Lecture 11.
Diffusion in biological systems

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Main contents

- Diffusion in the cell
- Diffusive dynamics
- Biological applications of diffusion
§11.1 Diffusion in the cell
Brownian motion

• Brown (1828)
  - Pollen micro-grains (1μm) suspended in water do a peculiar dance
  - The motion of the pollen has never stopped
  - Totally lifeless particles do exactly the same thing

• Einstein (1905)
  - Quantitative explanation from thermal motion of water molecules
Active vs passive transport

- Opening of ion channel & diffusion of ions

When channel is open, ions diffusion inward—Passive transport (no energy input)
• Diffusive & directed motions of RNA polymerase

**Passive:** Free RNA polymerase molecule **diffusing** in a bacterial cell

**Active:** One-dimensional motion of RNA polymerase along DNA

*Energy source: NTP*
Patterns of *E. coli* swimming at different scales

At low magnification, the swimming movement of a single bacterium appears to be a random walk.

At higher magnification, it is clear that each step of this random walk is made up of very straight, regular movements.
Biological distances measured in diffusion times

- Diffusion time as a function of the length

\[ t \approx \frac{L^2}{D} \]

\[ D = 100 \, \mu m^2/s \]

\[ L \approx 10^6 \, \mu m \, (1 \, m) \]

\[ t = 10^{10} s = 300 y \]
• Diffusion is no effective over large cellular distances

Time scale of the active transport by virtue of molecular motors is shortened by many orders of magnitude than passive diffusion
Experimental techniques: measuring diffusive dynamics

- Fluorescence recovery after photobleaching (光漂白)

![Diagram showing the process of fluorescence recovery after photobleaching](image)

Figure 13.6. Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Fluorescently labeled molecule

Photobleached region by laser pulse

Fluorescently labeled molecules diffuse into the region
FRAP experiment showing recovery of a GFP-labeled protein confined to the membrane of the endoplasmic reticulum

The boxed region is photobleached at time instant, $t = 0$. In subsequent frames, fluorescent molecules from elsewhere in the cell diffuse into the bleached region.
Fluorescence correlation spectroscopy

1. Measure the fluorescence intensity in a small region of the cell as a function of time.
2. By analyzing the temporal fluctuations of the intensity through the use of time-dependent correlation functions, the diffusion constant and other characteristics of the molecular motion can be uncovered.
• Single-particle tracking

Record trajectory \(\{x(t), y(t), z(t)\}\) of a particle

Calculate Diffusion constant
§11.2 Diffusive dynamics
Random Walk (Redux)

- **1D random walk**

  \[ x_n = x_{n-1} + k_n L \]

  - \( L \) --- Length of each step
  - \( x_0 = 0 \) --- start point
  - \( x_n \) --- position after the \( n \)-th step
  - \( k_n \) --- displacement of the \( n \)-th step with \( P(k_n = 1) = P(k_n = -1) = 1/2 \)

  \[ \langle x_N^2 \rangle = NL^2 \]
  \[ \langle x_t^2 \rangle = 2Dt \]

  \( t = N \Delta t \), \( D = L^2 / 2 \Delta t \)
Diffusion & Random Walk

• What's meaning of the $\langle \ldots \rangle$

$\langle x_t^2 \rangle = \lim_{M \to \infty} \frac{1}{M} \sum_{i=1}^{M} x_i^2(t) = 2Dt$

Equivalent to release simultaneously $M$ particles at origin and then let them do independently random walk (or diffuse to other places)
• **Fick's law**

Assumption--
- Large number particles
- Uniform in $y, z$ direction
- Nonuniform in $x$ direction
- Jump distance $L$ per time $\Delta t$
- Same jump probability to left and right

$N(x,t)$: the number of particles in the box between $x-L/2$ and $x+L/2$ at time $t$. $(1/2)N(x,t)$ particles will pass through $x-L/2$ to the left in $\Delta t$.

Simultaneously, $(1/2)N(x-L,t)$ particles pass through $x-L/2$ to the right.

Density of number
$$ c(x,t) = \frac{N(x,t)}{A \times L} $$

Flux
$$ j = \frac{1}{2} \left[ N(x-L,t) - N(x,t) \right] \frac{1}{\Delta t \times A} = -D \frac{\partial c}{\partial x} $$

$$ D = \frac{L^2}{2 \Delta t} $$
Question: why is there a flux since each particle has the same jump probability to left and right?

