Engineering Molecular Cell Biology
Lecture 7, Fall 2010

Diffusion (II)

Comments on Reading Assignment 1 (I)

- What is systems biology?

  - System integration in different dimensions: not just across different molecules, but across different scales.

- Benefits, challenges, limitations?

  “Though systems biology has been touted for its potential, the fact is that it has not yet produced a useful predictive model.”

  “This type of study sounds ideal…The theory of systems biology is slightly ahead of the technology able to harness it; a major, but hopefully only temporary, drawback.

  “Although we can apply methods used in analyzing engineering systems to investigate biological systems, we still cannot obtain better understanding of these biological systems through these methods. This is due to lots of differences between an engineering system and a biological systems. ……More additional structure information is needed to comprehend a biological system.”

Comments on Reading Assignment 1 (II)

- Where we are? What we can do?

- Does modeling equal understanding?

  "I have wondered for a while about the question of whether it is enough to simply model something, or whether scientists should generate models that can be understood. I think that the prevailing feeling in science is that we want to understand things, but I am not convinced that we can truly understand biology. <u>That is, we may (at some point) be able to accurately model all the effects of a drug on the body, but I doubt whether any human will be able to explain why these effects occur.</u> Such a model would be highly useful but deeply unsatisfying. Does systems biology aim to make models that are both simple to understand and accurate, and is that a reasonable goal?"

Diffusion

- Diffusion: microscopic theory
- Diffusion: macroscopic theory
- Determination of diffusion coefficient

Introduction

Table 2–2 The Approximate Chemical Composition of a Bacterial Cell

	PERCENT OF TOTAL CELL WEIGHT	NUMBER OF TYPES OF EACH MOLECULE
Water	70	1
Inorganic ions	1	20
Sugars and precursors	1	250
Amino acids and precursors	0.4	100
Nucleotides and precursors	0.4	100
Fatty acids and precursors	1	50
Other small molecules	0.2	~300
Macromolecules (proteins, nucleic acids, and	26	~3000

- Cellular molecules are subject to <u>thermal force</u> due to collisions with water and other molecules.

- The resulting motion and energy are called thermal motion and thermal energy.

Movement of a Free Molecule (I)

- The average kinetic energy of a particle of mass m and velocity v is

$$\left\langle \frac{1}{2} m v_x^2 \right\rangle = \frac{kT}{2}$$

Boltzmann constant=1.381×10^{-23} J/K

$t_K = t_C + 273.15$

where k is Boltzmann's constant and T is absolute temperature (Einstein 1905).

- Principle of equipartition of energy

$$\left\langle \frac{1}{2} m v^2 \right\rangle = \frac{3 \cdot kT}{2}$$

Movement of a Free Molecule (II)

- Molecular mass of GFP is 27 kDa. One atomic mass unit (Da) is 1.6606×10^{-24}g. So the mass of one GFP molecule is 4.48×10^{-20}g.

  At 27 degree C, kT is 4.14×10^{-14}g·cm^2/sec^2.

$$\sqrt{\left\langle v_x^2 \right\rangle} = \sqrt{\frac{kT}{m}} = 961.3 \text{ cm/sec}$$

1D Random Walk in Solution (I)

- Assumptions:

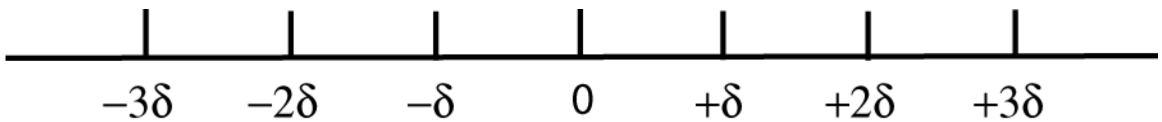
  (1) A particle *i* has equal probabilities to walk to the left and to the right.

  (2) Particle movement at consecutive time points are independent.

  (3) Movement of different particles are independent.

  (4) Each particle moves at a average step size of $\delta = v_x \cdot \tau$

$$x_i(n) = x_i(n-1) \pm \delta$$



$$\langle x(n) \rangle = \frac{1}{N}\sum_{i=1}^{N} x_i(n) = \frac{1}{N}\sum_{i=1}^{N}\left[x_i(n-1) \pm \delta\right]$$
$$= \frac{1}{N}\sum_{i=1}^{N} x_i(n-1) = \langle x(n-1) \rangle$$

- Property 1: The mean position of a particle (or an ensemble of particles) undergoing random walk remains at the origin.

