sqrt{3}}{2}X, \lambda_3 = -1 - \frac{1}{2}X - i\frac{\sqrt{3}}{2}X$, stable fixed point $\Leftrightarrow$ $\mathrm{Re}(\lambda_i)$ negative $\Leftrightarrow -2 < X < 1 \Rightarrow \frac{\alpha n p^{n-1}}{(1+p^n)^2} < 2$.

For large α, $\alpha \approx p(1+p^n) \Rightarrow n \lesssim 2 \Rightarrow n \gtrsim 2$ gives oscillation.

Example 2: the translation of mRNA: $\frac{dX_2}{dt} = k_p X_1 - \beta_2 X_2$ where k_p is the translation rate constant and β_2 is the decay rate constant of the protein X_2. $X_2^s = \frac{k_p}{\beta_2} X_1^s$.

When X_2 and X_1 are normalized to their steady state values, $\frac{dx_2}{dt} = \beta_2(x_1 - x_2)$.



Thus $\frac{dx_1}{dt} = \beta_1(f_1 - x_1)$, $\frac{dx_2}{dt} = \beta_2(x_1 - x_2)$, $\frac{dx_3}{dt} = \beta_3(f_3 - x_3)$, $\frac{dx_4}{dt} = \beta_4(x_3 - x_4)$, $\frac{dx_5}{dt} = \beta_5(f_5 - x_5)$, $\frac{dx_6}{dt} = \beta_6(x_5 - x_6)$.

The functions f_1, f_3 and f_5 describe the transcriptional regulation and are defined by triphasic functions. $f_1 = \begin{cases} B : x_2^{g_{12}} x_4^{g_{14}} < B \\ x_2^{g_{12}} x_4^{g_{14}} : B < x_2^{g_{12}} x_4^{g_{14}} < M \\ M : x_2^{g_{12}} x_4^{g_{14}} > M \end{cases}$, $f_3 = \begin{cases} B : x_2^{g_{32}} < B \\ x_2^{g_{32}} : B < x_2^{g_{32}} < M \\ M : x_2^{g_{32}} > M \end{cases}$. In the case of only one fixed point, $x_1 = x_2 = x_3 = x_4 = 1$.

$$A = \begin{pmatrix} -\beta_1 & \beta_1 g_{12} & 0 & \beta_1 g_{14} \\ \beta_2 & -\beta_2 & 0 & 0 \\ 0 & \beta_3 g_{32} & -\beta_3 & 0 \\ 0 & 0 & \beta_4 & -\beta_4 \end{pmatrix}.$$ $|\lambda I - A| = 0 \Rightarrow a_0\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4 = 0$ where $a_0 = 1, a_1 = \beta_1 + \beta_2 + \beta_3 + \beta_4, a_2 = \beta_1\beta_2(1 - g_{12}) + \beta_1\beta_3 + \beta_1\beta_4 + \beta_2\beta_3 + \beta_2\beta_4 + \beta_3\beta_4, a_3 = \beta_1\beta_2\beta_3(1 - g_{12}) + \beta_1\beta_2\beta_4(1 - g_{12}) + \beta_2\beta_3\beta_4 + \beta_1\beta_3\beta_4, a_4 = \beta_1\beta_2\beta_3\beta_4(1 - g_{14}g_{32} - g_{12})$.

Routh-Hurwitz criterion: a system is stable if (1) all coefficients are possible; (2) all elements in the first column of R-H matrix are positive. This matrix is constructed as follows:

The matrix has n+1 (in our case 5) rows:

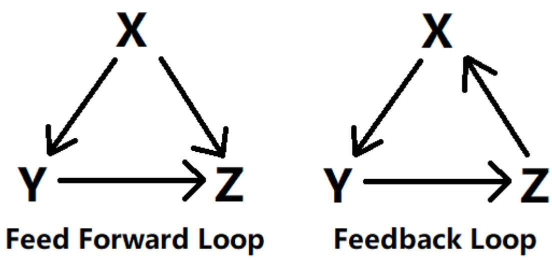
$$\begin{array}{c|ccccc} \lambda^n & a_0 & a_2 & a_4 & a_6 & \cdots \\ \lambda^{n-1} & a_1 & a_3 & a_5 & a_7 & \cdots \\ \lambda^{n-2} & b_1 & b_2 & b_3 & b_4 & \cdots \\ \lambda^{n-3} & c_1 & c_2 & c_3 & c_4 & \cdots \\ \lambda^{n-4} & d_1 & d_2 & d_3 & d_4 & \cdots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \\ \lambda^1 & f_1 & & & & \\ \lambda^0 & g_1 & & & & \end{array}$$

where $b_1 = \frac{a_1a_2 - a_0a_3}{a_1}, b_2 = \frac{a_1a_4 - a_0a_5}{a_1}, b_3 = \frac{a_1a_6 - a_0a_7}{a_1}, c_1 = \frac{b_1a_3 - a_1b_2}{b_1}, c_2 = \frac{b_1a_5 - a_1b_3}{b_1}, c_3 = \frac{b_1a_7 - a_1b_4}{b_1}, d_1 = \frac{c_1b_2 - b_1c_2}{c_1}, d_2 = \frac{c_1b_3 - b_1c_3}{c_1}, \cdots$.

6 Feed Forward Loop Network Motif

Q: How many possible n-node patterns? A: $n = 3, 13; n = 4, 199; n = 5, 9364$.

Two traditional patterns in 3-node system("→" just means a kind of relation, which can be either positive or negative).



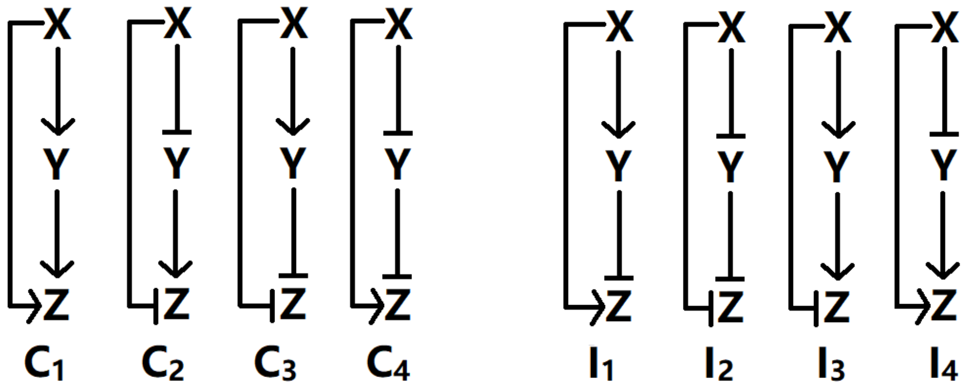
In Ecoli, $N \sim 400$ genes, $E \sim 500$ interactions, $P = \frac{E}{N^2} \sim 0.003 << 1$, average number of subgraph G in the network $\langle N_G \rangle = \frac{1}{a}N^nP^g$, where n: nodes in G, g: edges in G, a: combinational factors for structure (how many times the subgraph G can repeat but keep the same structure).

Define mean connectivity $\lambda = E/N$, then $P = E/N^2 = \lambda/N \Rightarrow \langle N_G \rangle = \frac{1}{a}\lambda^g N^{n-g}$. Scaling relation: $\langle N_G \rangle \sim N^{n-g}$.

In random network, $\lambda \sim 500/400 = 1.25, \langle N_{\text{FFL}} \rangle_{\text{rand}} = 1.25^3 \approx 2, \langle N_{\text{Loop}} \rangle_{\text{rand}} = 1.25^3/3 \approx 0.6$. In Ecoli, # of FFL = 42, # of feedback loop = 0 ⇒ FFL is a network motif. In fact, FFL is the only significant motif of the 13 possible 3-node network.

Structure of FFL: total # of FFL $= 2^3 = 8$ (remind that "$\rightarrow$" can represent either positive or negative relations).

Coherent FFL and Incoherent FFL:



6.1 C1-FFL

Input functions of Z: (AND/OR means Z can be produced only when X and/or Y are available, ON/OFF means signals of X (S_x) are suddenly on/off, ✓ means the changes of concentration of Z are delayed when giving the corresponding conditions)

delay \ S_x / gate	ON	OFF
AND	✓	×
OR	×	✓

Consider AND gate first. Product rate of $y = \beta_y I(x^* > k_{xy}), z = \beta_z I(x^* k_{xz}) I(y^* > k_{yz}) \Rightarrow \frac{dy}{dt} = \beta_y I(x^* > k_{xy}) - \alpha_y Y$, $\frac{dz}{dt} = \beta_z I(x^* > k_{xz}) I(y^* > k_{yz}) - \alpha_z Z$. Assume S_x is present, $Y^*(t) = Y_{st}(1 - e^{-\alpha_y t})$ where $Y_{st} = \beta_y / \alpha_y$. For Z, the delay T_{on} satisifies $Y^*(T_{on}) = Y_{st}(1 - e^{-\alpha_y T_{on}}) = k_{yz} \Rightarrow T_{on} = \frac{1}{\alpha_y} \log(\frac{1}{1 - k_{yz}/Y_{st}})$.

