

# Computational Systems Biology

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## 目录

<b>1</b>	<b>Michaelis-Menten Kinetics</b>	<b>3</b>
1.1	Law of Mass Action . . . . .	3
1.2	MM Kinetics . . . . .	3
<b>2</b>	<b>Equilibrium Binding and Cooperativity</b>	<b>4</b>
2.1	Identical and Independent Binding Sites . . . . .	4
2.2	Identical and Interacting Binding Sites . . . . .	4
2.3	Non-Identical and Interacting Binding Sites . . . . .	4
<b>3</b>	<b>Transcription Networks</b>	<b>4</b>
3.1	Basic Models . . . . .	4
3.2	Ultrasensitivity . . . . .	5
3.3	Autoregulation . . . . .	5
<b>4</b>	<b>Positive Feedback and Multistability</b>	<b>6</b>
<b>5</b>	<b>Stability and Oscillation</b>	<b>8</b>
5.1	Stability Analysis . . . . .	8
5.2	Biological Oscillations . . . . .	8
5.3	Ruling out Closed Orbits . . . . .	9
5.4	Synthetic Genetic Oscillators . . . . .	9
<b>6</b>	<b>Feed Forward Loop Network Motif</b>	<b>11</b>
6.1	C1-FFL . . . . .	12
6.2	I1-FFL . . . . .	12
6.3	Other FFLs . . . . .	13

## 目录

<b>7</b>	<b>Adaptation</b>	<b>13</b>
7.1	Spiro's model . . . . .	13
7.2	Barkai's Model . . . . .	14
7.3	Ma's Model . . . . .	14
<b>8</b>	<b>Stochastic Chemical Kinetics</b>	<b>15</b>
8.1	Probabilistic Formulation of Reaction Kinetics . . . . .	15
8.2	Fluctuation-Dissipation Thm . . . . .	16
8.3	Steady State of Master Equation . . . . .	17
8.4	Fokker-Planck Equation . . . . .	17
8.5	Waiting Time Between Reactions . . . . .	18
8.6	Stochastic Simulation Algorithm . . . . .	18
8.7	Chemical Langevin Equation . . . . .	19
8.8	$\tau$ -Leaping Algorithm . . . . .	19
<b>9</b>	<b>Diffusion</b>	<b>20</b>
9.1	Simple Random Walk . . . . .	20
9.2	Fick's Law . . . . .	20
9.3	Reaction Diffusion Equation . . . . .	21
9.4	Chemotaxis . . . . .	21
9.5	Biological Waves . . . . .	21
<b>10</b>	<b>Turing Pattern</b>	<b>22</b>

# 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:  $A \xrightleftharpoons[k_-]{k_+} B$ .  $k_+$ : forward rate constant,  $k_-$ : backward rate constant.

If  $k_+ \gg k_-$ , 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  $[A]_{eq} = A_0 \frac{k_-}{k_+ + k_-}$ ,  $[B]_{eq} = A_0 \frac{k_+}{k_+ + k_-}$ .

Bimolecular Chemical Reaction:  $A + B \xrightleftharpoons[k_-]{k_+} C$ .  $\frac{d[A]}{dt} = k_-[C] - k_+[A][B] = -\frac{d[C]}{dt}$ .

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.

$A + A \xrightleftharpoons[k_-]{k_+} C$ . Q: Which one is conserved? 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.  $E + S \xrightleftharpoons[k_-]{k_+} ES$ ,  $k_+ = k_1[E][S]$ ,  $k_- = k_{-1}[ES]$ .

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

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

$[S]_T \rightarrow 0 \Rightarrow f_B \rightarrow 0$ ;  $[S]_T \rightarrow \infty \Rightarrow f_B \rightarrow 1$ ;  $[E]_T \rightarrow \infty \Rightarrow f_B \rightarrow 0$ ;  $[E]_T \rightarrow 0 \Rightarrow 0 < f_B < 1$ .

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

$E + S \xrightleftharpoons[k_{-1}]{k_1} ES \xrightarrow{k_2} E + P$ . 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  $\gg$  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:  $S_0 \gg E_0$ .

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

时间尺度分离: Let  $\tau = k_1E_0t$ ,  $\overline{ES} = \frac{[ES]}{E_0}$ ,  $\overline{S} = \frac{[S]}{S_0}$ ,  $\frac{d[\overline{S}]}{d\tau} \Rightarrow \frac{d\overline{S}}{d\tau} = -\overline{S} + (\overline{S} + k - \lambda)\overline{ES}$  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 sites.  $S + P_{j-1} \xrightleftharpoons[k_{-j}]{k_{+j}} P_j, j = 1, 2, \dots, n$ .

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

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

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

### 2.1 Identical and Independent Binding Sites

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

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

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

### 2.2 Identical and Interacting Binding Sites

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

$k = k^{*}$  (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).  $P_0 + 2S \xrightleftharpoons[k_{-}]{k_{+}} P_2, k = k_{+}/k_{-}, k_{+}[P_0][S]^2 = K_{-}[P_2] \Rightarrow k = k_{+}/k_{-} = [P_2]/[P_0][S]^2 \Rightarrow Y = \frac{[P_2]}{[P_0] + [P_2]} = \frac{k[S]^2}{1+k[S]^2}$  (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  $n_H \rightarrow 2$ ? A:  $x \rightarrow 0, \beta \rightarrow \infty$ .

### 2.3 Non-Identical and Interacting Binding Sites

$P_0 \xrightleftharpoons[k_{1-}]{k_{1+}} P_1, P_0 \xrightleftharpoons[k_{2-}]{k_{2+}} P'_1, P_1 \xrightleftharpoons[k_{3-}]{k_{3+}} P_2, P'_1 \xrightleftharpoons[k_{4-}]{k_{4+}} P_2, k_j = k_{j+}/k_{j-}$ .

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).

$Y = \frac{1}{2} \frac{[P'_1] + [P_1] + 2[P_2]}{[P_0] + [P'_1] + [P_1] + [P_2]} = \frac{k_1[S] + k_2[S] + 2k_1k_2[S]^2}{1 + k_1[S] + k_2[S] + k_1k_2[S]^2}, J = \frac{1}{2}(k_1 + k_2), J^{*} = \frac{2k_1k_2}{(k_1 + k_2)}, x' = J[S], \beta' = \frac{J^{*}}{J} \Rightarrow Y = \frac{x'(1+x'\beta')}{1+2x'+\beta'x'^2}$ .

## 3 Transcription Networks

### 3.1 Basic Models

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

## TRANSCRIPTION NETWORKS

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

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

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  $\beta$ , 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  $\alpha \rightarrow$  rapid change in concentration.  $\beta \rightarrow$  only affects steady state level.

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

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:  $T + I \xrightleftharpoons[k_-]{k_+} TI$ .  $T$ : 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.  $T_t \ll I_t + 1 \Rightarrow T = \frac{T_t}{I_t + 1}$ , buffering agent.