1D Random Walk in Solution (II)

- Property 2: The mean square displacement of a particle undergoing random walk increases linearly w.r.t. time.

$$\left\langle x^2(n)\right\rangle = \frac{1}{N}\sum_{i=1}^{N} x_i^2(n) = \frac{1}{N}\sum_{i=1}^{N}\left[x_i^2(n-1) \pm 2\delta x_i(n-1) + \delta^2\right]$$
$$= \left\langle x^2(n-1)\right\rangle + \delta^2$$

$$\left\langle x^2(n)\right\rangle = n\delta^2 = \frac{t}{\tau}\delta^2 = 2Dt \qquad \left\langle r^2(n)\right\rangle = \left\langle x^2(n) + y^2(n)\right\rangle = 4Dt$$

$$\left\langle r^2(n)\right\rangle = \left\langle x^2(n) + y^2(n) + z^2(n)\right\rangle = 6Dt$$

Application of the Microscopic Theory (I)

Object	Distance diffused			
	1 µm	**100 µm**	**1 mm**	**1 m**
K^+	0.25ms	2.5s	2.5×10^4s (7 hrs)	2.5×10^8s (8 yrs)
Protein	5ms	50s	5.0×10^5s (6 days)	5.0×10^9s (150 yrs)
Organelle	1s	10^4s (3 hrs)	10^8s (3 yrs)	10^{12}s (31710 yers)

K+: Radius = 0.1nm, viscosity = 1mPa·s^{-1}; T = 25°C; D=2000 µm^2/sec
Protein: Radius = 3nm, viscosity = 0.6915mPa·s^{-1}; T = 37; D = 100 µm^2/sec
Organelle: Radis = 500nm, viscosity = 0.8904mPa·s^{-1}; T = 25°C; D = 0.5 µm^2/sec

1D Random Walk in Solution (II)

- Property 3: The displacement of a particle follows a normal distribution.

$$p(k;n) = \frac{n!}{k!(n-k)!}\frac{1}{2^k}\frac{1}{2^{n-k}}$$

$$p(k) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(k-\mu)^2}{2\sigma^2}} \text{ where } \sigma^2 = \frac{n}{4} \text{ and } \mu = \frac{n}{2}$$

$$x(n) = \left[k - (n-k)\right]\delta = (2k-n)\delta \qquad \langle x(n)\rangle = \left(2\langle k\rangle - n\right)\delta = 0$$

$$\langle x^2(n)\rangle = \left(4\langle k^2\rangle - 4\langle k\rangle n + n^2\right)\delta^2 = \left(n^2 + n - 2n^2 + n^2\right)\delta^2 = n\delta^2$$

$$p(x) = \frac{1}{\sqrt{4\pi Dt}} e^{-\frac{x^2}{4Dt}} \text{ where } n\delta^2 = 2Dt$$

1D Random Walk in Solution (III)