Advantage: robust to input fluctuations.

For OR gate, it is a sign-sensitive delay for off step, $Y^*(t) = Y_{st} e^{-\alpha_y t} \Rightarrow Y^*(T_{off}) = k_{yz} \Rightarrow T_{off} = \frac{1}{\alpha_y} \log(Y_{st}/k_{yz})$.

6.2 I1-FFL

β_z: prod rate of Z when only X is available (strong). β_z': prod rate of Z when both X and Y are available (weak). repression factor $F = \beta_z / \beta_z'$.

When $Y^* < k_{yz}$, $\frac{dY}{dt} = \beta_y - \alpha_y Y \Rightarrow Y(t) = Y_{st}(1 - e^{-\alpha_y t})$ where $Y_{st} = \beta_y / \alpha_y$.

$\frac{dZ}{dt} = \beta_z - \alpha_z Z \Rightarrow Z(t) = Z_m(1 - e^{-\alpha_z t})$ where $Z_m = \beta_z / \alpha_z$.

When $Y^* \geq k_{yz}$, product rate of $Z : \beta_z \to \beta'_z$. $Y(T_{rep}) = Y_{st}(1 - e^{-\alpha_y T_{rep}}) = k_{yz} \Rightarrow T_{rep} = \frac{1}{\alpha_y}\log(\frac{1}{1-k_{yz}/Y_{st}})$. After T_{rep}, Z decays exponentially to a new low steady point $Z_{st} = \beta'_z/\alpha_z \Rightarrow Z(t) = Z_{st} + (Z_0 - Z_{st})e^{-\alpha_z(t-T_{rep})}$ where $Z_0 = Z_m(1 - e^{-\alpha_z T_{rep}})$.

Function: I1-FFL is a pulse generator and speeds up response time.

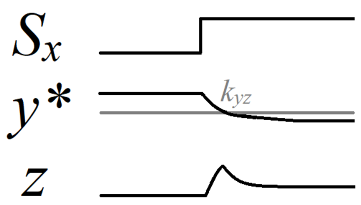
$Z_{\frac{1}{2}} = \frac{Z_{st}}{2} = Z_m(1 - e^{-\alpha_z T_{\frac{1}{2}}}) \Rightarrow T_{\frac{1}{2}} = \frac{1}{\alpha_z}\log(\frac{2F}{2F-1})$ where $F = \frac{Z_m}{Z_{st}}$. $F >> 1, T_{\frac{1}{2}} \to 0$. Thus, I1-FFL is a sign-sensitive response accelerator for ON step.

6.3 Other FFLs

Q1: Can X be both activator & regressor? A: Yes.

Q2: Dynamics: Is I4-FFL a sign-sensitive accelerator? A: Yes.

Q3: What's the difference between I1 & I4? A: steady state logic.

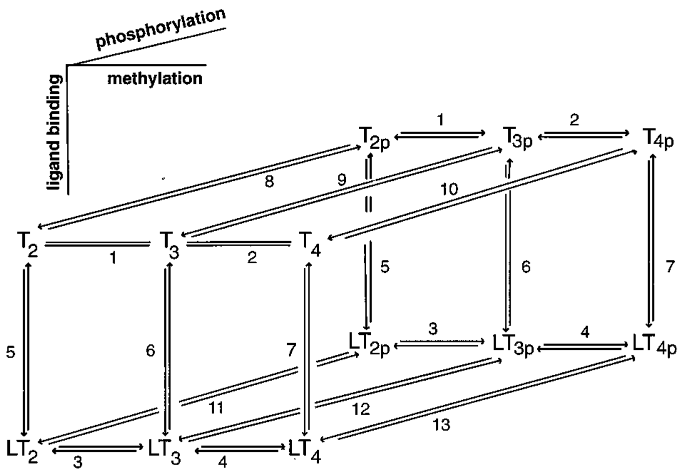


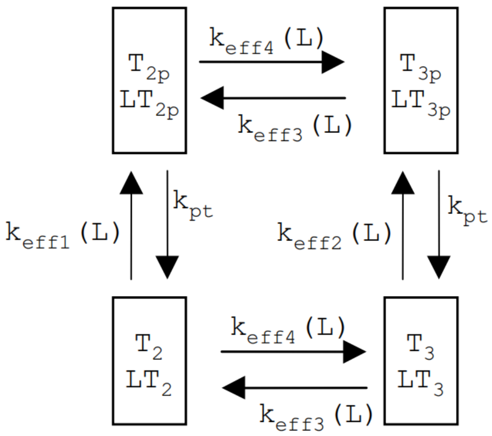
S_x	S_y	z in I1	z in I4
0	0	0	0
0	1	0	0
1	0	1, High	0, Low
1	1	0, Low	0, Low

Therefore, I4-FFL is rare in E-coli because the steady concentration of z won't change when regulating S_x and S_y.

7 Adaptation

7.1 Spiro's model





Fraction of receptors that are bound to a ligand: $f_b = \frac{[LT_2]}{[T_2]+[LT_2]} = \frac{K_b L}{1+K_b L}$ where $K_b = \frac{k_5}{k_{-5}} = \frac{k_6}{k_{-6}} = \frac{k_7}{k_{-7}} \sim 10^{-6}$.

Effective rates: $k_{\text{eff1}}(L) = k_8(1-f_b) + k_{11}f_b = \frac{k_8+k_{11}K_bL}{1+K_bL}, k_{\text{eff2}}(L) = k_9(1-f_b) + k_{12}f_b = \frac{k_9+k_{11}K_bL}{1+K_bL}, k_{\text{eff3}}(L) = k_{-1}(1-f_b) + k_{-3}f_b = \frac{k_{-1}+k_{-3}K_bL}{1+K_bL}$.

Methylation rates: $r = \frac{V_{\max 1}(1-f_b)[2]}{k_R+(1-f_b)[2]} + \frac{V_{\max 3} f_b [2]}{k_R + f_b[2]}, r_p = \frac{V_{\max 1}(1-f_b)[2_p]}{k_R+(1-f_b)[2_p]} + \frac{V_{\max 3} f_b [2_p]}{k_R + f_b[2_p]}$ where [2] and $[2_p]$ are the total concentrations of non-phosphorylated and phosphorylated receptors with two methylation sites.

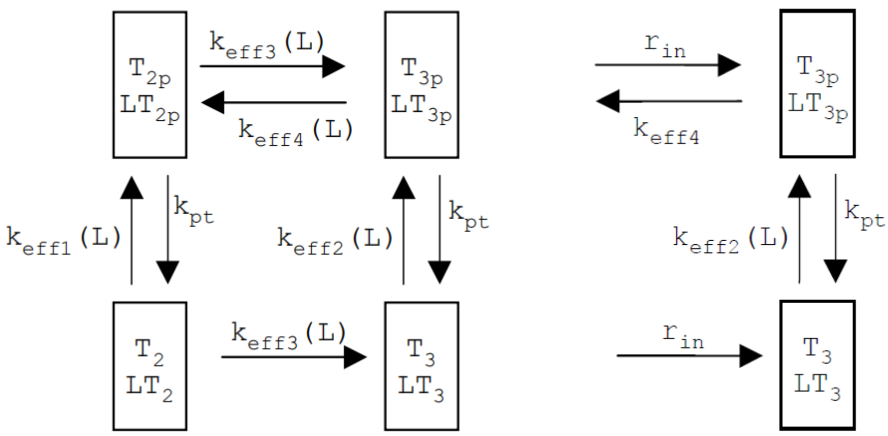
Q: What is needed for perfect adaptation?
$\frac{[2_p]}{2} = \frac{k_{\text{eff1}}(L)}{k_{pt}}, \frac{[3_p]}{[3]} = \frac{k_{\text{eff2}}(L)}{k_{pt}}, \frac{[3]}{[2]} = \frac{[3_p]}{[2_p]} = \frac{k_{\text{eff4}}(L)}{k_{\text{eff3}}(L)}, [2_p] + [2] + [3_p] + [3] = Const.$
Problem: 4 unknowns, 5 equations $\rightarrow$ introduce an additional variable.

Perfect adaptation: in steady state, # of phosphorylated receptors is independent of $L \Rightarrow$ effective phosphorylation rate is independent of L.

$k_{\text{phos}} = (1-\alpha) k_{\text{eff1}}(L) + \alpha k_{\text{eff2}}(L) \Rightarrow \alpha(L) = \frac{k_{\text{phos}}(L) - k_{\text{eff1}}(L)}{k_{\text{eff2}}(L) - k_{\text{eff1}}(L)} = \frac{k_{\text{phos}}(1+K_B L) - k_8 - k_{11} K_B L}{(k_9 - k_8) + (k_{12} - k_{11}) K_B L}.$

7.2 Barkai's Model

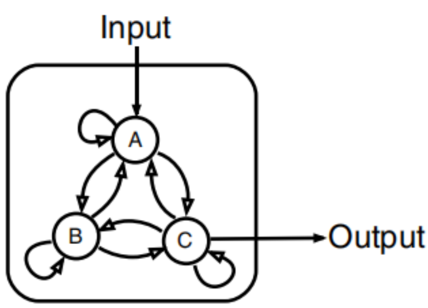
Assumption: 1. CheB only demethylates phosphorylated receptors; 2. methylation rates operate at saturation; 3. demethylation is independent of ligand binding.