2.  $T_t \gg I_t + 1 \Rightarrow T = T_t - (I_t + 1)$ , 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:  $E_{\text{max}} = \frac{1}{2}N(N-1) \cdot 2 + N = N^2, P = E/N^2$ .  $\langle N_{\text{self}} \rangle_{\text{rand}} = N \times P = E/N \approx 1.2$ , 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: =.

## POSITIVE FEEDBACK AND MULTISTABILITY

$\frac{dx}{dt} = f(x) - \alpha x$  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 early times,  $x(t) \sim \beta t$ . NAR: strong promotion  $\beta$  can give rapid product.

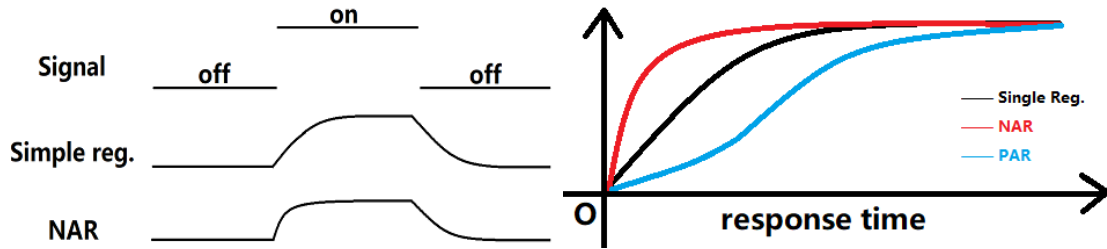
2. Robustness

$X_{eq}^{NAR}$  robust to small changes on  $\alpha$  and  $\beta$ , i.e. fluctuation in prod rate and deg rate.

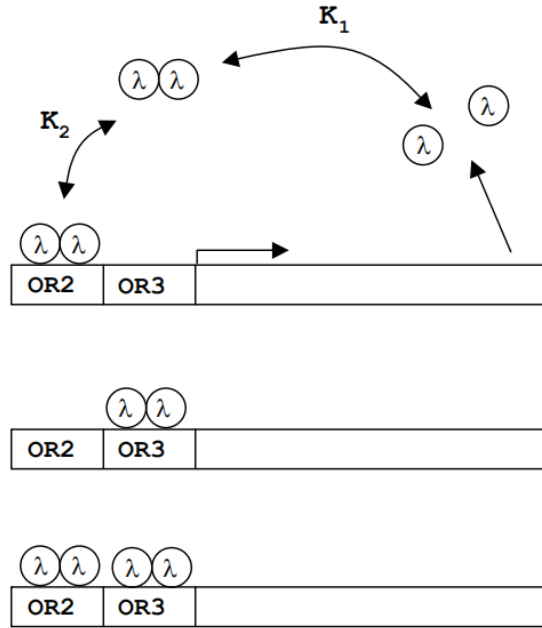
## 4 Positive Feedback and Multistability

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

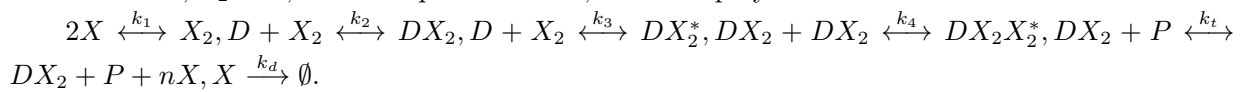
1. slow response time: development process, relatively long time process; prolonged delay.
2. bistability:  $\frac{dx}{dt} = 0$  has 1 – 3 solutions for  $x$ .



Consider the following reactions:



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



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  $y = [X_2], d = [D], u = [DX_2], v = [DX_2^*], z = [DX_2X_2^*]$ .

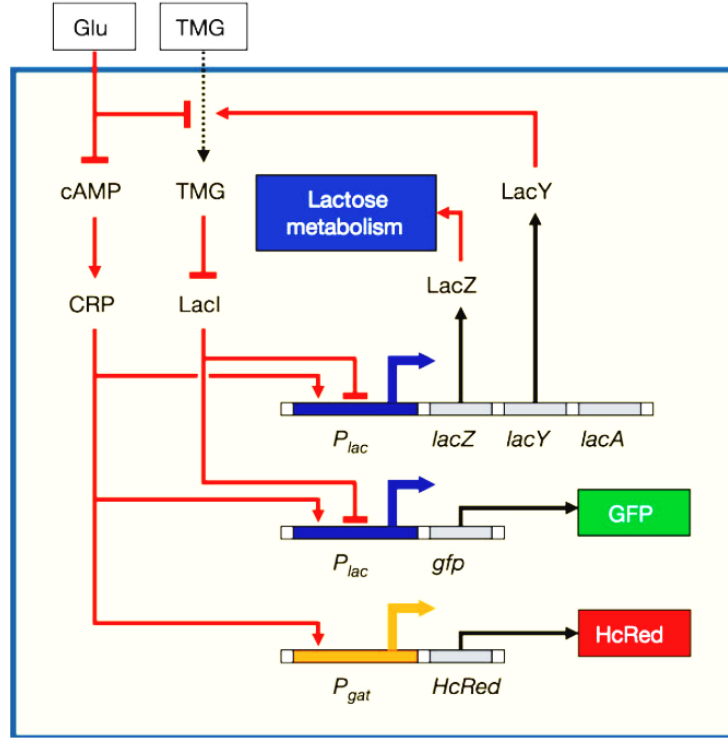
$y = k_1[X]^2, u = k_2dy = k_1k_2d[X]^2, v = \sigma_1k_2dy = \sigma_1k_1k_2d[X]^2, z = \sigma_2k_2uy = \sigma_2(k_1k_2)^2d[X]^4$ .

# POSITIVE FEEDBACK AND MULTISTABILITY

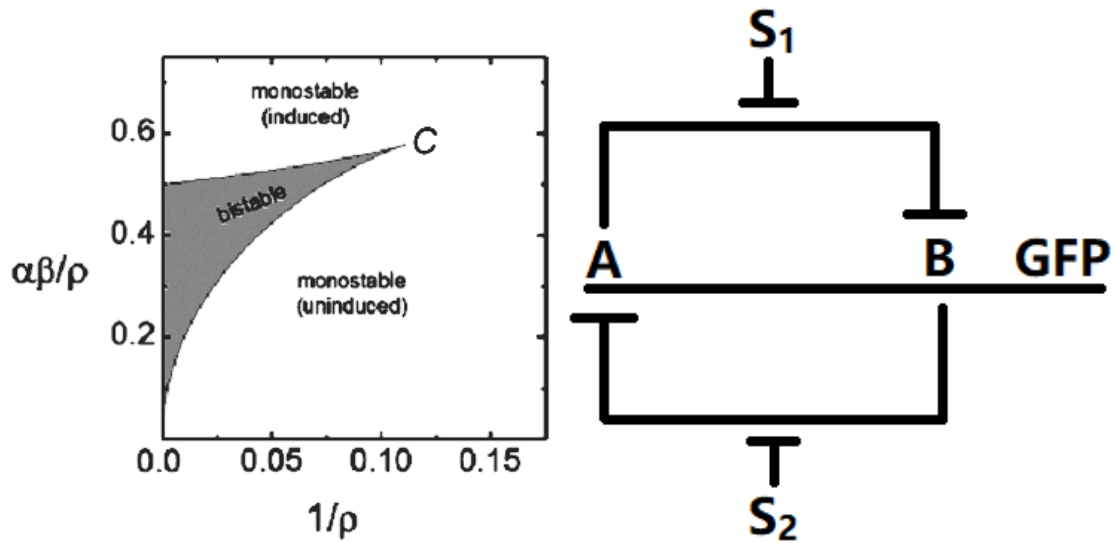
$$\frac{d[X]}{dt} = nk_t P_0 u - k_d[X] + r \quad (r : \text{basal rate}). \quad d_T = d + u + v + z \Rightarrow d_T = d[1 + (1 + \sigma_1)k_1 k_2[X]^2 + \sigma_2 k_1^2 k_2^2[X]^4] \Rightarrow \frac{d[X]}{dt} = \frac{nk_t P_0 k_1 k_2 d_T [X]^2}{1 + (1 + \sigma_1)k_1 k_2[X]^2 + \sigma_2 k_1^2 k_2^2[X]^4}.$$

