Ctrl & Comp in Bio Sys - Westlake Univ., Fall 2025

Lecture 2: Biochemical reaction networks and its dynamics

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1 Biochemical reactions in cells

Cellular changes occur through chemical reactions, which are fundamentally governed by **diffusion** kinetics. These reactions typically take place under the prevailing cellular conditions of **temperature** and **pressure**. Whether and when a reaction proceeds is largely determined by the presence of enzymes, which act as catalysts. From a thermodynamic perspective, many favorable reactions could take years to complete on their own (e.g., spontaneous glucose degradation, peptide bond cleavage, or ATP hydrolysis). However, enzymes accelerate such processes dramatically, often by factors of 10^{10} or more.

1.1 notations of (Bio)chemical reactions

Reaction Type	Notation	Meaning	Examples
Elementary ( )	Straight Arrows ($\rightarrow$)	Implies reaction mechanism (all key players included)	$E+S \Leftrightarrow C \rightarrow E+P$; $\text{Gene} + \text{RNAP} \Leftrightarrow C_0 \rightarrow C_1 \rightarrow \ldots \rightarrow C_n \rightarrow \text{Gene} + \text{RNAP} + \text{mRNA}$
Composite ( )	Squiggly Arrows ($\rightsquigarrow$)	May have hidden mechanism, reaction	$S \rightsquigarrow P$; $\text{Gene} \rightsquigarrow \text{Gene} + \text{mRNA}$; $(S,P) \rightsquigarrow (S-1,P+1)$

Implies reaction mechanism, meaning it's an irreducible reaction step, you CAN'T break

it down further, or it's useless to do so, for your concern
e.g. E+S $\Leftrightarrow$ C $\rightarrow$ E+P; Gene + RNAP $\Leftrightarrow$ $C_0 \rightarrow C_1 \rightarrow$ ...... $\rightarrow$ C~n $\rightarrow$ Gene + RNAP +mRNA
it may have Hidden mechanism, meaning it's reaction only describes the net change of several steps of reactions
e.g. S $\rightsquigarrow$ P; Gene $\rightsquigarrow$ Gene + mRNA;
(S,P) $\rightsquigarrow$ (S-1,P+1) (another notation for Composite, focused on change of molecular numbers)

Examples:

1. Cell replication, N becomes 2N: N $\rightsquigarrow$ 2N or N $\rightsquigarrow$ N+1
2. Photon doubles in a laser: photon + atom activated $\rightarrow$ 2photon + atom ground
3. Diffusion into a cell through a passive channelon membrane: $A_{out} \rightarrow A_{in}$
4. ATPase pumping H^+ and of the cell: ${H^+}_{in} \rightsquigarrow {H^+}_{out}$

1.2 Estimates of enzymatic reaction rates

Enzymatic reactions occur when an enzyme and its substrate collide and then bind; the enzyme's atoms then orient the substrate in specific ways, ultimately transforming it into a product with atoms in different positions. Thus, there's a two-step process: binding and catalysis.

$$E + S \Leftrightarrow C \rightsquigarrow E + P$$

The fastest reaction rate is limited by association rate (react immediately after association), which is governed by diffusion, so called **"diffusion limited on rate"**, for example in heat diffusion:

flux at a point on E surface:

$$j(a) = D\frac{\alpha C}{\alpha R}$$

Roughly,

$$j(a) = D\frac{\alpha C}{\alpha R}|_a \backsim \frac{C_\infty}{a} \Rightarrow j = D\frac{C_\infty}{a}$$

More details: cons. of mass $\Rightarrow$ $4\pi\, R^2 j$ is constant, so

$$j \propto \frac{1}{R^2}\frac{\alpha C}{\alpha R} = j \propto \frac{1}{R^2} \Rightarrow C(R) = \frac{A}{B} + C$$

A,B is constant, Boundary condition: C(a)=0, C(∞)=C∞, so B=C∞, A=-aC∞

$$J = j \cdot 4\pi a^2 = 4\pi D a \cdot C_\infty \;\Rightarrow\; K_{on} C_\infty \tag{1}$$

$$k_{on} = 4\pi D a \;\backsim\; 10 \cdot 10^2\,\mu m^2/s \cdot 1\,nm \cdot \frac{6 \cdot 10^{23}}{\mathrm{mol}} \cdot \frac{1L}{10^{15}\,\mu m^3} \;\backsim\; 10^9\,s^{-1}\,mol^{-1}$$

So, if $C \backsim 1\,\mathrm{mM}$, then it's about 10^6 reactions/s per enzyme.