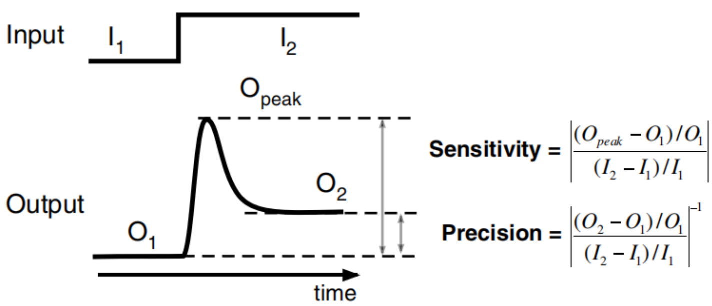


$\frac{d[3_p]}{dt} = r_{\text{in}} - k_{\text{eff4}}[3_p] - k_{pt}[3_p] + k_{\text{eff2}}[3], \frac{d[3]}{dt} = r_{\text{in}} + k_{\text{pt}}[3_p] - k_{\text{eff2}}[3] \Rightarrow \frac{d[3_T]}{dt} = \frac{d[3]}{dt} + \frac{d[3_p]}{dt} = 2r_{\text{in}} - k_{\text{eff4}}[3_p] = 0 \Rightarrow [3_p] = \frac{2r_{\text{in}}}{k_{\text{eff4}}}$ independent of L.

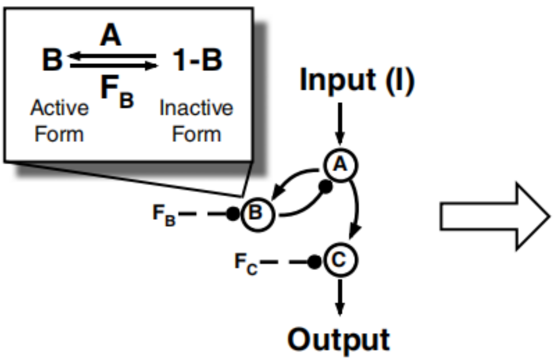
7.3 Ma's Model

Define newtwork topologies that can achieve Biochemical Adaptation.





Here, A is the input node, B is a buffering node and C is the output node. The definitions of sensitivity and precision are shown in the right figure.



$$\frac{dA}{dt} = k_{IA} I \frac{(1-A)}{(1-A)+K_{IA}} - k'_{BA} B \frac{A}{A+K'_{BA}}$$
$$\frac{dB}{dt} = k_{AB} A \frac{(1-B)}{(1-B)+K_{AB}} - k'_{F_B B} F_B \frac{B}{B+K'_{F_B B}}$$
$$\frac{dC}{dt} = k_{AC} A \frac{(1-C)}{(1-C)+K_{AC}} - k'_{F_C C} F_C \frac{C}{C+K'_{F_C C}}$$

8 Stochastic Chemical Kinetics

Michaelis-Menten kinetics: $E + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_3} E + P$.

Assumption: (1) well mixed $\Rightarrow$ 均匀分布, 各向同性;

(2) 分子间大量无规则的频繁碰撞 $\Rightarrow$ 分子速率处于某一稳定分布;

(3) T is constant.

Reaction Rate Equation (deterministic): $\begin{cases} \frac{d[S]}{dt} = k_2[ES] - k_1[E][S] \\ \frac{d[ES]}{dt} = -(k_2+k_3)[ES] + k_1[E][S] \\ \frac{d[P]}{dt} = k_3[ES] := v \end{cases}$.

Good for micro-scale system, # of molecules >> 1 $\Rightarrow$ neglect fluctuations in systems, which can be very important in biology.

Consider N molecules $\{S_1, \cdots, S_N\}$ and M reactions $\{R_1, \cdots, R_M\}$, $X_i = \#$ of S_i, $X = \{X_1, \cdots, X_N\}$. When a reaction happens, status of X will change.

$R_j = \begin{cases} v_j = (v_{1j}, \cdots, v_{Nj}), \text{状态改变向量} \\ a_j(x), \text{反应速率函数 (丰度)} \end{cases}$. In M-M, $v = \begin{pmatrix} -1 & 1 & 0 \\ -1 & 1 & 1 \\ 1 & -1 & -1 \\ 0 & 0 & 1 \end{pmatrix}$, $S = \begin{pmatrix} S \\ E \\ ES \\ P \end{pmatrix}$, $a_1 = k_1[E][S], a_2 = k_2[ES], a_3 = k_3[ES]$.

When $X(t) = x$ in $(t, t+dt)$, 系统中每个反应独立于其他反应以 $P = a_j(x)dt$ 发生. 一旦反应 R_j 发生, 系统状态改变到 $x + v_j \Rightarrow$ Markov jump process.

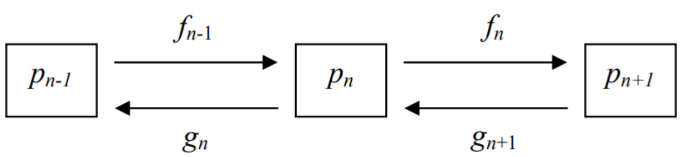
8.1 Probabilistic Formulation of Reaction Kinetics

(A) Single molecule: $P_n(t)$: # of these systems having n molecules of time t.

Reactions for $P_n(t)$:

$+1 \Rightarrow$ a X is created in some systems having $n-1$ molecules.

$-1 \Rightarrow$ a X is destroyed $\cdots n+1 \cdots$.



Master Equation: $\frac{dP_n}{dt} = -(f_n+g_n)P_n + f_{n-1}P_{n-1} + g_{n+1}P_{n+1}$—(1). This is an infinite set of equations.

$\frac{P_n}{\sum_{n=1}^{\infty} P_n} := P_n(t)$ prob of any given systems in state n. To solve (1) is very difficult. But it is possible to obtain all the monents of $P_n(t)$ without explicitly solving master equation.

For example, mean # of molecules: $\langle n\rangle = \sum_n nP_n$, $\frac{dn}{dt} = k - \gamma n := f_n - g_n$, $\frac{d\langle n\rangle}{dt} = -k\sum nP_n - \gamma\sum n^2P_n + k\sum nP_{n-1} + \gamma\sum n(n+1)P_{n+1} = k - \gamma\langle n\rangle$.

(B) Multiple molecules: Assume $X(t_0) = x_0, \langle x\rangle = \sum xP(x,t|x_0,t_0)$.

Master equation: $P(x,t+dt|x_0,t_0) - P(x,t|x_0,t_0) = J_{\text{in}}(t,t+dt) - J_{\text{out}}(t,t+dt) \Rightarrow J_{\text{in}}(t,t+dt) = \sum_{j=1}^{M} p(x-v_j,t|x_0,t_0)a_j(x-v_j)dt, J_{\text{out}}(t,t+dt) = P(x,t|x_0,t_0)\sum_{j=1}^{M} a_j(x)dt \Rightarrow P(x,t+dt) - P(x,t) = \sum_{j=1}^{M} p(x-v_j,t)a_j(x-v_j) - P(x,t)\sum_{j=1}^{M} a_j(x)dt \Rightarrow \frac{\partial P(x,t)}{\partial t} = \sum_{j=1}^{M}[a_j(x-v_j)P(x-v_j,t) - a_j(x)P(x,t)]$—(2). Define $P_x(t) = P(x,t) \Rightarrow \frac{dP_x(t)}{dt} = \sum_{j=1}^{M}[a_j(x-v_j)P_{x-v_j}(t) - a_j(x)P_x(t)]$

Define A coeff matrix, $A_{x,x-v_j} = a_j(x-v_j), A_{x,x} = -\sum_{j=1}^{M} a_j(x) \Rightarrow \frac{dP_x(t)}{dt} = AP_x(t)$.

$P_x(t) \geq 0, \sum_x P_x(t) = 1$.

If X is a finite set, $P_x(t) = e^{A(t-t_0)}P_x(t_0)$.

A: 非对角线元素都非负, 对角线元素都非正 ⇒ Metzler Matrix ⇒ 没有正实部特征值 ⇒ 可收敛到系统的平稳分布.