Reason for net flow: there are more particles in one slot than in the neighboring one due to nonuniform.

- **Continuity equation**

\[
\Delta N(x, t) = \left[ j\left(x - \frac{L}{2}\right) - j\left(x + \frac{L}{2}\right) \right] A \Delta t
\]

\[
= - \frac{\partial j}{\partial x} L \times A \times \Delta t \quad \Rightarrow
\]

\[
\frac{\partial c}{\partial t} = - \frac{\partial j}{\partial x}
\]
• Diffusion equation and its solution

\[
j = -D \frac{\partial c}{\partial x}
\]

\[
\frac{\partial c}{\partial t} = -\frac{\partial j}{\partial x}
\]

\[
\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2}
\]  
(Diffusion equation)

Pulse solution

\[
\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2}
\]  
(Diffusion equation)

\[
c(x, 0) = \delta(x)
\]  
(initial condition)

\[
c(x, t) = \frac{1}{\sqrt{4\pi D t}} e^{-x^2/4Dt}
\]

Problem: Does the solution satisfy the diffusion equation and initial condition?
• Fluctuation

Molecular thermal motion (random) ==> Diffusion equation

Question: Why is diffusion equation deterministic?

Answer: Average on ensemble (collection of large number repeated systems). Available to describe a system of large number particles.

Finite particle system: its behavior deviated from the prediction of diffusion equation. This deviation is called statistical fluctuation.

Few particle system: Statistical fluctuations will be significant, and the system's evolution really will appear random, not deterministic.

Nanoworld of single molecules: need to take fluctuations seriously
Einstein relation

- A ball in viscous fluid (macroscopic analysis)

\[ f_{\text{friction}} = \xi v \]

\[ a = \frac{f_{\text{ext}} - f_{\text{friction}}}{m} = \frac{f_{\text{ext}} - \xi v}{m} \]

(i): \( v < \frac{f_{\text{ext}}}{\xi} \Rightarrow a > 0 \Rightarrow v \uparrow \Rightarrow v \rightarrow \frac{f_{\text{ext}}}{\xi} \)

(ii): \( v > \frac{f_{\text{ext}}}{\xi} \Rightarrow a < 0 \Rightarrow v \downarrow \Rightarrow v \rightarrow \frac{f_{\text{ext}}}{\xi} \)

\[ v_{\text{drift}} \equiv \frac{f_{\text{ext}}}{\xi} \iff f_{\text{ext}} = f_{\text{friction}} \]
The process to reach the drift velocity in micrometer scale

\[
dv/dt = a = (f_{ext} - \xi v)/m = \xi (v_{\text{drift}} - v)/m \Rightarrow
\]

\[
v(t) = v_{\text{drift}} + [v(0) - v_{\text{drift}}] e^{-\xi t/m}
\]

The larger \( \zeta/m \), \( v \) reaches more quickly to \( v_{\text{drift}} \)

Stokes formula: \( \xi = 6 \pi \eta R \)  
\( \eta -- \text{viscosity} \)

\( \eta_{\text{water}} \approx 10^{-3} \text{kg m}^{-1} \text{s}^{-1} \)
\( R_{\text{pollen}} \approx 1 \mu\text{m} \)

\[ \tau_c \equiv m/\xi \approx 10^{-7} \text{s} \]

\( v \rightarrow v_{\text{drift}} \) very quickly such that we can omit the process!
A ball in viscous fluid (microscopic analysis)

Assumption:

1. The collisions occur exactly once per $\Delta t$
2. In between kicks, the ball is free of random influences, so $a = f_{ext}/m$
3. $v_0$ is the starting value just after a kick
4. Each collision obliterates all memory of the previous step

\[
\begin{align*}
(1) - (3) & \Rightarrow \Delta x = v_{0x} \Delta t + (1/2) a \Delta t^2 = v_{0x} \Delta t + (1/2) (f_{ext}/m) \Delta t^2 \\
(4) & \Rightarrow \langle v_{0x} \rangle = 0
\end{align*}
\]

\[v_{drift} = \frac{\langle \Delta x \rangle}{\Delta t} = \frac{f_{ext}}{\xi} \quad \xi = 2m/\Delta t\]
• Einstein relation

\[
D = \frac{L^2}{2 \Delta t} \\
\xi = \frac{2m}{\Delta t}
\]

\[
\xi D = m \left( \frac{L}{\Delta t} \right)^2
\]