However, most enzymes operate much more slowly, being bottlenecked by the catalysis step, typically around $10{-}10^2$ reactions/s.
Note that for elementary reactions, i.e., reactions that occur immediately upon collision, the flux of $E + S \to C$ is given by $K_{on}ES$ (where E and S denote the concentrations), since each enzyme reacts at a rate of $K_{on}S$. This relationship is called the **law of mass action**, and it describes how the flux scales with reactant concentrations.

1.2.1 Detailed Derivation of Diffusion-Limited Flux

Based on the steady-state diffusion model, we consider an enzyme E as the center point, with substrate molecules diffusing throughout the solution. Under steady-state conditions, the flux through any spherical surface of radius R centered at the enzyme remains constant, i.e., $4\pi R^2 \cdot j = \text{constant} \neq 0$. This conservation relation indicates that the amount of substrate C consumed at the enzyme surface is exactly balanced by the amount diffusing into the sphere from the external environment.

Derivation of the Spherically Symmetric Diffusion Equation The general diffusion equation (Fick's second law) in three dimensions is:

$$\frac{\partial C}{\partial t} = D\nabla^2 C$$

where ∇^2 is the Laplace operator.

In spherical coordinates (r, θ, φ), the Laplace operator is expressed as:

$$\nabla^2 C = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial C}{\partial r}\right) + \frac{1}{r^2 \sin\theta}\frac{\partial}{\partial \theta}\left(\sin\theta \frac{\partial C}{\partial \theta}\right) + \frac{1}{r^2 \sin^2\theta}\frac{\partial^2 C}{\partial \varphi^2}$$

Due to the spherical symmetry of the problem (enzyme is spherical and substrate diffusion is isotropic), the concentration C depends only on the radial distance r:

$$C = C(r), \quad \frac{\partial C}{\partial \theta} = 0, \quad \frac{\partial^2 C}{\partial \varphi^2} = 0$$

Substituting these conditions into the Laplace operator gives:

$$\nabla^2 C = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial C}{\partial r}\right)$$

Under steady-state conditions ($\frac{\partial C}{\partial t} = 0$, i.e., $4\pi R^2 \cdot j =$ constant (non-zero)), the diffusion equation simplifies to:

$$D \cdot \frac{1}{r^2}\frac{d}{dr}\left(r^2\frac{dC}{dr}\right) = 0$$

Since $D \neq 0$, we obtain the spherically symmetric steady-state diffusion equation:

$$\frac{1}{r^2}\frac{d}{dr}\left(r^2\frac{dC}{dr}\right) = 0$$

Solving the Diffusion Equation Multiplying both sides by r^2 and integrating once:

$$\frac{d}{dr}\left(r^2\frac{dC}{dr}\right) = 0 \quad \Rightarrow \quad r^2\frac{dC}{dr} = A$$

where A is an integration constant.

Rearranging and integrating again:

$$\frac{dC}{dr} = \frac{A}{r^2} \quad \Rightarrow \quad C(r) = -\frac{A}{r} + B$$

where B is another integration constant.