$$p(k;n)=\frac{n!}{k!(n-k)!}\frac{1}{2^k}\frac{1}{2^{n-k}}$$

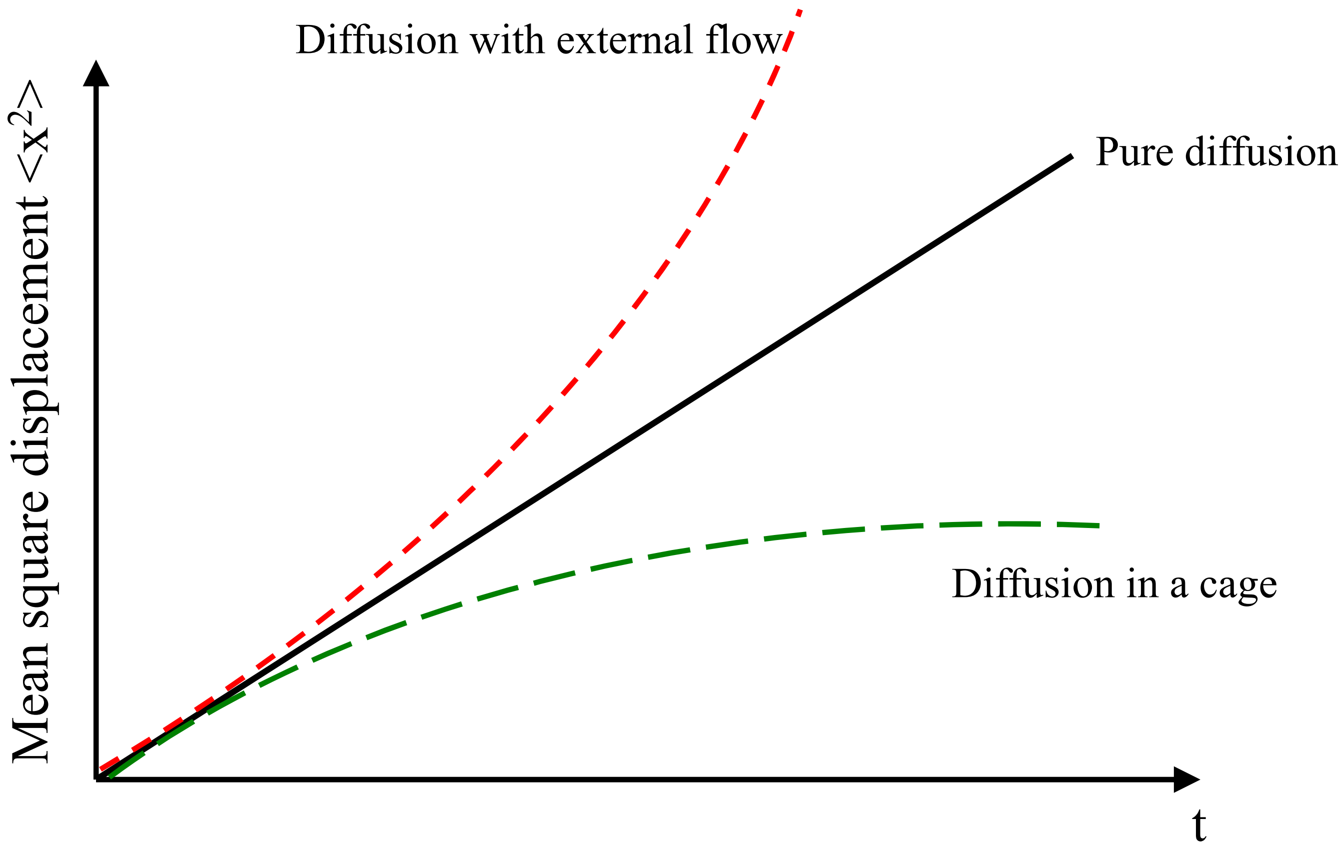
$$p(k)=\frac{1}{\sqrt{2\pi\sigma^2}}e^{-\frac{(k-\mu)^2}{2\sigma^2}} \text{ where } \sigma^2=\frac{n}{4} \text{ and } \mu=\frac{n}{2}$$

$$x(n)=\left[k-(n-k)\right]\delta=(2k-n)\delta \qquad \langle x(n)\rangle=\left(2\langle k\rangle-n\right)\delta=0$$

$$\langle x^2(n)\rangle=\left(4\langle k^2\rangle-4\langle k\rangle n+n^2\right)\delta^2=\left(n^2+n-2n^2+n^2\right)\delta^2=n\delta^2$$

$$p(x)=\frac{1}{\sqrt{4\pi Dt}}e^{-\frac{x^2}{4Dt}} \text{ where } n\delta^2=2Dt$$

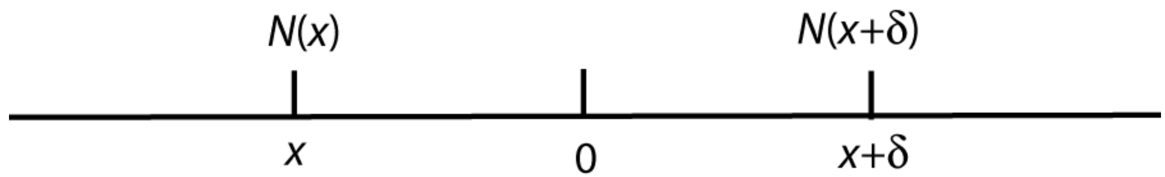
Application of the Microscopic Theory (II)



H. Qian, M. P. Sheetz, E. L. Elson, *Single particle tracking: analysis of diffusion and flow in two-dimensional systems*, Biophysical Journal, 60(4):910-921, 1991.