$\frac{\partial}{\partial t}\sum_x xP(x,t) = \sum_x\sum_{j=1}^{M}[xa_j(x-v_j)P(x-v_j,t) - xa_j(x)P(x,t)](x-v_j = x) = \sum_{j=1}^{M}\sum_x(x+v_j)a_j(x)P(x,t) - \sum_{j=1}^{M}\sum_x xa_j(x)P(x,t) = \sum_{j=1}^{M} v_j\sum_x a_j(x)P(x,t) \Rightarrow \frac{d\langle X_i\rangle}{dt} = \sum_{j=1}^{M} v_{ji}\langle a_j(X)\rangle$ where $\langle a_j(X)\rangle = \sum_x a_j(x)P(x,t) = a_j(\langle X\rangle)$ (we assume $a_j(x)$ is linear) $\Rightarrow \frac{d\langle X_i\rangle}{dt} = \sum_{j=1}^{M} v_{ji}a_j(\langle X\rangle)$.

8.2 Fluctuation-Dissipation Thm

Consider the covariance matrix of the multiple-molecule system and its derivative w.r.t. t.

$$\sigma_{ik} = \sum_x (x_i - \langle X_i\rangle)(x_k - \langle X_k\rangle)P(x,t)$$

$$\Rightarrow \frac{d\sigma_{ik}}{dt} = \sum_x\left(-\frac{d\langle X_i\rangle}{dt}\right)(x_k - \langle X_k\rangle)P(x,t) + \sum_x\left(-\frac{d\langle X_k\rangle}{dt}\right)(x_i - \langle X_i\rangle)P(x,t) + \sum_x(x_i - \langle X_i\rangle)(x_k - \langle X_k\rangle)\frac{\partial P(x,t)}{\partial t}$$

前面两项为 0, 最后一项使用 Master Equation

$$\begin{aligned}
\Rightarrow \frac{d\sigma_{ik}}{dt} &= \sum_x(x_i - \langle X_i\rangle)(x_k - \langle X_k\rangle)\sum_{j=1}^{M}[a_j(x-v_j)P(x-v_j,t) - a_j(x)P(x,t)] \\
&= \sum_{j=1}^{M}\sum_x(x_i - \langle X_i\rangle)(x_k - \langle X_k\rangle)a_j(x-v_j)P(x-v_j,t) - \sum_{j=1}^{M}\sum_x(x_i - \langle X_i\rangle)(x_K - \langle X_k\rangle)a_j(x)P(x,t) \\
&= \sum_{j=1}^{M}\sum_x(x_i + v_{ji} - \langle X_i\rangle)(x_k + v_{jk} - \langle X_k\rangle)a_j(x)P(x,t) \\
&= \sum_x\sum_{j=1}^{M}[v_{ji}a_j(x)(x_k - \langle X_k\rangle) + v_{jk}a_j(x)(x_i - \langle X_i\rangle)]P(x,t) + \sum_x\sum_{j=1}^{M} v_{ji}v_{jk}a_j(x)P(x,t) \\
&:= \sum_x[A_i(x)(x_k - \langle X_k\rangle) + A_k(x)(x_i - \langle X_i\rangle)]P(x,t) + \sum_x B_{ik}(x)P(x,t)
\end{aligned}$$

$$\Rightarrow \frac{d\sigma_{ik}}{dt} = \langle A_i(X)(X_k - \langle X_k\rangle)\rangle + \langle A_k(X)(X_i - \langle X_i\rangle) + \langle B_{ik}(X)\rangle$$

仅考虑一阶反应 ⇒ $a_j(x)$ 都是线性函数, $\frac{d\langle X_i\rangle}{dt} = \sum_{j=1}^{M} v_{ji}a_j(\langle X_i\rangle)$.

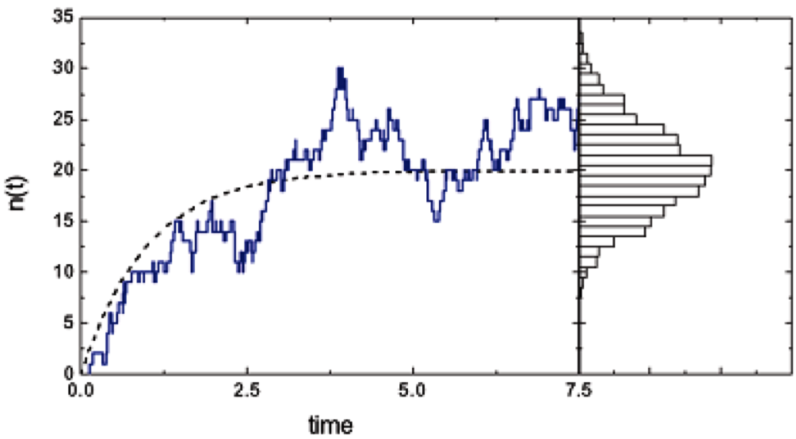
弱随机条件下, 当 $x_i - \langle X_i\rangle$ 很小时, 在 $x = \langle X\rangle$ 附近做 Taylor Expansion,

$\Rightarrow A_i(x) = A_i(\langle X\rangle) + \sum_{l=1}^{N} \frac{\partial A_i(\langle X\rangle)}{\partial x_l}(x_l - \langle X_l\rangle), B_{ik}(x) = B_{ik}(\langle X\rangle) + \sum_{l=1}^{N} \frac{\partial B_{ik}(\langle X\rangle)}{\partial x_l}(x_l - \langle X_l\rangle)$
$\Rightarrow \frac{d\sigma_{ik}}{dt} = \sum_{l=1}^{N}[\frac{\partial A_i(\langle X\rangle)}{\partial x_l}\sigma_{ik} + \frac{\partial A_k(\langle X\rangle)}{\partial x_l}\sigma_{il}] + B_{ik}(\langle X\rangle)$
$\Rightarrow \frac{d\sigma}{dt} = (A\sigma + \sigma A^T) + B$ (近平衡态时系统协方差的近似演化方程)
Q: A, B physical meaning? A: dissipation, B: fluctuation.
A: linear coefficient matrix, $\mathrm{Re}(\lambda(A)) < 0$ for steady equilium $\Rightarrow$ dissipation.
$\frac{d\sigma}{dt} = 0 \Rightarrow B = -A\sigma - \sigma A^T$, $\sigma \neq 0 \Rightarrow B_{ii}(x) = \sum_{j=1}^{M} v_{ji}^2 a_j(x) \geq 0$.

8.3 Steady State of Master Equation

For single molecule, $\frac{dP_n}{dt} = -(k+\gamma n)P_n + kP_{n-1} + \gamma(n+1)P_{n+1} = 0 \Rightarrow P_n = \frac{\bar{n}}{n}P_{n-1} = \cdots = \frac{\bar{n}^n}{n!}P_0$ where $\bar{n} = k/\gamma \Rightarrow \sum_n P_n = \sum_n \frac{\bar{n}^n}{n!}P_0 = 1 \Rightarrow P_0 = e^{-\bar{n}} \Rightarrow P_n = \frac{\bar{n}^n}{n!}e^{-\bar{n}}$.

Limit of large numbers: mean & variance: $\langle n\rangle = \langle \delta n^2\rangle = \bar{n} = k/\gamma$. Coefficient of variation (relative standard deviation) $= \frac{\sqrt{\langle \delta n^2\rangle}}{\langle n\rangle} = \frac{1}{\sqrt{\langle n\rangle}}$.



8.4 Fokker-Planck Equation

From discrete to constant variable. Tool: Taylor expansion.

Master Equation: $\frac{dP_x(t)}{dt} = \sum_{j=1}^{M}[a_j(x-v_j)P_{x-v_j}(t) - a_j(x)P_x(t)]$. Assume $x >> v_j$, $\frac{\partial P(x,t)}{\partial t} = \sum_{j=1}^{M}[a_j(x)P(x,t) - \sum_{i=1}^{M}\frac{\partial}{\partial x_i}a_j(x)P(x,t)v_{ji} + \frac{1}{2}\sum_{i,k=1}^{n}\frac{\partial^2}{\partial x_i \partial x_k}a_j(x)P(x,t)v_{ji}v_{jk} - a_j(x)P(x,t)]$.

Define $A_i(x) = \sum_{j=1}^{M} v_{ji}a_j(x), B_{ik}(x) = \sum_{j=1}^{M} v_{ji}v_{jk}a_j(x)$.

$\frac{\partial P(x,t)}{\partial t} = -\sum_{i=1}^{N}\frac{\partial}{\partial x_i}A_i(x)P(x,t) + \frac{1}{2}\sum_{1\leq i,k\leq N}\frac{\partial^2}{\partial x_i \partial x_k}B_{ik}(x)P(x,t)$. (Fokker-Planck Equation)

Assume $A_i(x) = 0, B_{ik}(x) = D\delta_{ik}, \Rightarrow \frac{\partial P(x,t)}{\partial t} = \frac{D}{2}\sum_{i=1}^{N}\frac{\partial^2 P(x,t)}{\partial x_i^2}$. (Diffusion Equation)

Example: 1-D case: $\frac{dP_n}{dt} = -(f_n + g_n)P_n + f_{n-1}P_{n-1} + g_{n+1}P_{n+1}$.