Applying Boundary Conditions Applying the boundary conditions:

- At the enzyme surface ($r = a$): $C(a) = 0$
- At infinity ($r \to \infty$): $C(\infty) = C_\infty$

Substituting the boundary conditions to solve for the integration constants:

$$\begin{cases} 0 = -\frac{A}{a} + B \\ C_\infty = B \end{cases} \Rightarrow A = aC_\infty, \quad B = C_\infty$$

Thus, the concentration distribution is:

$$C(r) = C_\infty\left(1 - \frac{a}{r}\right)$$

Calculating Flux and Reaction Rate Calculating the concentration gradient:

$$\frac{\partial C}{\partial r} = \frac{aC_\infty}{r^2}$$

The gradient at the enzyme surface ($r = a$):

$$\left.\frac{\partial C}{\partial r}\right|_{r=a} = \frac{C_\infty}{a}$$

According to Fick's first law, the flux is:

$$j = D \cdot \frac{C_\infty}{a}$$

The total reaction rate is the flux multiplied by the enzyme surface area:

$$J = j \cdot 4\pi a^2 = 4\pi D a C_\infty$$

Defining the reaction rate constant $k_m = 4\pi D a$, we obtain $J = k_m C_\infty$.

This derivation provides a rigorous mathematical foundation for understanding diffusion-limited reaction kinetics, following the approach consistent with the file's content.

1.2.2 How to understand $j = D\frac{\partial c}{\partial R}$?

From the perspective of dimensional analysis: j represents the number of molecules passing per unit area per unit time.

- Dimension of j: $\frac{\text{molecules}}{\text{area}\cdot\text{time}} = \frac{N}{L^2 \cdot T}$
- Dimension of D: diffusion coefficient, $\frac{\text{length}^2}{\text{time}} = \frac{L^2}{T}$
- Dimension of $\frac{\partial c}{\partial R}$: concentration gradient, $\frac{\text{concentration}}{\text{length}} = \frac{(N/L^3)}{L} = \frac{N}{L^4}$

Therefore, dimensional verification of $j = D\frac{\partial c}{\partial R}$:

$$[D] \cdot \left[\frac{\partial c}{\partial R}\right] = \frac{L^2}{T} \cdot \frac{N}{L^4} = \frac{N}{L^2 \cdot T} = [j]$$

The dimensions are consistent, validating the physical relationship.

1.3 Dynamics of chemical reaction networks(CRN)

A generic chemical reaction (Elementary or Composite)

$$\alpha_1X_1+\alpha_2X_2+...+\alpha_nX_n \to \beta_1X_1+\beta_2X_2+...+\beta_nX_n\alpha_1X_1+\alpha_2X_2+...+\alpha_nX_n \rightsquigarrow \beta_1X_1+\beta_2X_2+...+\beta_nX_n$$

α stand for reaction stoichiometry, β stand for product stoichiometry
Reaction stoichiometry: $\gamma_j = \beta_j - \alpha_j (j = 1, 2, 3, ..., n)$
Net change notation: $(X_1, X_2, ..., X_n) \to (X_1 + P_1, X_2 + P_2, ..., X_n + P_n)$
Every time this reaction happens, x_j~ flux caused by this reaction is $\gamma_j * \nu$

Several reactions form a network (GRN)

m stand for reactions, $i = 1, 2, ..., m$
n stand for species, $j - 1, 2, 3, ..., n$

$$\alpha_{i1}X_1 + \alpha_{i2}X_2 + \cdots + \alpha_{in}X_n \quad \to \quad \beta_{i1}X_1 + \beta_{i2}X_2 + \cdots + \beta_{in}X_n$$

$$\frac{d}{dt}x_j = \sum_i \gamma_{ij}\nu_i = \sum_{i:\gamma_{ij}>0} V_{ij}\nu_i - \sum_{i:\gamma_{ij}<0} V_{ij}\nu_i = f_j^+ - f_j^- = f_j$$

$$\frac{dx}{dt} = \Gamma\nu = f^+ - f^-$$

Note that this hold always, for both elementary and composite, Since all we're done is "accounting", for where molecules went. Only depends on γ, not α or β, so "net change notation" is enough. We can write this even if we don't know the regulation mechanism. But to have a full description of the dynamics.