$$\text{Def } \bar{X} = \sqrt{k_1 k_2} [X], \bar{t} = t(r\sqrt{k_1 k_2}), \quad \frac{d\bar{X}}{d\bar{t}} = \frac{\sqrt{nk_t P_0 d_T \bar{X}^2}/r}{1 + (1 + \sigma_1)\bar{X}^2 + \sigma_2 \bar{X}^4} - \frac{k_d/r}{\sqrt{k_1 k_2}} \bar{X} = \frac{\alpha \bar{X}^2}{1 + (1 + \sigma_1)\bar{X}^2 + (1 + \sigma_2)\bar{X}^4} - \gamma \bar{X}.$$

Consider the following reactions:



Denote TMG as  $X$ , LacI as  $R$  and LacY as  $Y$ , and consider  $X + R + Y \rightarrow X$ . 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 be  $(y - a)(y - b)(y - \theta a) = 0$  (bistable), we get  $\rho = (1 + 2\theta)(1 + 2/\theta)$ ,  $\alpha\beta = (2 + \theta)^{3/2}/\theta^{1/2}$ .



## STABILITY AND OSCILLATION

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 lifetime of  $u$  vs  $v$ ? A:  $\tau_u = \tau_v$ .

Q: If degradation rates go up, what parameters change? A:  $\alpha_1$  and  $\alpha_2, \downarrow$ .

Equilibrium reactions:  $P_1 + R_2^\beta \xrightleftharpoons{k_1} P_1 R_2^\beta, P_2 + R_1^\gamma \xrightleftharpoons{k_2} P_2 R_1^\gamma, \gamma R_1 \xrightleftharpoons{k_3} R_1^\gamma, \beta R_2 \xrightleftharpoons{k_4} R_2^\beta$ .

$$[P^T] = [P_1^T] = [P_1] + [P_1 R_2^\beta] = [P_2^T] = [P_2] + [P_2 R_1^\gamma].$$

$$R_{\text{gen1}} = a_1[P_1] = a_1[P^T] \frac{[P_1]}{[P_1] + [P_1 R_2^\beta]} = a_1[P^T] \frac{1}{1 + k_1[R_2^\beta]} = \frac{a_1[P^T]}{1 + k_1 k_4 [R_2]^\beta}.$$

$$R_{\text{gen2}} = a_2[P_2] = a_2[P^T] \frac{[P_2]}{[P_2] + [P_2 R_1^\gamma]} = a_2[P^T] \frac{1}{1 + k_2[R_1^\gamma]} = \frac{a_2[P^T]}{1 + k_2 k_3 [R_1]^\gamma}.$$

$$\frac{d[R_1]}{dt} = \frac{a_1[P^T]}{1 + k_1 k_4 [R_2]^\beta} - \delta[R_1], \frac{d[R_2]}{dt} = \frac{a_2[P^T]}{1 + k_2 k_3 [R_1]^\gamma} - \delta[R_2] (\delta : \text{decay rate}).$$

Def  $\tilde{t} = t\delta, u = [R_1](k_2 k_3)^{1/\gamma}, v = [R_2](k_1 k_4)^{1/\beta}$ , then

$$\frac{du}{dt} = \frac{a_1[P^T](k_2 k_3)^{1/\gamma}}{\delta} \frac{1}{1+v^\beta} - u = \frac{\alpha_1}{1+v^\beta}, \frac{dv}{dt} = \frac{a_2[P^T](k_1 k_4)^{1/\beta}}{\delta} \frac{1}{1+u^\gamma} - v = \frac{\alpha_2}{1+u^\gamma}. \quad u_{st} = \frac{\alpha_1}{1+v^\beta}, v_{st} = \frac{\alpha_2}{1+u^\gamma}.$$

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

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

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

Assumption: 1. large  $\alpha_1, \alpha_2$ ; 2. ratio between on or off is large (either  $u/v \gg 1$  or  $v/u \gg 1$ ).

In the case when  $u \gg v, u \approx \alpha_1, v \approx \frac{\alpha_2}{\alpha_1} \Leftrightarrow \log(\alpha_1) \approx \frac{1}{\gamma} \log(\alpha_2)$ . When  $v \ll u, \log(\alpha_2) = \frac{1}{\beta} \log(\alpha_1)$ . 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, because  $\dot{x}(t)$  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,  $\beta$ : lifetime of mRNA.

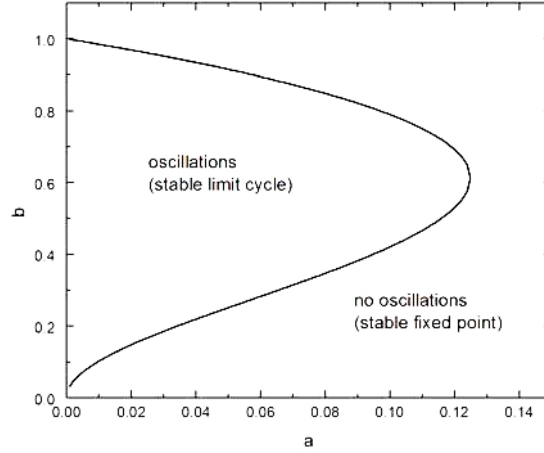
$\beta \ll 1$ . Q: possible oscillation? A: No.  $A = \begin{pmatrix} -1 & -\frac{\alpha n p^{n-1}}{(1+p^n)^2} \\ \beta & -\beta \end{pmatrix} \Rightarrow \text{tr}(A) < 0, \det(A) > 0 \Rightarrow \lambda_{1,2} < 0 \Rightarrow \text{stable}.$



## STABILITY AND OSCILLATION

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

$A = \begin{pmatrix} -1 + 2x^*y^* & a + x^{*2} \\ -2x^*y^* & -a - x^{*2} \end{pmatrix}$ .  $\text{tr}(A) = -\frac{b^4 + (2a-1)b^2 + (a+a^2)}{a+b^2}$ ,  $\det(A) = a + b^2 > 0$ . When  $\text{tr}(A) < 0$ , stable fixed point; when  $\text{tr}(A) > 0$ , 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.  $\Delta V$ : 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  $R$ .