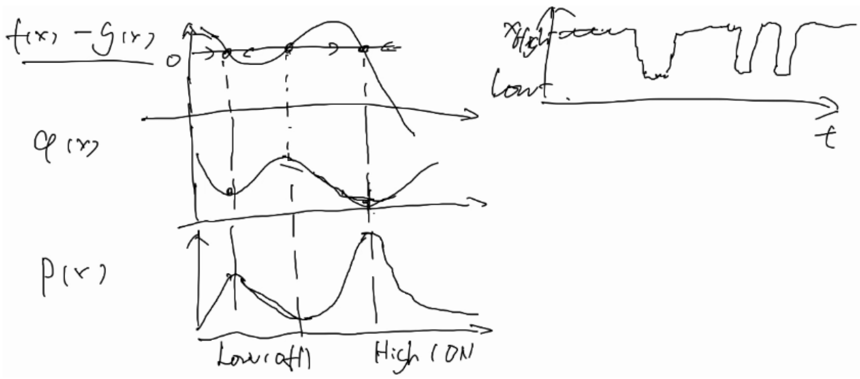
$$\begin{cases} f(n-1)P(n-1) = f(n)P(n) - \frac{\partial}{\partial n}f(n)P(n) + \frac{1}{2}\frac{\partial^2}{\partial n^2}f(n)P(n) \\ g(n+1)P(n+1) = g(n)P(n) + \frac{\partial}{\partial n}g(n)P(n) + \frac{1}{2}\frac{\partial^2}{\partial n^2}g(n)P(n) \end{cases}$$

$$\Rightarrow \frac{\partial P(u,t)}{\partial t} = -\frac{\partial}{\partial n}[(f-g)P - \frac{1}{2}\frac{\partial}{\partial n}(f+g)P] := -\frac{\partial}{\partial n}J$$

where J: prob flux. At steady state, $J = Const. = 0$ (flux at $n = 0 = 0 \Rightarrow J = 0$ everywhere).

Then $(f-g)P = \frac{1}{2}\frac{\partial}{\partial n}(f+g)P$. Define $q=(f+g)P$, $\frac{f-g}{f+g}q = \frac{1}{2}\frac{\partial q}{\partial n} \Rightarrow q = A\exp(2\int \frac{f-g}{f+g}dn') \Rightarrow P(n) = \frac{A}{f+g}e^{-\phi(n)}$ where $\phi(n) = -2\int \frac{f-g}{f+g}dn'$ (potential).

Example: stochastic bistable system: $\frac{dx}{dt} = \frac{v_0+v_1x^2}{k+x^2} - \gamma x$.



8.5 Waiting Time Between Reactions

Suppose chem reaction occurs at rate r. The prob that the reaction occurs in dt is rdt.

The prob that it occurs only after some time τ is $P(\tau) = P(\text{next occurence is in } (\tau, \tau+d\tau)) = P(\text{does not occur for } t<\tau)P(\text{occurs in } \tau \text{ to } \tau+d\tau)$. Define $Q(\tau)$ = the former.

$Q(\tau) = Q(\tau-d\tau)(1-rd\tau) \Rightarrow \log Q(\tau) - \log Q(\tau-d\tau) = \log(1-rd\tau) \approx -rd\tau \Rightarrow \frac{d\log Q(\tau)}{d\tau} = -r \Rightarrow Q = e^{-r\tau}$ where $Q(0)=1 \Rightarrow P(\tau) = e^{-r\tau}rd\tau$.

8.6 Stochastic Simulation Algorithm

Numerically simulate the time evolution of a well-mixed chemically reacting system, is exact in the sense that it is rigorously based on chemical Master Equation.

Consider $N \geq 1$ molecular species $\{S_1, \cdots, S_N\}$, $M \geq 1$ reactions $\{R_1, \cdots, R_M\}$, $x(t) = (x_1(t), \cdots, x_N(t))$ where $x_i(t) = \#$ of S_i at time t.

$t : x(t) \to t+\tau$ 下一个反应 R_μ, $(t, t+\tau), x \to x + v_\mu \Rightarrow x(t) = x$ 计算下一个反应发生的时间 $t+\tau$ 和反应 R_μ.

Q: Key factors for SSA? A: $\tau \to$ when will reaction occur? $\mu \to$ which reaction?

下一次反应在 $(t+\tau, t+\tau+d\tau)$ 内且发生第 μ 个反应的 $P(\tau,\mu;x)d\tau$ = the prob given $x(t)=x$ that one R_j will occur in the next infinitesimal time interval.

$P(\tau,\mu;x)d\tau = P_0(\tau,x)a_\mu(x)d\tau$. $P_0(\tau,x)$: $(t,t+\tau)$ 不发生反应的概率, $a_\mu(x)d\tau$: $(t+\tau,t+\tau+d\tau)$ 发生反应 μ 的概率.

$P_0(0,x)=1$. 在 $(t,t+\tau')$ 没发生反应的概率 $P_0(\tau'+d\tau',x) = P_0(\tau',x)(1-\sum_{v=1}^M a_v(x)d\tau') \Rightarrow \frac{\partial P_0(\tau',x)}{\partial \tau'} = -\sum_{v=1}^M a_v(x)P_0(\tau',x)$ with $P_0(0,x)=1 \Rightarrow P_0(\tau,x) = \exp(-\sum_{v=1}^M a_v(x)\tau) \Rightarrow P(\tau,\mu;x) = a_\mu(x)\exp(-a_0(x)\tau)$ where $a_0(x) = \sum_{v=1}^M a_v(x)$.

SSA 算法 (Gillespie): (1) $x(0)=x_0, t=0$; (2) 计算 $a_v = a_v(x), v=1,\cdots,M$, $a_0 = \sum_{v=1}^M a_v(x)$; (3) 生成服从参数为 a_0 的指数分布 τ, 作为下一个反应的等待时间; (4) 生成 $[0,1]$ 上均匀分布随机变量 r, 找到满足 $\sum_{v=1}^{\mu-1} a_v < ra_0 \leq \sum_{v=1}^{\mu} a_v$; (5) $t=t+\tau, R_\mu, x_i \to x_i + R_\mu$; (6) goto (2).

Remark: (1) SSA: $t \to t+\tau$, 模拟长时间行为, 为了模拟每一步反应, 步长 τ 很小; (2) 原始 SSA 中随即搜索反应 μ 的运算, 跟系统中反应 $\#M$ 成线性关系, 有加速设计.

8.7 Chemical Langevin Equation

Chemical Master Equation: 最根本, 不方便分析、计算.

Reaction Rate Equation: 确定性, 方便分析、计算, 不能描述随机性.

$x(t) = x$, 令 $k_j(x,\tau)$: 反应 R_j 在 $[t, t+\tau)$ 内发生的次数, 每次反应分子 S_i 的个数增加 v_{ji}. 则 $x_i(t+\tau) = x_i + \sum_{j=1}^{M} k_j(x,\tau)v_{ji}, i = 1, \cdots, N$. 希望对这个方程有一个很好的近似.

Condition 1: $[t, t+\tau)$, 系统状态的改变量相对于状态本身只有微小的改变 $\Rightarrow a_j(x(t')) \approx a_j(x(t))$, $t' \in [t, t+\tau), j = 1, \cdots, M$.

反应 R_j 在 $[t, t+\tau)$ 内任意无穷小时间段 $d\tau$ 内发生的概率可认为是相互独立, $P = a_j(x)d\tau \Rightarrow$ $k_j(x,\tau)$ 满足独立的泊松分布, 记为 $P_j(a_j(x), \tau)$.

当分子数 $>> 1$, 只要 τ 充分小, condition 1 容易满足.

求解 $P(a,\tau) = n$ 的概率 $Q(n; a, \tau)$. 数学归纳: $n = 0, Q(0; a, \tau) = e^{-a\tau}$.

$\forall n \geq 1$, 时间 τ 内发生 n 次反应分成 3 部分: (1) $Q(n-1; a, \tau')$, 在 $\tau' < \tau$ 发生 $n-1$ 次反应; (2) $[\tau', \tau' + d\tau')$ 发生一次反应 P 为 $ad\tau'$; (3) $[\tau' + d\tau', \tau)$ 不发生反应, $Q(0; a, \tau - \tau')$.

$Q(n; a, \tau) = \int_0^{\tau} Q(n-1; a, \tau')ad\tau' Q(0; a, \tau - \tau')$. 数学归纳验证 $Q(n; a, \tau) = \frac{e^{-a\tau}(a\tau)^n}{n!}$.

$x_i(t+\tau) = x_i(t) + \sum_{j=1}^{M} v_{ji} P_j(a_j(x), \tau)$.

Condition 2: 时间区间 τ 充分大使得在 $[t, t+\tau)$ 内发生反应次数 $>> 1$, 即 $a_j(x)\tau >> 1, \forall 1 \leq j \leq M$.

$\Rightarrow$ C1 和 C2 有矛盾 $\Rightarrow a_j(x)$ 为大数, 选取合适的 τ 满足 C1 和 C2.