Macroscopic Theory of Diffusion (I)

- Fick's first equation: net flux is proportional to the slope of the concentration function.

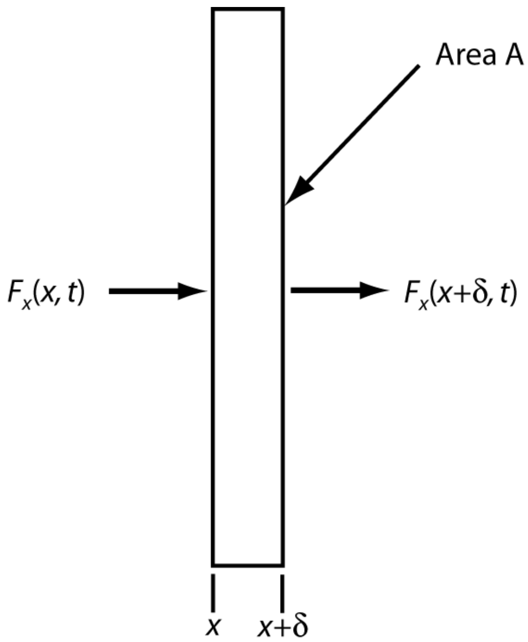


$$-\frac{1}{2}\left[N(x+\delta)-N(x)\right]$$

$$\begin{aligned}
F_x &= \lim_{\delta\to 0} -\frac{1}{2}\left[N(x+\delta)-N(x)\right]/A\tau \\
&= \lim_{\delta\to 0} -\frac{\delta^2}{2\tau}\frac{1}{\delta}\left[\frac{N(x+\delta)}{A\delta}-\frac{N(x)}{A\delta}\right] \\
&= \lim_{\delta\to 0} -D\frac{1}{\delta}\left[C(x+\delta)-C(x)\right] \\
&= -D\frac{\partial C}{\partial x}
\end{aligned}$$

Macroscopic Theory of Diffusion (II)

- Fick's second equation



$$\left[C(t+\tau)-C(t)\right] = -\frac{1}{A\delta}\left[F_x(x+\delta)-F_x(x)\right]A\tau$$

$$\begin{aligned}\frac{1}{\tau}\left[C(t+\tau)-C(t)\right] &= -\frac{1}{\tau}\frac{1}{A\delta}\left[F_x(x+\delta)-F_x(x)\right]A\tau \\ &= -\frac{1}{\delta}\left[F_x(x+\delta)-F_x(x)\right]\end{aligned}$$

$$\frac{\partial C}{\partial t} = -\frac{\partial F_x}{\partial x} = D\frac{\partial^2 C}{\partial x^2}$$

The time rate of change in concentration is proportional to the curvature of the concentration function.

Calculation of Diffusion Coefficient

- Einstein-Smoluchowski Relation

$$v_d = \frac{1}{2} a\tau = \frac{1}{2}\frac{F_x}{m}\tau \qquad f = \frac{F_x}{v_d} = \frac{2m}{\tau} = \frac{2m\dfrac{\delta^2}{\tau^2}}{\dfrac{\delta^2}{\tau}} = \frac{mv_x^2}{D} = \frac{kT}{D}$$

$$D = \frac{kT}{f}$$

f: viscous drag coefficient

- Stokes' relation: the viscous drag coefficient of a sphere moving in an unbounded fluid

$$f = 6\pi\eta r$$

η: viscousity
r: radius

An example of D calculation

- Calculation of diffusion coefficient

$$D = \frac{kT}{6\pi\eta r}$$

- $k=1.381\times10^{-23}$J/k$=1.381\times10^{-17}$ N·μm/k
- T = 273.15 + 25
- $\eta=0.8904$mPa·s$=0.8904\times10^{-3}\times10^{-12}$N·μm^{-2}·s
- r= 500nm=0.5μm
- D=0.5 μm^2/s

An example of direct measurement of D

M. B. Elowitz et al, *Protein mobility in the cytoplasm of E. coli*,
J. Bacteriology, 181:197-203, 1999

Questions? Comments?

References

- Howard Berg, *Random Walks in Biology*, Princeton University Press, 1993.

- Jonathon Howard, *Mechanics of Motor Proteins and the Cytoskeleton*, Sinauer Associated, 2001.