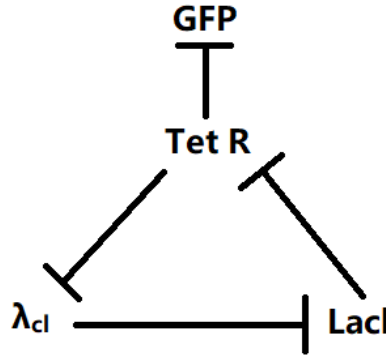
Then either  $C$  is a closed orbit or it spirals toward a closed orbit as  $t \rightarrow \infty$ .

### 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  $i = [\text{lacI}, \text{tetR}, \text{cl}], j = [\text{cl}, \text{lacI}, \text{tetR}]$ .

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  $p = \frac{\alpha}{1+p^n} + \alpha_0$ .

# STABILITY AND OSCILLATION



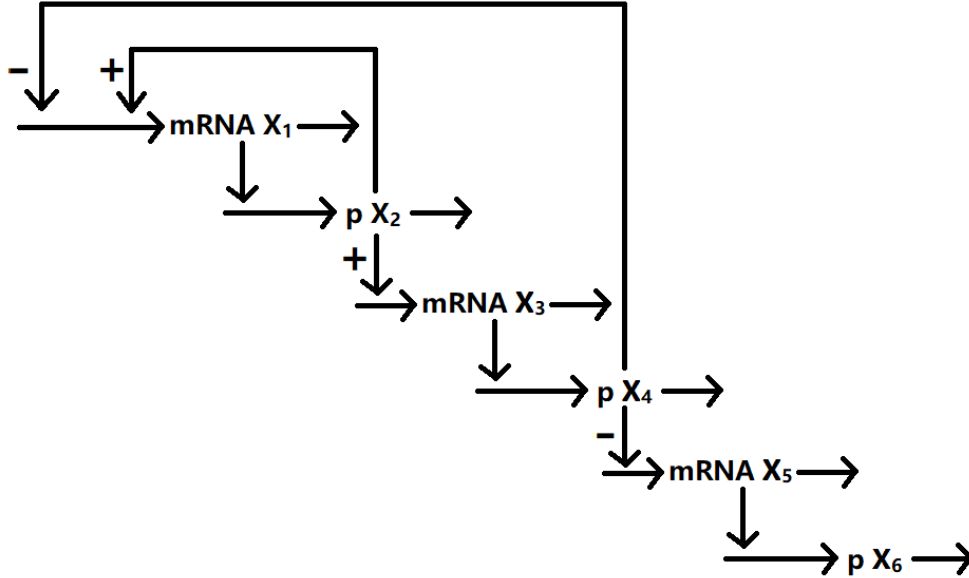
$$A = \begin{pmatrix} -1 & 0 & X \\ X & -1 & 0 \\ 0 & X & -1 \end{pmatrix} \text{ where } X = -\frac{\alpha n p^{n-1}}{(1+p^n)^2}. \text{ Eigenvalue } \lambda_1 = X - 1, \lambda_2 = -1 - \frac{1}{2}X + i\frac{\sqrt{3}}{2}X, \lambda_3 =$$

$-1 - \frac{1}{2}X - i\frac{\sqrt{3}}{2}X$ , stable fixed point  $\Leftrightarrow \text{Re}(\lambda_i)$  negative  $\Leftrightarrow -2 < X < 1 \Rightarrow \frac{\alpha n p^{n-1}}{(1+p^n)^2} < 2$ .

For large  $\alpha$ ,  $\alpha \approx p(1+p^n) \Rightarrow n \lesssim 2 \Rightarrow n \gtrsim 2$  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  $\beta_2$  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

$$\text{functions. } f_1 = \begin{cases} B : x_2^{g_{12}} x_4^{g_{14}} < B \\ x_2^{g_{12}} x_4^{g_{14}} : B < x_2^{g_{12}} x_4^{g_{14}} < M \\ M : x_2^{g_{12}} x_4^{g_{14}} > M \end{cases}, f_3 = \begin{cases} B : x_2^{g_{32}} < B \\ x_2^{g_{32}} : B < x_2^{g_{32}} < M \\ M : x_2^{g_{32}} > M \end{cases}. \text{ In the case of only}$$

one fixed point,  $x_1 = x_2 = x_3 = x_4 = 1$ .

## FEED FORWARD LOOP NETWORK MOTIF

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

$$a_0 = 1, a_1 = \beta_1 + \beta_2 + \beta_3 + \beta_4, a_2 = \beta_1 \beta_2 (1 - g_{12}) + \beta_1 \beta_3 + \beta_1 \beta_4 + \beta_2 \beta_3 + \beta_2 \beta_4 + \beta_3 \beta_4, a_3 = \beta_1 \beta_2 \beta_3 (1 - g_{12}) + \beta_1 \beta_2 \beta_4 (1 - g_{12}) + \beta_2 \beta_3 \beta_4 + \beta_1 \beta_3 \beta_4, a_4 = \beta_1 \beta_2 \beta_3 \beta_4 (1 - g_{14} g_{32} - g_{12}).$$

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:

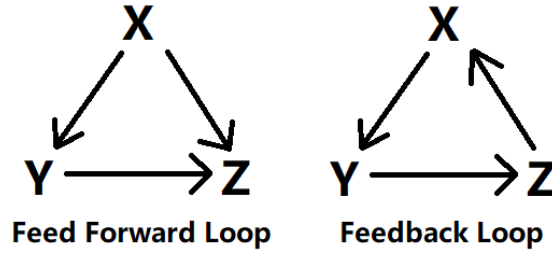
$$\begin{array}{c|cccc} \lambda^n & a_0 & a_2 & a_4 & a_6 & \cdots \\ \lambda^{n-1} & a_1 & a_3 & a_5 & a_7 & \cdots \\ \lambda^{n-2} & b_1 & b_2 & b_3 & b_4 & \cdots \\ \lambda^{n-3} & c_1 & c_2 & c_3 & c_4 & \cdots \\ \lambda^{n-4} & d_1 & d_2 & d_3 & d_4 & \cdots \\ \vdots & \vdots & \vdots & \vdots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

where  $b_1 = \frac{a_1 a_2 - a_0 a_3}{a_1}, b_2 = \frac{a_1 a_4 - a_0 a_5}{a_1}, b_3 = \frac{a_1 a_6 - a_0 a_7}{a_1}, c_1 = \frac{b_1 a_3 - a_1 b_2}{b_1}, c_2 = \frac{b_1 a_5 - a_1 b_3}{b_1}, c_3 = \frac{b_1 a_7 - a_1 b_4}{b_1}, d_1 = \frac{c_1 b_2 - b_1 c_2}{c_1}, d_2 = \frac{c_1 b_3 - b_1 c_3}{c_1}, \dots$

## 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 (“ $\rightarrow$ ” just means a kind of relation, which can be either positive or negative).