Does ν depend on x ? i.e. reaction kinetics

Kinetics: Law of mass actin Elementary reactions' kinetics follow the law of mass action:

$$\alpha_1X_1 + \alpha_2X_2 + \cdots + \alpha_nX_n \xrightarrow{k \text{ (reaction rate constant)}} \beta_1X_1 + \beta_2X_2 + \cdots + \beta_nX_n$$

$$\nu(x) \ = \ \text{reaction rate} \ = \ \text{flux} \ = \ k X_1^{\alpha_1}X_2^{\alpha_2}\cdots X_n^{\alpha_n}$$

e.g. $E + S \underset{\to}{K} C, rate = K_{on}ES(K = K_{on})$

Now with several reactions forming a network

$$\alpha_{i1}X_1 + \alpha_{i2}X_2 + \cdots + \alpha_{in}X_n \ \underset{\rightarrow}{k_i}\ \beta_{i1}X_1 + \beta_{i2}X_2 + \cdots + \beta_{in}X_n$$

$$\nu_i \ = \ k_i X_1^{\alpha_{i1}} \cdots X_n^{\alpha_{in}} \ = \ k_i X^{\alpha_i}$$

$$\frac{d}{dt}x_j \ = \sum_{i:\gamma_{ij}>0} \gamma_{ij}\nu_i \ - \sum_{i:\gamma_{ij}<0} |\gamma_{ij}|\nu_i \ = \ f_j^+(x) - f_j^-(x)$$

$$\frac{dx}{dt} \ = \ \Gamma\nu(x) \ = \ \Gamma \wedge_k x_\alpha \ = \ f(x) \ = \ f^+(x) - f^-(x)$$

1.4 Analysis of 1D and 2D dynamics by phase portrait

These are autonomous dynamical systems $\frac{dx}{dt} = f(x)$. How to understand their dynamics? We start simple from low dimensions:

Exp1

$$\frac{dx}{dt} = f(x) = -x$$

Fixed point: x^* s.t. $F(x^*) = 0$
Feature of $f(x) = -x$

Fixed point: You **DON'T** change if you start from a fixed point, if you start at a different initial condition, you'll go to $x = 0$ until you are stable at a fixed point.

Exp2

$$\frac{dx}{dt} = f(x) = x^3$$

Fixed point: x^* s.t. $F(x^*) = 0$
Feature of $f(x) = x^3$ Fixed point: You **DON'T** change if you start from Fixed point, but you'll go further and further if you're not

Exp3

$$\frac{dx}{dt} = f(x) = x^2 - r$$

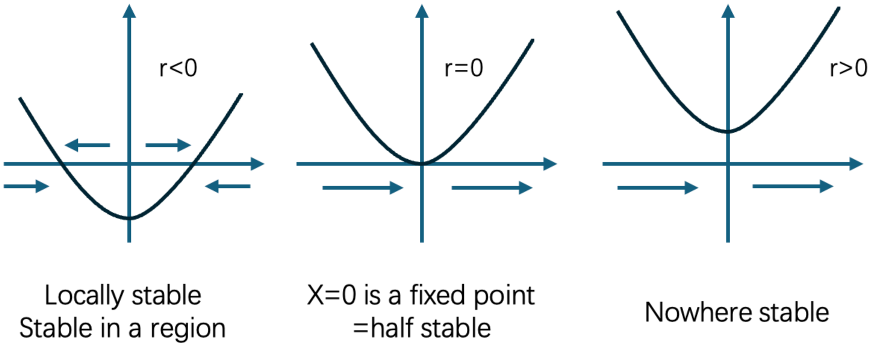

Figure 1 Exp3 $f(x) = x^2 - r$

1D can only define stable or unstable, "go away" or "coverage", because trajectory is 1D as well, and the point **CAN'T go back**