In our discussion, we have confined \( L \) and \( \Delta t \) to be constant. In fact, they are also stochastic quantities. Strict derivation gives

\[
\xi D = m \left\langle \left( \frac{L}{\Delta t} \right)^2 \right\rangle = m \langle v_x^2 \rangle
\]

\[
\frac{1}{2} m \langle v_x^2 \rangle = \frac{1}{2} k_B T
\]

Hypothesis
Heat is disordered molecular motion

Testable prediction
Einstein relation

\[
\xi D = k_B T
\]
• Mean field thought---more rigorous treatment

The **collisions** of water molecules are simplified as a white noise (force)

\[ \langle \Gamma(t) \rangle = 0, \quad \langle \Gamma(t) \Gamma(t') \rangle = g \delta(t-t') \]

Newton's law=>

\[ m \frac{dv_x}{dt} = -\xi v_x + \Gamma(t) \] (Langevin equation)

Solution:

\[ v_x = v_0 e^{-t/\tau_c} + \frac{1}{m} \int_0^t e^{-(t-s)/\tau_c} \Gamma(s) ds , \quad \tau_c \equiv m/\xi \]

\[ x(t) = \int_0^t v_x dt = v_0 \tau_c \left[ 1 - e^{-t/\tau_c} \right] + \frac{1}{\xi} \int_0^t \left[ 1 - e^{-(t-s)/\tau_c} \right] \Gamma(s) ds \]
\[ v_x^2 = v_0^2 e^{-2t/\tau_c} + \frac{1}{m^2} \left[ \int_0^t e^{-(t-s)/\tau_c} \Gamma(s) \, ds \right]^2 + \frac{2v_0}{m} e^{-t/\tau_c} \int_0^t e^{-(t-s)/\tau_c} \Gamma(s) \, ds \]

Assume that \( v_0 \) is independent of \( \Gamma(s) \):

\[ \langle v_0 \Gamma(s) \rangle = \langle v_0 \rangle \langle \Gamma(s) \rangle = 0 \]

\[ \langle v_x^2 \rangle = \langle v_0^2 \rangle e^{-2t/\tau_c} + \frac{1}{m^2} \left[ \int_0^t e^{-(t-s)/\tau_c} \Gamma(s) \, ds \right]^2 \]

\[ = \frac{g}{2m\xi} + \left( \langle v_0^2 \rangle - \frac{g}{2m\xi} \right) e^{-2t/\tau_c} \]

The observed time scale \( t \gg \tau_c \)

\[ \langle v_x^2 \rangle = \frac{g}{2m\xi} \]

\[ \frac{1}{2}m\langle v_x^2 \rangle = \frac{1}{2}k_B T \]

\[ \frac{g}{2\xi} = k_B T \]
\[ x^2(t) = v_0^2 \tau_c^2 \left[ 1 - e^{-t/\tau_c} \right]^2 + \frac{1}{\xi^2} \left\{ \int_0^t \left[ 1 - e^{-(t-s)/\tau_c} \right] \Gamma(s) \, ds \right\}^2 \]

\[ + 2 \frac{v_0 \tau_c}{\xi} \left[ 1 - e^{-t/\tau_c} \right] \int_0^t \left[ 1 - e^{-(t-s)/\tau_c} \right] \Gamma(s) \, ds \]

\[ \langle x^2(t) \rangle = \langle v_0^2 \rangle \tau_c^2 \left[ 1 - e^{-t/\tau_c} \right]^2 + \frac{1}{\xi^2} \left\{ \left\langle \int_0^t \left[ 1 - e^{-(t-s)/\tau_c} \right] \Gamma(s) \, ds \right\rangle \right\}^2 \]

\[ = \left( \langle v_0^2 \rangle - \frac{g}{2m\xi} \right) \tau_c^2 \left[ 1 - e^{-t/\tau_c} \right]^2 + \frac{g}{\xi^2} \left[ t + \tau_c \left( 1 - e^{-t/\tau_c} \right) \right] \]