In Ecoli,  $N \sim 400$  genes,  $E \sim 500$  interactions,  $P = \frac{E}{N^2} \sim 0.003 \ll 1$ , average number of subgraph  $G$  in the network  $\langle N_G \rangle = \frac{1}{a} N^n P^g$ , 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:  $\langle N_G \rangle \sim N^{n-g}$ .

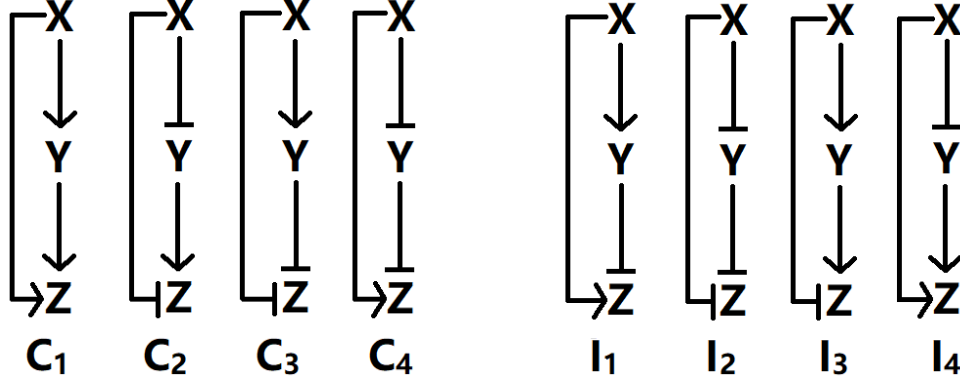
In random network,  $\lambda \sim 500/400 = 1.25$ ,  $\langle N_{\text{FFL}} \rangle_{\text{rand}} = 1.25^3 \approx 2$ ,  $\langle N_{\text{Loop}} \rangle_{\text{rand}} = 1.25^3/3 \approx 0.6$ . In Ecoli, # of FFL = 42, # of feedback loop = 0  $\Rightarrow$  FFL is a network motif. In fact, FFL is the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

## FEED FORWARD LOOP NETWORK MOTIF

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,  $\checkmark$  means the changes of concentration of Z are delayed when giving the corresponding conditions)

delay \ gate \ $S_x$	ON	OFF
AND	$\checkmark$	$\times$
OR	$\times$	$\checkmark$

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  $T_{on}$  satisfies  $Y^*(T_{on}) = Y_{st}(1 - e^{-\alpha_y T_{on}}) = k_{yz} \Rightarrow T_{on} = \frac{1}{\alpha_y} \log(\frac{1}{1 - k_{yz}/Y_{st}})$ .

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

$\beta_z$ : prod rate of Z when only X is available (strong).  $\beta'_z$ : 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  $Z_m = \beta_z / \alpha_z$ .

## ADAPTATION

When  $Y^* \geq k_{yz}$ , product rate of  $Z : \beta_z \rightarrow \beta'_z$ .  $Y(T_{rep}) = Y_{st}(1 - e^{-\alpha_y T_{rep}}) = k_{yz} \Rightarrow T_{rep} = \frac{1}{\alpha_y} \log(\frac{1}{1 - k_{yz}/Y_{st}})$ . 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  $F = \frac{Z_m}{Z_{st}}$ .  $F \gg 1, T_{\frac{1}{2}} \rightarrow 0$ . 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.

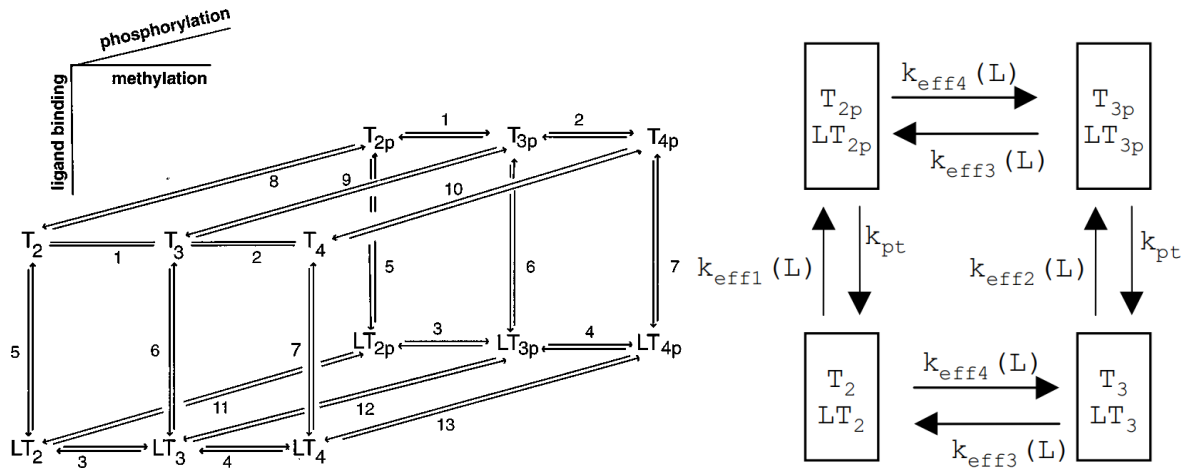
Q3: What's the difference between I1 & I4? A: steady state logic.

$S_x$		$S_x$	$S_y$	$z$ in I1	$z$ in I4
$y^*$		0	0	0	0
$Z$		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:  $k_{eff1}(L) = k_8(1 - f_b) + k_{11}f_b = \frac{k_8 + k_{11}K_b L}{1 + K_b L}$ ,  $k_{eff2}(L) = k_9(1 - f_b) + k_{12}f_b = \frac{k_9 + k_{12}K_b L}{1 + K_b L}$ ,  $k_{eff3}(L) = k_{-1}(1 - f_b) + k_{-3}f_b = \frac{k_{-1} + k_{-3}K_b L}{1 + K_b L}$ .

## ADAPTATION

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?

$$\frac{[2_p]}{2} = \frac{k_{\text{eff}1}(L)}{k_{pt}}, \frac{[3_p]}{[3]} = \frac{k_{\text{eff}2}(L)}{k_{pt}}, \frac{[3]}{[2]} = \frac{[3_p]}{[2_p]} = \frac{k_{\text{eff}4}(L)}{k_{\text{eff}3}(L)}, [2_p] + [2] + [3_p] + [3] = \text{Const.}$$

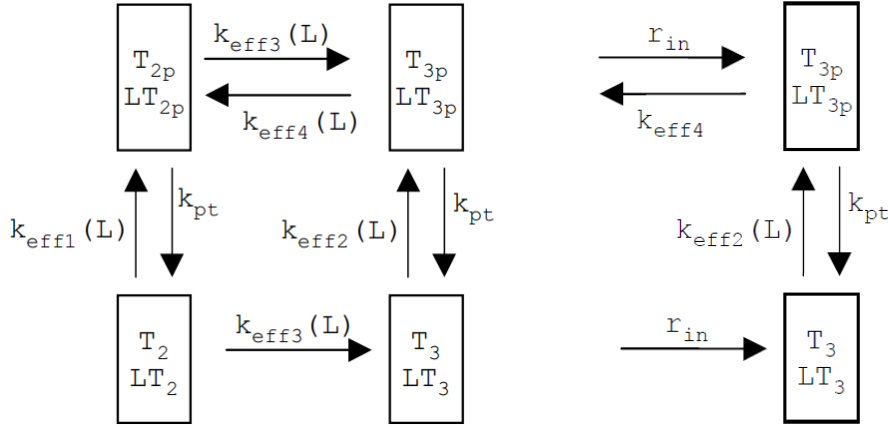
Problem: 4 unknowns, 5 equations  $\rightarrow$  introduce an additional variable.