Exp4 Bio product minus degradation

$$\dot{x} = \mu - x$$

Fixed point: $x = \mu$ ***Exp5***: bistable

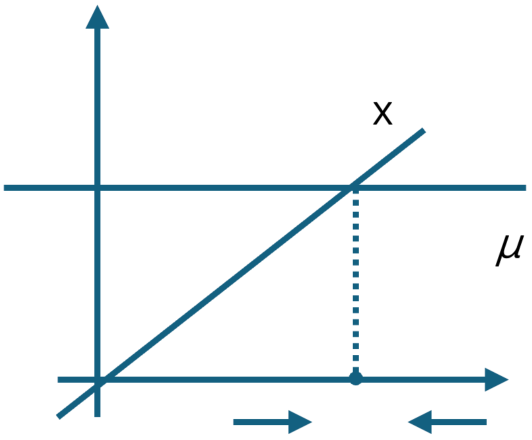

Figure 2 $\dot{x} = \mu - x$

$$\dot{x} = f^{+}(x) - x$$

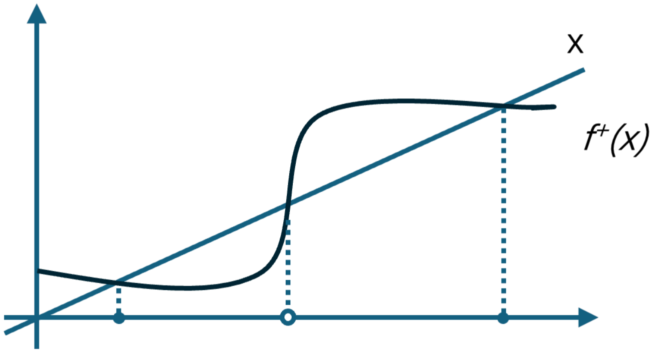

Figure 3 $\dot{x} = f^{+}(x) - x$

How to create a 1D (Bio) bistable system?

2D system In 2D system trajectories **can "go back"** along any axis, but trajectories **can't overlap itself**
On top of fixed points: $f_1(X^*) = f_2(x^*) = 0$, also nullelines $f_1(X^*) = 0 | f_2(x^*) = 0$, These are enough to determined dynamics.

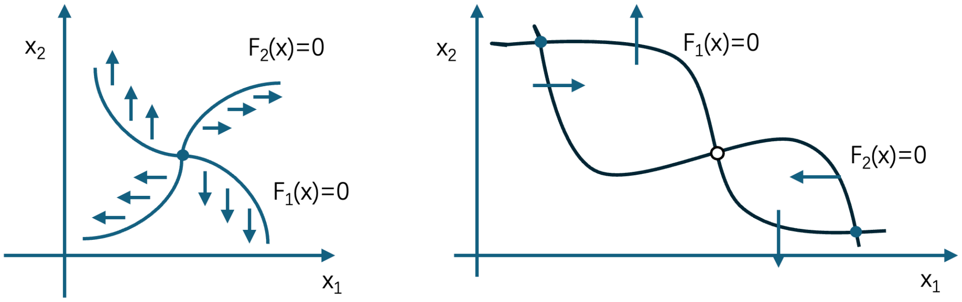

Figure 4

1.5 Types of dynamics in 2D

Dynamics about a fixed point graph needed

New in 2D: center *Exp1* Spring question

$$F = m\ddot{x} F = -kx \Rightarrow m\ddot{x} + kx = 0 \Rightarrow x_1 = x_1,\ x_2 = \dot{x} \text{ ,so } m\dot{x}_2 + kx_1 = 0 \frac{d}{dt}\begin{bmatrix} x_1 \\ x_2 \end{bmatrix} = \begin{bmatrix} 0 & 1 \\ -k/m & 0 \end{bmatrix}\begin{bmatrix} x_1 \\ x_2 \end{bmatrix}$$

Trajectories neither spiral in or out, $x = 0$ is a **center**, not stable

Also, we can look at energy, which is conserved:

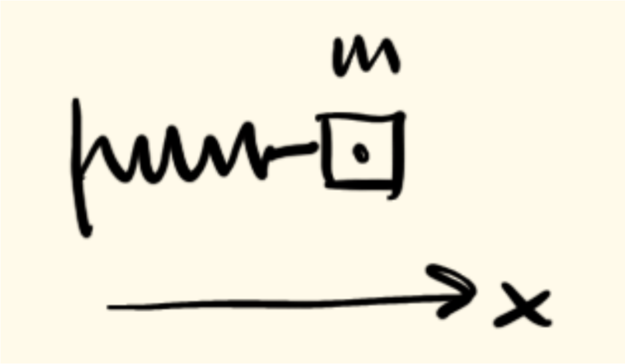

Figure 5 Spring

$$\frac{1}{2}mx_2^2+\frac{1}{2}kx_1^2=E\frac{dE}{dt}=mx_2\dot{x_2}+mx_1\dot{x_1}\Rightarrow\frac{dE}{dt}=-mx_2\frac{k}{m}+kx_1x_2\Rightarrow-kx_1x_2+kx_1x_2=0$$

If there's friction:

$$m\ddot{x}+k_f\dot{x}+k_sx=0 \tag{2}$$

Define the state variables $x_1=x$, $x_2=\dot{x}$. Then

$$\frac{d}{dt}\begin{bmatrix}x_1\\x_2\end{bmatrix}=\begin{bmatrix}0 & 1\\-k_s/m & -k_f/m\end{bmatrix}\begin{bmatrix}x_1\\x_2\end{bmatrix}. \tag{3}$$

The total mechanical energy is

$$E=\tfrac{1}{2}mx_2^2+\tfrac{1}{2}k_sx_1^2. \tag{4}$$

Taking the time derivative gives

$$\frac{dE}{dt}=-mx_2\big(\tfrac{k_s}{m}x_1+\tfrac{k_f}{m}x_2\big)+k_sx_1x_2=-k_fx_2^2<0. \tag{5}$$

means the circle shrunks overtime.

1.5.1 3D and beyond

3d-system Trajectories can roam freely, no constraint anymore due to dimensions, e.g. graph needed The best way to analyze is to **stimulate** and to **look**, lack of structure, **Nothing** very useful can be said.

system beyond 3D To say something for >=3 dimensions, still by dimension reduction
⇒ Reduce to 0 dimension: fixed point
⇒ Reduce to 1 dimension: fixed point, limit cycles
⇒ Reduce to 2 dimensions: then analyze on 2D....

1.6 Local stability analysis

Local dynamics in general ⇒ Local is always Linear
assuming $\frac{d}{dt}(xt\Delta x) = f(x) \Rightarrow$ consider small perturbationΔx around x

$$\frac{d}{dt}(xt\Delta x) = \frac{d}{dt}\Delta x = f(x+\Delta x) \approx f(x) + \frac{\alpha f}{\alpha x}(x)\Delta x$$

Assuming at $x = x^*$, a fixed point, so $f(x^*) = 0$

$$\frac{d\Delta x}{dt} = A\Delta x \Rightarrow A = \frac{\alpha f}{\alpha x}(x^*)$$

$$\frac{dx}{dt} = ax \quad \Rightarrow \quad x(t) = x(0)e^{at}$$

Eigenvector (λ, v) $s.t.$ $Av = \lambda v$, let $x(0) = y(0)v$, then:

$$\frac{1}{\Delta t}\big(x(\Delta t) - x(0)\big) = Ax(0)$$

$$\frac{1}{\Delta t}\big(y(\Delta t) - y(0)\big)v = Avy(0) = \lambda v y(0)$$

$$\Rightarrow \frac{dy}{dt} = \lambda y \quad \Rightarrow \quad y(t) = y(0)e^{\lambda t}$$

$$\Rightarrow x(t) = y(0)e^{\lambda t}v$$

So, behaviors can be decomposed in terms of Eigenvector

When $\mathrm{Re}(\lambda) > 0$, Eigenvector is unstable, When $\mathrm{Re}(\lambda) < 0$, Eigenvector is stable
A is **Hurwitz**: When $\mathrm{Re}(\lambda) < 0$, for all $\lambda \in \mathrm{Eigenvector}(A)$, this guarantees $x = 0$ is stable.