$Q(n; a, \tau) \xrightarrow{\text{Stirling 公式}} \log \frac{e^{-a\tau}(a\tau)^n}{n!} = -a\tau + n\log(a\tau) - \log n! \approx -a\tau + n\log(a\tau) - n\log n + n + o(n) \xrightarrow{n \sim a\tau >> 1} \approx n - a\tau - n\log(1 + \frac{n-a\tau}{a\tau}) \approx n - a\tau - n(\frac{n-a\tau}{a\tau} - \frac{1}{2}(\frac{n-a\tau}{a\tau})^2) = -\frac{(n-a\tau)^2}{2a\tau}\frac{2a\tau - n}{a\tau} \approx -\frac{(n-a\tau)^2}{2a\tau} \Rightarrow Q(n; a, \tau) \approx C\exp(-\frac{(n-a\tau)^2}{2a\tau})$. 由 $a\tau >> 1, Q(n; a, \tau) \to$ 均值和方差为 $a\tau$ 的正态分布 $\to P(a,\tau) \approx \mathcal{N}(a\tau, a\tau)$ 当 $a\tau >> 1$.

当 C1 和 C2 同时满足, $x_i(t+\tau) = x_i(t) + \sum_{j=1}^{M} v_{ji}\mathcal{N}(a_j(x)\tau, a_j(x)\tau), i = 1, \cdots, N \Rightarrow x_i(t+\tau) = x_i(t) + \sum_{j=1}^{M} v_{ji}a_j(x)\tau + \sum_{j=1}^{M} v_{ji}[a_j(x)]^{\frac{1}{2}}\mathcal{N}_j(0,1)$.

White noise: $\xi_j(t) : t$ 时刻满足 $\mathcal{N}_j(0,1)$ 的随机变量, $\langle \xi(t) \rangle = 0, \langle \xi_i(t), \xi_j(t') \rangle = \delta_{ij}(t-t') \Rightarrow$ $x_i(t+dt) = x_i(t) + \sum_{j=1}^{M} v_{ji}a_j(x(t))dt + \sum_{j=1}^{M} v_{ji}a_j^{\frac{1}{2}}(x)\xi_j(t)(dt)^{\frac{1}{2}}$.

引入 Wiener process $W_j : dW_j = W_j(t+dt) - W_j(t) = \xi_j(t)(dt)^{\frac{1}{2}} \Rightarrow dx_i = \sum_{j=1}^{M} v_{ji}a_j(x)dt + \sum_{j=1}^{M} v_{ji}a_j^{\frac{1}{2}}(x)dW_j, i = 1, \cdots, N$ (Chemical Langevin Equation).

8.8 τ-Leaping Algorithm

一次近似步长 τ 内每个反应发生的数目.

τ-Leaping 条件: $[t, t+\tau)$ 改变小, $a(x)$ 几乎不变: (1) 反应物的分子数比较大, $N_C = 10$ 或 20 为临界值, 分子数 $< 20 \to$ SSA; (2) τ 的选取不能过大.

对于适当选取的 τ, $x_i(t+\tau) = x_i(t) + \sum_{j=1}^{M} v_{ji}P(a_j(x), \tau)$, 算法: (1) 按泊松分布 $P(a_j(x), \tau)$ 产生随机数 k_j; (2) 系统的增量: $\lambda = \sum_{j=1}^{M} k_j v_j$; (3) $\to t+\tau, x+\lambda$.

Key: 如何选取合适的 τ?

(1) 对于给定的 τ, 检验 $|a_j(x+\lambda)-a_j(x)|, j=1,\cdots,M$, 若对每一个 j 都是小量, 则 $\tau\checkmark$; 对 τ 从小到大进行检验, 直到找到符合条件的最大的 τ, 作为算法的跳跃时间. 缺点: 计算量太大.

(2) 预跳跃方法: $\langle P(a_j(x),\tau)\rangle = a_j(x)\tau$, 在 $[t,t+\tau)$ 增量的平均值 $\bar\lambda=\sum_{j=1}^M a_j(x)\tau v_j=\tau\xi(x)$. $|a_j(x+\bar\lambda)-a_j(x)|\le \epsilon a_0(x)$ where $a_0(x)=\sum_{j=1}^M a_j(x)$, 则认为跳跃条件是满足的.

$a_j(x+\bar\lambda)-a_j(x)\approx\bar\lambda\cdot\nabla a_j(x)=\sum_{i=1}^N \tau\xi_i(x)\frac{\partial a_j(x)}{\partial x_i}\Rightarrow\tau|\sum_{i=1}^N\xi_i(x)b_{ji}|\le\epsilon a_0(x)$ where $b_{ji}=\frac{\partial a_j(x)}{\partial x_i}\Rightarrow\tau\le\epsilon a_0/|\sum_{i=1}^N\xi_i(x)b_{ji}|$. 取 $\tau=\min_{j\in[1,M]}\{\epsilon a_0/|\sum_{i=1}^N\xi_i(x)b_{ji}|\}$.

Remark: (1) SSA 中每步反应时间间隔 $\tau\sim\frac{1}{a_0(x)}$, 若 $\tau>>\frac{1}{a_0(x)}$ 可达到加速效果, 否则用 SSA;

(2) $a_j(x)$ 在 $[t,t+\tau)$ 内基本不变, 取为中间时刻的函数值估计. 算法: 给定 $\bar\lambda=\tau\sum_j a_j(x)v_j$, 令 $x'=x+\frac{\bar\lambda}{2}\to P(a_j(x'),\tau)$ 的随机数 k_j, 计算 $\lambda=\sum_j k_jv_j$, 令 $t+\tau$ 为新的时间, $x+\lambda$.

9 Diffusion

9.1 Simple Random Walk

1-D case: Starting from $x=0$, after time $N\Delta t$, $[-N\Delta x, N\Delta x]$.

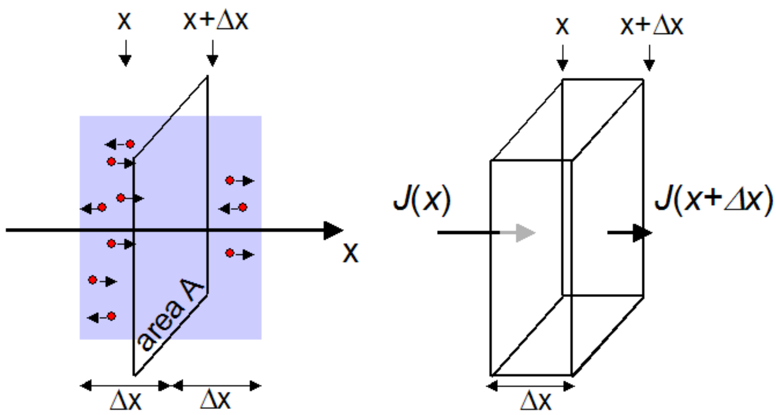
Prob $p(m,n), x=m\Delta x$ after n time-steps, a steps to right, b steps to left $\Rightarrow a=\frac{n+m}{2}, b=\frac{n-m}{2}\Rightarrow p(m,n)=C_n^a/2^n=\frac{1}{2^n}\frac{n!}{a!(n-a)!}, \sum_{m=-n}^n p(m,n)=1$.

If n is large, and $n\pm m$ are large, $n!\sim(2\pi n)^{\frac12}e^{-n}n^n, n>>1\Rightarrow p(m,n)\sim(\frac{2}{\pi n})^{\frac12}e^{-m^2/2n}$ (Gaussian prob. dist.).

Set $x=m\Delta x, t=n\Delta t$ are constant space & time variables.

Def $u=\frac{p(x/\Delta x,t/\Delta t)}{2\Delta x}\sim(\frac{\Delta t}{2\pi t(\Delta x)^2})^{1/2}\exp\left(-\frac{x^2}{2t}\frac{\Delta t^2}{(\Delta x)^2}\right)$. If assume $\lim_{\Delta x\to0,\Delta t\to0}\frac{(\Delta x)^2}{2\Delta t}=D\neq0$, D is diffusion coefficient $\Rightarrow u(x,t)=(\frac{1}{4\pi Dt})^{1/2}e^{-\frac{x^2}{4Dt}}$.

9.2 Fick's Law



Fick's First Law:

Q1: How many particels will cros the area A to the right? A: $-\frac12(N(x+\Delta x)-N(x))$.

Flux of molecules: $J=\frac{-\frac12(N(x+\Delta x)-N(x))}{A\Delta t}$. Concentration: $C(x):=\frac{N(x)}{A\Delta x}$

$\Rightarrow J=-\frac{\Delta x^2}{2\Delta t}\frac{C(x+\Delta x)-C(x)}{\Delta x}=-D\frac{\partial C(x)}{\partial x}$. J is propotional to concentration gradient.