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

$$k_{\text{phos}} = (1 - \alpha)k_{\text{eff}1}(L) + \alpha k_{\text{eff}2}(L) \Rightarrow \alpha(L) = \frac{k_{\text{phos}}(L) - k_{\text{eff}1}(L)}{k_{\text{eff}2}(L) - k_{\text{eff}1}(L)} = \frac{k_{\text{phos}}(1 + K_B L) - k_8 - k_{11}K_B L}{(k_9 - k_8) + (k_{12} - k_{11})K_B L}.$$

## 7.2 Barkai's Model

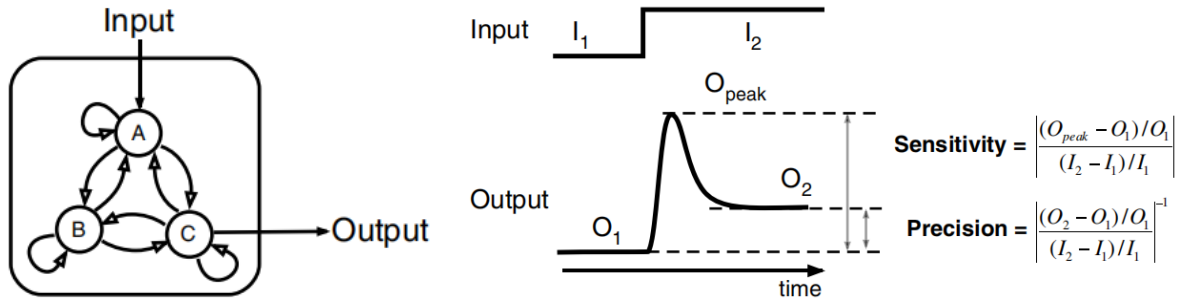
Assumption: 1. CheB only demethylates phosphorylated receptors; 2. methylation rates operate at saturation; 3. demethylation is independent of ligand binding.



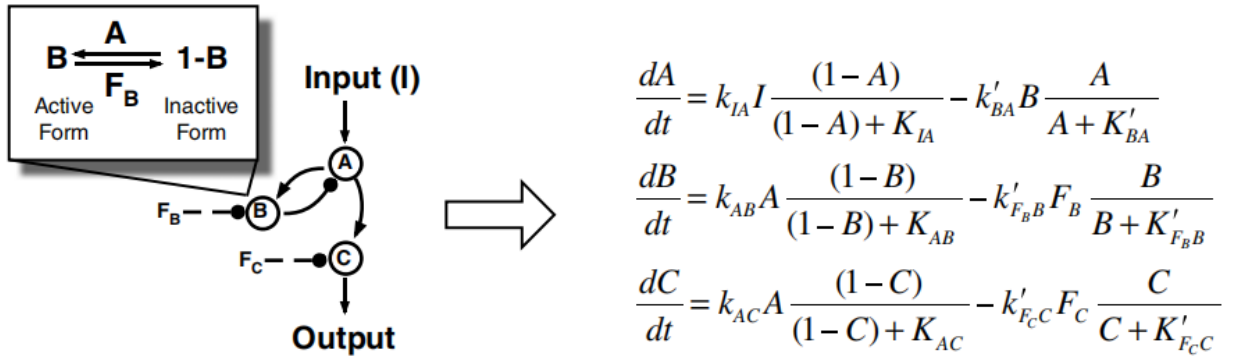
$$\frac{d[3_p]}{dt} = r_{\text{in}} - k_{\text{eff}4}[3_p] - k_{pt}[3_p] + k_{\text{eff}2}[3], \frac{d[3]}{dt} = r_{\text{in}} + k_{pt}[3_p] - k_{\text{eff}2}[3] \Rightarrow \frac{d[3_T]}{dt} = \frac{d[3]}{dt} + \frac{d[3_p]}{dt} = 2r_{\text{in}} - k_{\text{eff}4}[3_p] = 0 \Rightarrow [3_p] = \frac{2r_{\text{in}}}{k_{\text{eff}4}} \text{ independent of } L.$$

## 7.3 Ma's Model

Define network 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.



## 8 Stochastic Chemical Kinetics

Michaelis-Menten kinetics:  $E + S \xrightleftharpoons[k_2]{k_1} ES \xrightarrow{k_3} E + P$ .

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  $\gg 1 \Rightarrow$  neglect fluctuations in systems, which can be very important in biology.

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

$$R_j = \begin{cases} v_j = (v_{1j}, \dots, v_{Nj}), \text{状态改变向量} \\ a_j(x), \text{反应速率函数 (丰度)} \end{cases} \quad \text{In M-M, } v = \begin{pmatrix} -1 & 1 & 0 \\ -1 & 1 & 1 \\ 1 & -1 & -1 \\ 0 & 0 & 1 \end{pmatrix}, S = \begin{pmatrix} S \\ E \\ ES \\ P \end{pmatrix}, a_1 =$$

$$k_1[E][S], a_2 = k_2[ES], a_3 = k_3[ES].$$

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.

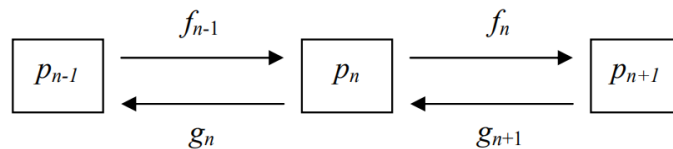
### 8.1 Probabilistic Formulation of Reaction Kinetics

(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  $\dots n + 1 \dots$ .



## STOCHASTIC CHEMICAL KINETICS

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 moments of  $P_n(t)$  without explicitly solving master equation.