The observed time scale \( t \gg \tau_c \)

\[ \langle x^2(t) \rangle = \left( \frac{g}{\xi^2} \right) t \equiv 2Dt \Rightarrow \]

\[ \Rightarrow D = \frac{g}{2\xi^2} \]

\[ \frac{g}{2\xi} = k_B T \]

\[ \xi D = k_B T \]
Diffusion equation in a potential

- **Revised Fick's law**
  
  Assumption--
  - Large number particles
  - Uniform in $y, z$ direction
  - Nonuniform in $x$ direction
  - Jump distance $L$ per time $\Delta t$
  - Jump probability to left $\neq$ right

$$P(k_x = 1) \neq P(k_x = -1)$$

$k_x = 1$ step right, $k_x = -1$ step left
Heuristic views:

(1) \( h'(x)=0 \), i.e., \( h(x) = \text{const.} \)

\[
\begin{align*}
x_n &= x_{n-1} + k_n L \\
P(k_n=1) &= P(k_n=-1) = 1/2
\end{align*}
\]

(2) \( h'(x) \neq 0 \), i.e., \( h(x) \neq \text{const.} \)

\[
\begin{align*}
x_n &= x_{n-1} + k_n L \\
P(k_n) &= \frac{1}{2} \left[ 1 - f \left[ k_n L h'(x_{n-1}) \right] \right]
\end{align*}
\]

\( f \) : odd function, mono-increasing

Assume the step \( L \) is small enough, then up to the linear term,

\[
P(k_n) = \frac{1}{2} \left[ 1 - \gamma k_n L h'(x_{n-1}) \right]
\]
How many particles will pass through \( x-L/2 \) to the left in \( \Delta t \)?

\[
P(k_x = -1) N(x, t) = \frac{1}{2} \left[ 1 + \gamma L h'(x) \right] N(x, t)
\]

Simultaneously, How many particles will pass through \( x-L/2 \) to the right?

\[
P(k_{x-L} = 1) N(x-L, t) = \frac{1}{2} \left[ 1 - \gamma L h'(x-L) \right] N(x-L, t)
\]

Keep the leading term, we have

\[
j = \frac{P(k_{x-L} = 1) N(x-L, t) - P(k_x = -1) N(x, t)}{A \Delta t} = -D \frac{\partial c}{\partial x} - 2D \gamma h'(x) c
\]

**Diffusion equation in a potential**

\[
j = -D \frac{\partial c}{\partial x} - 2D \gamma h'(x) c
\]

Continuity equation unchanged

\[
\frac{\partial c}{\partial t} = -\frac{\partial j}{\partial x}
\]
• Determine $\gamma$

Equilibrium state, no flux:

$$j = -D \frac{\partial c}{\partial x} - 2D \gamma h'(x) c = 0$$

$$\frac{\partial c}{\partial t} = -\frac{\partial j}{\partial x} = 0$$

$$\Rightarrow c(x) = \text{const.} \times e^{-2\gamma h(x)}$$

We have known, in equilibrium state, Boltzmann distribution

$$c(x) = \text{const.} \times e^{-\frac{h(x)}{k_B T}}$$

Compare both distributions, we obtain

$$\gamma = \frac{1}{2 k_B T}$$

Smoluchowski equation

$$\frac{\partial c}{\partial t} = D \left[ \frac{\partial^2 c}{\partial x^2} + \frac{1}{k_B T} \frac{\partial (h' c)}{\partial x} \right]$$
Potential: $U(x) = k_B T \sin x$

- Random walk
- $e^{-\sin x} / Z$
§3.6 Biological applications of diffusion
Limit on bacterial metabolism

- Idealized model

O₂ is dissolved in the water, with a concentration \( c_0 \):

\[
c(\infty) = c_0
\]

Bacterium immediately gobbles up (吞噬) O₂ at its surface:

\[
c(R) = 0
\]

Problem: Find the concentration profile \( c(r) \) and the maximum consumed number of O₂ per time.
• Solution

$I(r)$: the number of $O_2$ per time passing through the fictitious (假想的) spherical shell

Assume: quasi-steady state, oxygen does not pile up (累积) anywhere:

\[ I(r) = I \quad \text{(independent of } r) \]

Flux of $O_2$:

\[ j(r) = \frac{-I}{4\pi r^2} \]

Fick's law:

\[ j(r) = -D \frac{dc}{dr} \]

BCs:

\[ c(R) = 0 \quad \& \quad c(\infty) = c_0 \]

\[ I = 4\pi D c_0 R \]

maximum consumed number of $O_2$ per time
Limit on the size of the bacterium

The number of $O_2$ per time that a living body needs

$$\dot{Q} \propto M^{2/3} \propto R^2$$

Metabolic rate (ref. Lecture 4)