Fick's Second Law: $\frac{C(t+\Delta t)-C(t)}{\Delta t} = \frac{1}{\Delta t}\frac{(J(x)-J(x+\Delta x))A\Delta t}{A\Delta x} = -\frac{J(x+\Delta x)-J(x)}{\Delta x} \Rightarrow \frac{\partial C(x,t)}{\partial t} = \frac{\partial J(x)}{\partial x} \Rightarrow \frac{\partial C(x,t)}{\partial t} = D\frac{\partial^2 C(x,t)}{\partial x^2}$. If $C(x,0) = Q\delta(x), C(x,t) = \frac{Q}{2(\pi Dt)^{1/2}}e^{-\frac{x^2}{4Dt}}$.

Random walks: $x(0) = 0, \langle x(n)\rangle = \frac{1}{N}\sum_{i=1}^N x_i(n) = \frac{1}{N}\sum_{i=1}^N (x_i(n-1)\pm\Delta x) = \frac{1}{N}\sum_{i=1}^N x_i(n-1) = \cdots = \frac{1}{N}\sum_{i=1}^N x_i(0) = 0$.

Q2: For chemical conc $c(x,t)$, time to convey into conc over a distance L is ? A: L^2/D.

$\text{Var}(x(n)) = \langle x^2(n)\rangle - \langle x(n)\rangle^2 = \frac{1}{N}\sum_{i=1}^N x_i^2(n) = \frac{1}{N}\sum_{i=1}^N (x_i(n-1)\pm\Delta x)^2 = \langle x^2(n-1)\rangle + \Delta x^2 = \text{Var}(x(n-1)) + \Delta x^2 \Rightarrow \langle x^2(n)\rangle = n\Delta x^2 = t\frac{\Delta x^2}{\Delta t} = 2Dt$.

9.3 Reaction Diffusion Equation

Simple diffusion $\rightarrow$ reaction kinetics + diffusion $\rightarrow$ traveling wave.

$\frac{d}{dt}\int_V C(x,t)dx = -\int_S Jds + \int_V fdx$ (flux + source) $\Rightarrow \int_V[\frac{\partial C}{\partial t} + \nabla\cdot J - f(C,x,t)]dx = 0$ (V is arbitrary) $\Rightarrow \frac{\partial C}{\partial t} + \nabla\cdot J = f(C,x,t)$.

Fick's first law: $J = -D\nabla C \Rightarrow \frac{\partial C}{\partial t} = D\triangle C + f(C,x,t)$ (reaction-diffusion equation).

Example 1: Model for animal dispersal. There is an increase in diffusion due to population pressure: $\frac{dD}{dn} > 0$. $I = -D(n)\nabla n$, typical form $D(n) = D_0(\frac{n}{n_0})^m, m > 0$. Dispersal Equation without any growth: $\frac{\partial n}{\partial t} = D_0\nabla\cdot[(\frac{n}{n_0})^m\nabla n]$.

1-D case: $\frac{\partial n}{\partial t} = D_0\frac{\partial}{\partial x}[(\frac{n}{n_0})^m\frac{\partial n}{\partial x}]$ (porous medium equation).

Solution: $n(x,t) = \begin{cases} \frac{n_0}{\lambda(t)}[1-(\frac{x}{n_0\lambda(t)})^2]^{1/m}\ |x| \le r_0\lambda(t) \\ 0,\ x > r_0\lambda(t) \end{cases}$ $,\lambda(t) = (\frac{t}{t_0})^{1/(2+m)}, r_0 = \frac{D_0\Gamma(\frac{1}{m}+\frac{3}{2})}{\pi^{1/2}n_0\Gamma(\frac{1}{m}+1)}$.

9.4 Chemotaxis

A larger number of bacterium rely on an accurate sense of smell for conveying information between members of species. Chemicals: pheromones. Model this chemically directed movement are called chemotaxis.

Unlike the diffusion, directs the motion up a concentration gradient.

Suppose a gradient in attractant $a(x,t)$, the flux of cells will increase with # of cells $n(x,t)$. Chemotaxis flux: $J = n\chi(a)\nabla a$ where $\chi(a)$ is a function of attractant concentration.

In the conservation equation for $n(x,t)$, $\frac{\partial n}{\partial t} + \nabla\cdot J = f(n)$. Here $J = J_{\text{diffusion}} + J_{\text{chemotaxis}} \Rightarrow \frac{\partial n}{\partial t} = f(n) - \nabla\cdot n\chi(a)\nabla a + \nabla\cdot(D\nabla n)$ (Reaction-Diffusion-Chemotaxis Eqn).

$\frac{\partial a}{\partial t} = g(a,n) + \nabla\cdot(D_a\nabla a)$ and $D_a > D$.

In the seminal model of Keller & Segel (1971), $g(a,n) = h_n - k_a, h, k > 0$. Simple case: $f(n) = 0 \Rightarrow$ 1-D case (Keller-Segel): $\begin{cases} \frac{\partial n}{\partial t} = D\frac{\partial^2 n}{\partial x^2} - x_0\frac{\partial}{\partial x}(n\frac{\partial a}{\partial x}) \\ \frac{\partial a}{\partial t} = h_n - k_a + D_a\frac{\partial^2 a}{\partial x^2} \end{cases}$.

1-D diffusion system: $\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2}$. Q: the time to convey information over a distance L? A: $O(L^2/D)$. If $L = 1\text{mm}$, Diff ccoeff $D \sim 1\mu\text{m}^2/\text{sec} \Rightarrow$ time $\sim 10^6$sec – slow process.

9.5 Biological Waves

In contrast to simple diffusion, reaction kinetics + diffusion $\rightarrow$ travelling waves – much faster than diffusion.

1-D case: $\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + f(u)$.

Define travelling wave: $u(x,t) = u(x - ct) = u(z)$ – travelling wave is taken to be a wave which travels without change of shape. Wave moves along x-direction, dependent variable z is the wave variable. $\frac{\partial u}{\partial t} = -c\frac{du}{dz}, \frac{\partial u}{\partial x} = \frac{du}{dz}$. $u(z)$ has to be bounded for all z and nonnegative.

$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} \Rightarrow c\frac{du}{dz} + D\frac{d^2 u}{dz^2} = 0 \rightarrow$ linear parabolic equation $\Rightarrow u(z) = A + Be^{-cz/D}$. $z \rightarrow -\infty, u(z) \rightarrow \infty$ unbounded $\Rightarrow B = 0 \Rightarrow u(z) = A$ not a wave solu. Simple diffusion can't lead to travelling wave. It depends on the form of reaction term $f(u)$.

(1) Fisher-Kolmogoroff equation: nonlinear reaction diffusion equation: $\frac{\partial u}{\partial t} = ku(1-u) + D\frac{\partial^2 u}{\partial x^2}$. Let $t^* = kt, x^* = x(k/D)^{1/2} \Rightarrow \frac{\partial u}{\partial t} = u(1-u) + \frac{\partial^2 u}{\partial x^2} \Rightarrow$ 2 homogeneous solus: $u(x) = 0, u(x) = 1$. Q: stability? A: $u = 0$ unstable, $u = 1$ stable. Thus suggests we should look for travelling wave solus for $0 \le u \le 1$. $u''(z) + cu' + u(1-u) = 0 \Rightarrow \begin{cases} u' = v \\ v' = -cv - u(1-u) \end{cases} \Rightarrow \frac{dv}{du} = \frac{-cv-u(1-u)}{v}$. It has 2 singular points $(u,v) = (0,0), (1,0)$. Linear stability analysis: $(0,0) : \lambda_\pm = \frac{1}{2}[-c \pm (c^2-4)^{1/2}] \Rightarrow \begin{cases} \text{stable node if } c^2 > 4 \\ \text{stable spirals if } c^2 < 4 \end{cases}$, $(1,0) : \lambda_\pm = \frac{1}{2}[-c \pm (c^2+4)^{1/2}] \Rightarrow$ saddle point $\Rightarrow$ unstable. $c^2 < 4 \rightarrow$ stable spiral $\rightarrow$ oscillate near $(0,0)$, not physical. $c \ge c_{\min} = 2 \rightarrow$ stable node $(0,0)$. There is a trajectory from $(1,0)$ to $(0,0)$. $u \ge 0, u' \le 0$ with $0 \le u \le 1$ for $c \ge c_{\min} = 2(KD)^{1/2}$.