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

(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  $\Rightarrow$  Metzler Matrix  $\Rightarrow$  没有正实部特征值  $\Rightarrow$  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

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

仅考虑一阶反应  $\Rightarrow a_j(x)$  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,



$$\begin{aligned}
 &\Rightarrow A_i(x) = A_i(\langle X \rangle) + \sum_{l=1}^N \frac{\partial A_i(\langle X \rangle)}{\partial x_l} (x_l - \langle X_l \rangle), B_{ik}(x) = B_{ik}(\langle X \rangle) + \sum_{l=1}^N \frac{\partial B_{ik}(\langle X \rangle)}{\partial x_l} (x_l - \langle X_l \rangle) \\
 &\Rightarrow \frac{d\sigma_{ik}}{dt} = \sum_{l=1}^N \left[ \frac{\partial A_i(\langle X \rangle)}{\partial x_l} \sigma_{lk} + \frac{\partial A_k(\langle X \rangle)}{\partial x_l} \sigma_{il} \right] + B_{ik}(\langle X \rangle) \\
 &\Rightarrow \frac{d\sigma}{dt} = (A\sigma + \sigma A^T) + B \quad (\text{近平衡态时系统协方差的近似演化方程})
 \end{aligned}$$

Q:  $A, B$  physical meaning?  $A$ : dissipation,  $B$ : fluctuation.

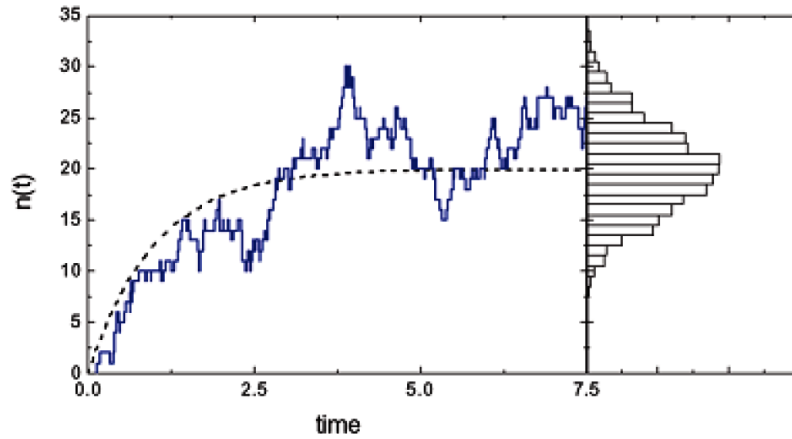
$A$ : linear coefficient matrix,  $\text{Re}(\lambda(A)) < 0$  for steady equilibrium  $\Rightarrow$  dissipation.

$$\frac{d\sigma}{dt} = 0 \Rightarrow B = -A\sigma - \sigma A^T, \sigma \neq 0 \Rightarrow B_{ii}(x) = \sum_{j=1}^M v_{ji}^2 a_j(x) \geq 0.$$

### 8.3 Steady State of Master Equation

For single molecule,  $\frac{dP_n}{dt} = -(k + \gamma n)P_n + kP_{n-1} + \gamma(n+1)P_{n+1} = 0 \Rightarrow P_n = \frac{\bar{n}}{n} P_{n-1} = \dots = \frac{\bar{n}^n}{n!} P_0$   
 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 continuous 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  $x \gg v_j$ ,  $\frac{\partial P(x,t)}{\partial t} = \sum_{j=1}^M [a_j(x)P(x,t) - \sum_{i=1}^M \frac{\partial}{\partial x_i} a_j(x)P(x,t)v_{ji} + \frac{1}{2} \sum_{i,k=1}^M \frac{\partial^2}{\partial x_i \partial x_k} a_j(x)P(x,t)v_{ji}v_{jk} - a_j(x)P(x,t)]$ .

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

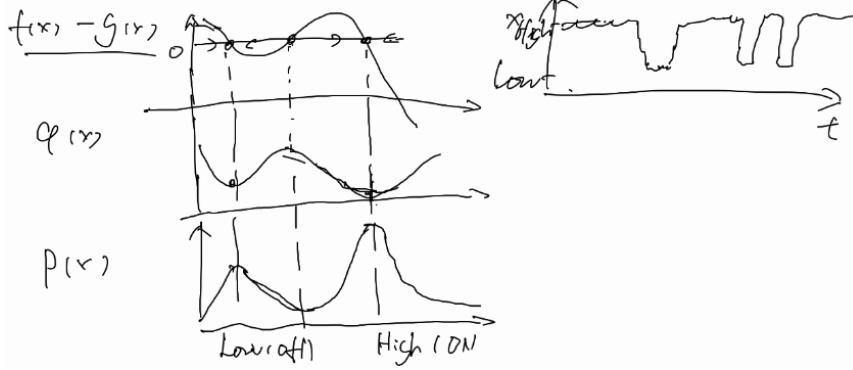
$$\begin{aligned}
 &\begin{cases} f(n-1)P(n-1) = f(n)P(n) - \frac{\partial}{\partial n} f(n)P(n) + \frac{1}{2} \frac{\partial^2}{\partial n^2} f(n)P(n) \\ g(n+1)P(n+1) = g(n)P(n) + \frac{\partial}{\partial n} g(n)P(n) + \frac{1}{2} \frac{\partial^2}{\partial n^2} g(n)P(n) \end{cases} \\
 &\Rightarrow \frac{\partial P(n,t)}{\partial t} = -\frac{\partial}{\partial n} [(f - g)P - \frac{1}{2} \frac{\partial}{\partial n} (f + g)P] := -\frac{\partial}{\partial n} J
 \end{aligned}$$

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

## STOCHASTIC CHEMICAL KINETICS

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:  $\frac{dx}{dt} = \frac{v_0 + v_1 x^2}{k + x^2} - \gamma x$ .



### 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  $\tau$  is  $P(\tau) = P(\text{next occurrence is in } (\tau, \tau + d\tau)) = P(\text{does not occur for } t < \tau)P(\text{occurs in } \tau \text{ to } \tau + d\tau)$ . 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  $Q(0) = 1 \Rightarrow P(\tau) = e^{-r\tau} r d\tau$ .

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

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

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

下一次反应在  $(t + \tau, t + \tau + d\tau)$  内且发生第  $\mu$  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  $\mu$  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  $a_v = a_v(x), v = 1, \dots, M, a_0 = \sum_{v=1}^M a_v(x)$ ; (3) 生成服从参数为  $a_0$  的指数分布  $\tau$ , 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)  $t = t + \tau, R_\mu, x_i \rightarrow x_i + R_\mu$ ; (6) goto (2).

Remark: (1) SSA:  $t \rightarrow t + \tau$ , 模拟长时间行为, 为了模拟每一步反应, 步长  $\tau$  很小; (2) 原始 SSA 中随即搜索反应  $\mu$  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  $x_i(t + \tau) = x_i + \sum_{j=1}^M k_j(x, \tau) v_{ji}, i = 1, \dots, N$ . 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  $\Rightarrow a_j(x(t')) \approx a_j(x(t)), t' \in [t, t + \tau), j = 1, \dots, M$ .

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  $\gg 1$ , 只要  $\tau$  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  $\tau$  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  $\tau$  充分大使得在  $[t, t + \tau)$  内发生反应次数  $\gg 1$ , 即  $a_j(x)\tau \gg 1, \forall 1 \leq j \leq M$ .

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

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

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

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

## 8.8 $\tau$ -Leaping Algorithm

一次近似步长  $\tau$  内每个反应发生的数目.