The maximum consumed number of $O_2$ per time

$$I = 4\pi Dc_0 R$$

$$\dot{Q} \leq I$$

There is an upper limit to the size of a bacterium!
Membrane potentials

- Drift and diffusion: ionic solution under E-field

\[
\Delta V = \frac{-\Delta V}{l} \\
E = -\frac{\Delta V}{l} \\
f_{\text{drift}} = qE = -q \frac{\Delta V}{l}
\]

\[
v_{\text{drift}} = f_{\text{drift}} = -q \frac{\Delta V}{l} \xi
\]

\[
\xi D = k_B T
\]

\[
\nu_{\text{drift}} = -\frac{Dq \Delta V}{lk_B T}
\]

\[
j_{\text{drift}} = c \nu_{\text{drift}} = -\left(\frac{Dq \Delta V}{lk_B T}\right)c
\]

\[
j_{\text{diffusion}} = -D \frac{\partial c}{\partial x}
\]

\[
j = j_{\text{drift}} + j_{\text{diffusion}} = -D \left[ \frac{\partial c}{\partial x} + \left(\frac{q \Delta V}{lk_B T}\right)c \right]
\]

(Nernst-Planck formula)
• Equilibrium state \( j = 0 \) at \( \Delta V = \Delta V_{eq} \)

\[
j = -D \left[ \frac{\partial c}{\partial x} + \left( \frac{q \Delta V_{eq}}{l k_B T} \right) c \right] = 0 \Rightarrow \frac{d c}{d x} = -\left( \frac{q \Delta V_{eq}}{l k_B T} \right) c
\]

\[
\Rightarrow \frac{d \ln c}{d x} = -\frac{q \Delta V_{eq}}{l k_B T} \Rightarrow \frac{\Delta (\ln c)}{l} = -\frac{q \Delta V_{eq}}{l k_B T}
\]

\[
\Delta (\ln c) = -\frac{q \Delta V_{eq}}{k_B T} \quad \text{(Nernst relation)}
\]

Membrane potentials maintains a concentration jump in equilibrium!

Discuss: Nernst relation and Boltzmann distribution.
FRAP

• 1D model for FRAP

Governing equation
\[ \frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} \]

Initial conditions
\[ c(x,0) = \begin{cases} 
  c_0, & (-1 < x < -1/2) \\
  0, & (-1/2 < x < 1/2) \\
  c_0, & (1/2 < x < 1) 
\end{cases} \]

Boundary conditions
\[ \left. \frac{\partial c}{\partial x} \right|_{x=-1} = \left. \frac{\partial c}{\partial x} \right|_{x=1} = 0 \]

the flux of fluorescent molecules vanishes at the boundaries of the one-dimensional cell
• Solutions

\[ c(x,t) = c_0 \left[ \frac{1}{2} - \sum_{n=1}^{\infty} \frac{2(-1)^{n-1}}{n \pi} e^{-D n^2 \pi^2 t} \cos n \pi x \right] \]

\[ N_f(t) = \int_{-1/2}^{1/2} c(x,t) \, dx = \frac{c_0}{2} \left[ 1 - \sum_{n=1}^{\infty} \frac{8}{n^2 \pi^2} e^{-D n^2 \pi^2 t} \right] \]

recovery curve
§. Summary & further reading
Summary

• Diffusion & Random walks \[ \langle x_t^2 \rangle = 2Dt \]

• Friction and diffusion
  - Einstein relation \[ \xi D = k_B T \]
  - Fick's law \[ j = -D \left[ \frac{\partial c}{\partial x} + \frac{h'(x)c}{k_BT} \right] \]
  - Diffusion equation \[ \frac{\partial c}{\partial t} = D \left[ \frac{\partial^2 c}{\partial x^2} + \frac{1}{k_BT} \frac{\partial (h'c)}{\partial x} \right] \]

• Biological applications of diffusion
  - Bacterial \textit{metabolism}
  - \textit{Permeability} of membranes, membrane \textit{potentials}
  - Electrical \textit{conductivity} of solutions
  - FRAP
Further reading

- Reichl, *A modern course in statistical physics*
- Phillips, *Physical biology of the cell, Ch13*
- Nelson, *Biological physics, Ch4*