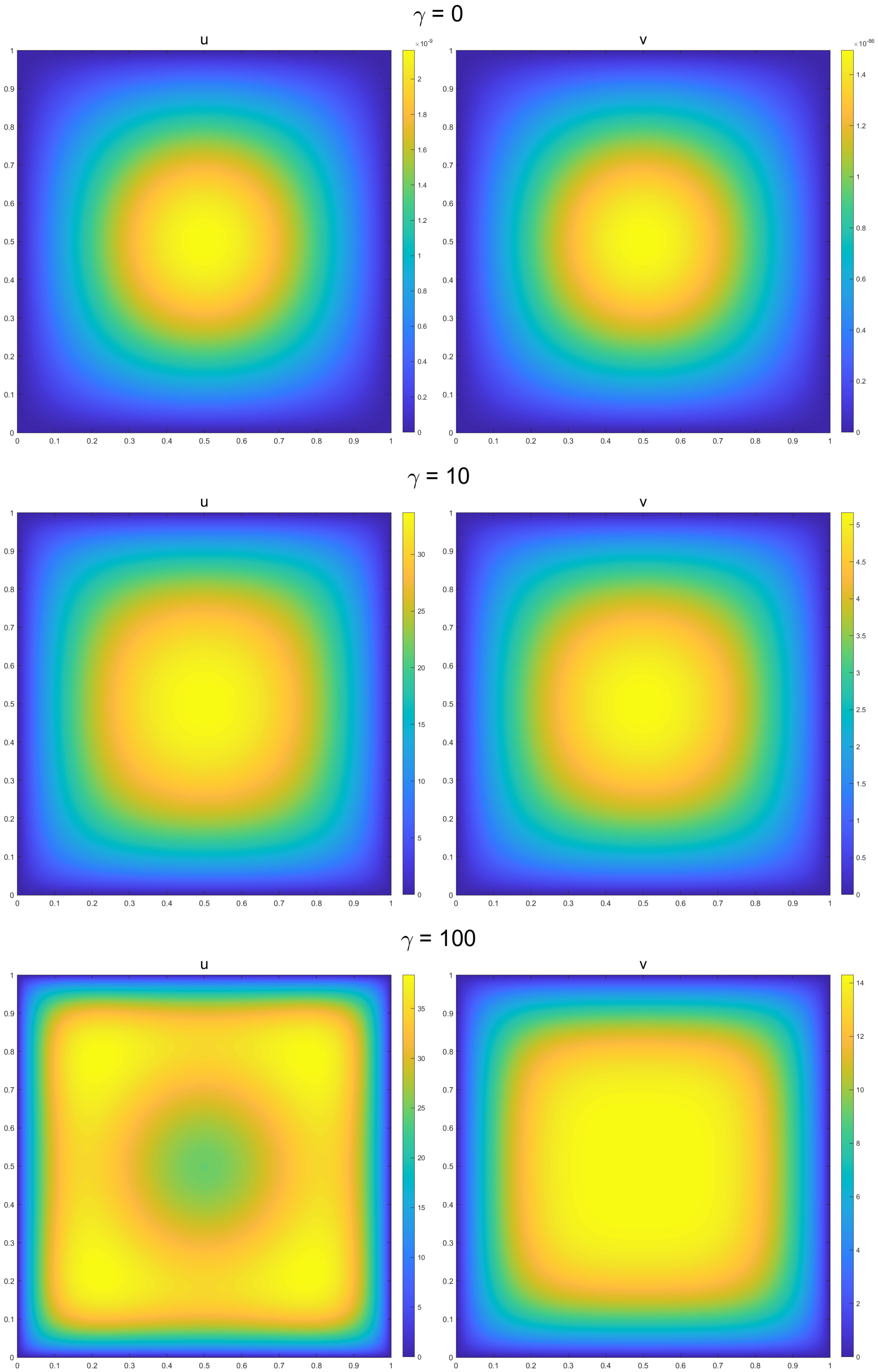
Q: What kind of initial condition $u(x,0)$ will evolve to a travelling wave solu? If such a solu exists, what is its wave speed c? Kolmogoroff (1937) proved that if $u(x,0)$ has compact support, that is, $u(x,0) = u_0(x) > 0, u_0(x) = \begin{cases} 1, & \text{if } x \le x_1 \\ 0, & \text{if } x \ge x_2,\ u_0(x) \end{cases}$ is continuous in $[x_1, x_2]$, then the solu $u(x,t)$ evolves to a travelling wavefront solu $u'(z)$ with $z = x - 2t$.

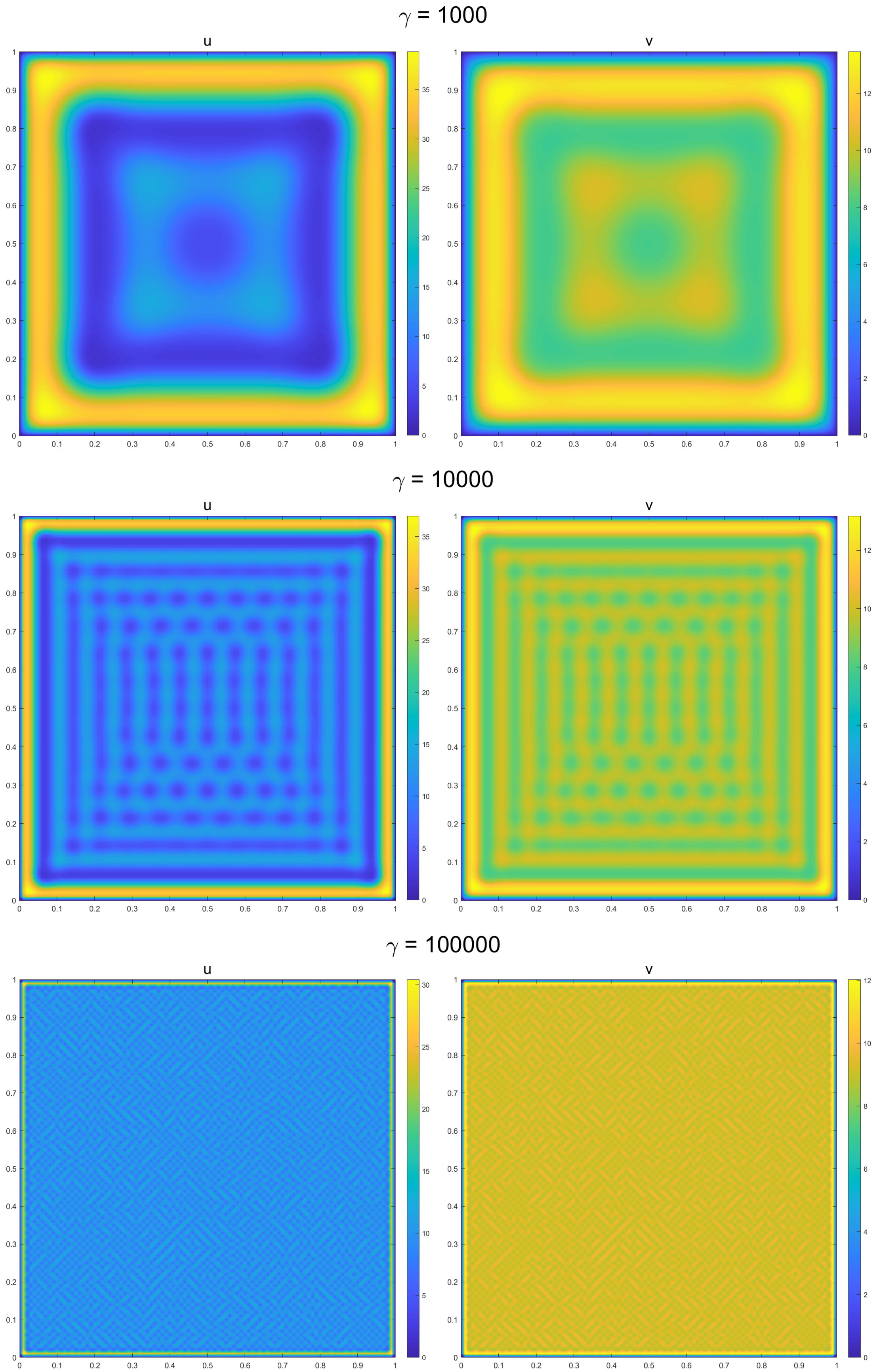
Fisher-Kolmogoroff Eqn is invariant under a change of sign of x: $x \rightarrow -x, u(x,t) = u(x+ct), c > 0, u(-\infty) = 0, u(+\infty) = 1$.

10 Turing Pattern

Diffusion-driven instability: $\begin{cases} \frac{\partial u}{\partial t} = D_u \triangle u(-d_u u) + F(u,v) \\ \frac{\partial v}{\partial t} = D_v \triangle v(-d_v v) + G(u,v) \end{cases}$. The terms in brackets might be omitted. An example: $\begin{cases} \frac{\partial u}{\partial t} = \gamma(a - u - \frac{\rho uv}{1+u+Ku^2}) + \nabla^2 u \\ \frac{\partial v}{\partial t} = \gamma(\alpha(b-v) - \frac{\rho uv}{1+u+Ku^2}) + d\nabla^2 v \end{cases}$.

Values of parameters: $d = 10, a = 92, b = 64, \alpha = 1.5, \rho = 18.5, K = 0.1$. When γ is small, the diffusion process mainly leads the changes of density of u, v with time going by so that Turing Pattern can't be formed. When γ is large, we can obtain Turing Pattern with complex structure.


γ = 0
u
v
γ = 10
u
v
γ = 100
u
v


γ = 1000
u
v
γ = 10000
u
v
γ = 100000
u
v