$\tau$ -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  $< 20 \rightarrow$  SSA; (2)  $\tau$  的选取不能过大.

对于适当选取的  $\tau, x_i(t + \tau) = x_i(t) + \sum_{j=1}^M v_{ji} P(a_j(x), \tau)$ , 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)  $\rightarrow t + \tau, x + \lambda$ .

Key: 如何选取合适的  $\tau$ ?

## DIFFUSION

(1) 对于给定的  $\tau$ , 检验  $|a_j(x + \lambda) - a_j(x)|, j = 1, \dots, M$ , 若对每一个  $j$  都是小量, 则  $\tau \checkmark$ ; 对  $\tau$  从小到大进行检验, 直到找到符合条件的最大的  $\tau$ , 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  $\bar{\lambda} = \sum_{j=1}^M a_j(x)\tau v_j = \tau \xi(x)$ .  $|a_j(x + \bar{\lambda}) - a_j(x)| \leq \epsilon a_0(x)$  where  $a_0(x) = \sum_{j=1}^M a_j(x)$ , 则认为跳跃条件是满足的.

$a_j(x + \bar{\lambda}) - a_j(x) \approx \bar{\lambda} \cdot \nabla a_j(x) = \sum_{i=1}^N \tau \xi_i(x) \frac{\partial a_j(x)}{\partial x_i} \Rightarrow \tau |\sum_{i=1}^N \xi_i(x) b_{ji}| \leq \epsilon a_0(x)$  where  $b_{ji} = \frac{\partial a_j(x)}{\partial x_i} \Rightarrow \tau \leq \epsilon a_0 / |\sum_{i=1}^N \xi_i(x) b_{ji}|$ . 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  $\tau \gg \frac{1}{a_0(x)}$  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  $x' = x + \frac{\bar{\lambda}}{2} \rightarrow P(a_j(x'), \tau)$  的随机数  $k_j$ , 计算  $\lambda = \sum_j k_j v_j$ , 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  $N\Delta t$ ,  $[-N\Delta x, N\Delta x]$ .

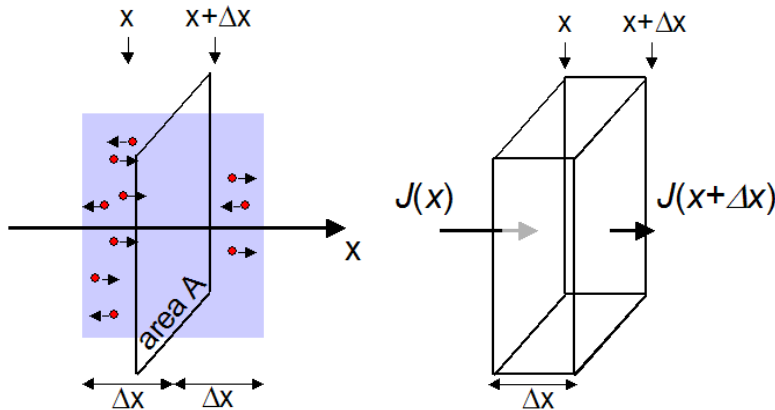
Prob  $p(m, n), x = m\Delta x$  after  $n$  time-steps,  $a$  steps to right,  $b$  steps to left  $\Rightarrow a = \frac{n+m}{2}, b = \frac{n-m}{2} \Rightarrow p(m, n) = C_n^a / 2^n = \frac{1}{2^n} \frac{n!}{a!(n-a)!}, \sum_{m=-n}^n p(m, n) = 1$ .

If  $n$  is large, and  $n \pm m$  are large,  $n! \sim (2\pi n)^{\frac{1}{2}} e^{-n} n^n, n \gg 1 \Rightarrow p(m, n) \sim (\frac{2}{\pi n})^{\frac{1}{2}} e^{-m^2/2n}$  (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  $\lim_{\Delta x \rightarrow 0, \Delta t \rightarrow 0} \frac{(\Delta x)^2}{2\Delta t} = D \neq 0$ ,  $D$  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 cross the area  $A$  to the right? A:  $-\frac{1}{2}(N(x + \Delta x) - N(x))$ .

Flux of molecules:  $J = \frac{-\frac{1}{2}(N(x + \Delta x) - N(x))}{A\Delta t}$ . 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.

## DIFFUSION

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

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.

$\frac{d}{dt} \int_V C(x,t) dx = - \int_S J ds + \int_V f dx$  (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:  $J = -D\nabla C \Rightarrow \frac{\partial C}{\partial t} = D\Delta C + f(C,x,t)$  (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:  $n(x,t) = \begin{cases} \frac{n_0}{\lambda(t)} [1 - (\frac{x}{n_0 \lambda(t)})^2]^{1/m} & |x| \leq r_0 \lambda(t) \\ 0, & x > r_0 \lambda(t) \end{cases}, \lambda(t) = (\frac{t}{t_0})^{1/(2+m)}, r_0 = \frac{D_0 \Gamma(\frac{1}{m} + \frac{3}{2})}{\pi^{1/2} n_0 \Gamma(\frac{1}{m} + 1)}$ .

### 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  $D \sim 1\mu\text{m}^2/\text{sec} \Rightarrow \text{time} \sim 10^6\text{sec}$  – slow process.

### 9.5 Biological Waves

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

## TURING PATTERN

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.

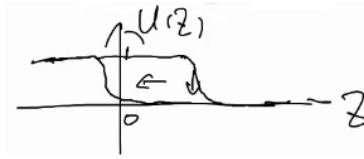
$\frac{\partial u}{\partial t} = D \frac{\partial^2 u}{\partial x^2} \Rightarrow c \frac{du}{dz} + D \frac{d^2 u}{dz^2} = 0 \rightarrow$  linear parabolic equation  $\Rightarrow u(z) = A + B e^{-cz/D}$ .  $z \rightarrow -\infty, u(z) \rightarrow \infty$  unbounded  $\Rightarrow B = 0 \Rightarrow u(z) = A$  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  $0 \leq u \leq 1$ .  $u''(z) + cu' + u(1-u) = 0 \Rightarrow \begin{cases} u' = v \\ v' = -cv - u(1-u) \end{cases} \Rightarrow \frac{dv}{du} = \frac{-cv - u(1-u)}{v}$ . 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.  $c \geq c_{\min} = 2 \rightarrow$  stable node  $(0, 0)$ . There is a trajectory from  $(1, 0)$  to  $(0, 0)$ .  $u \geq 0, u' \leq 0$  with  $0 \leq u \leq 1$  for  $c \geq c_{\min} = 2(KD)^{1/2}$ .



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,  $u(x, 0) = u_0(x) > 0, u_0(x) = \begin{cases} 1, & \text{if } x \leq x_1 \\ 0, & \text{if } x \geq x_2, u_0(x) \end{cases}$  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 Equn 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:  $\begin{cases} \frac{\partial u}{\partial t} = D_u \Delta u - d_u u + F(u, v) \\ \frac{\partial v}{\partial t} = D_v \Delta v - d_v v + G(u, v) \end{cases}$ .