Random Walk Models for Life in Motion

Diffusion in the Cell

Dynamics in cells is mostly driven by random jiggling of small molecules in solution: diffusion.

Because diffusion of molecules is powered by thermal energy, movement is random.

- Collisions in chemical reactions
- Ligand binding/unbinding
- Distribution of ions or newly made proteins
- Homogeneous distribution of abundant molecules
- Equilibrium of pressure and equipartition of energy
Brownian Motion

Diffusion can be modeled as one-, two- or three-dimensional random walk:

• Step size is fixed
• **Number of steps is not fixed and time dependent**
• Assume that the molecule takes one step at every $\Delta t$.

\[ t = N \cdot \Delta t \]

• From one-dimensional random walk:

\[ t = N \cdot \Delta t \]

\[ < x^2 > = N L^2 \text{ where } L \text{ is the step size} \]

\[ < x^2 > = \frac{t}{\Delta t} L^2 \text{ linearly increases with time} \]
The diffusion constant $D = \frac{L^2}{2\Delta t}$ and therefore in one dimension $< x^2 > = 2Dt$.

In two dimensions: $< r_N^2 > = < x_N^2 > + < y_N^2 >$

$< r^2 > = 2NL^2 = 4Dt$

In three dimensions: $< r^2 > = 3NL^2 = 6Dt$.

$D$ is an experimentally measurable parameter.
Friction of Water

From Physics 7A, we learned that freely falling object in air will reach a terminal velocity, due to the drag force of air molecules.

• In solution, collisions between small molecules give rise to drag forces.
• Consider the particle is being pulled in +x direction with force of F.
• Suppose collisions occur at every \( \Delta t \) seconds.
• Between collisions,

\[
\frac{dv_x}{dt} = \frac{F}{m}
\]

\[
\Delta x = v_{0,x} t + \frac{1}{2m} (\Delta t)^2
\]

• Suppose that each collision obliterates the memory of the previous step.

\[
<v_{0,x} > = 0
\]

\[
<v_{\Delta x} > = \frac{1}{2m} (\Delta t)^2
\]

\[
\frac{v_{\Delta x}}{\Delta t} = v_{drift} = \frac{1}{2m} \Delta t
\]
Viscous Drag: Stokes Formula

\[ F = \zeta v_{\text{drift}} \text{ where viscous drag coefficient } \zeta = \frac{2m}{\Delta t} \]

\[ \zeta = 6\pi\eta R \]

\( \zeta \) is an experimentally measurable parameter. Determines how fast a particle settles in viscous drag of water. \( \Delta t \) depends on the size of the particle and viscosity of the liquid.

Viscosity of water is roughly 10^{-3} Pa.s at room temperature. Viscosity of cytoplasm depends on particle size:

a) for molecules smaller than 1 nm, it is less than that of water.
b) for particles of diameter 6, it is 3 times higher than that of water.
c) 50-500 nm particles, it is 30-300 times that of water.
Einstein Relation

We assumed molecular scale parameters $L$ and $\Delta t$, which are not experimentally measurable.

To verify the idea that diffusion and friction are manifestations of thermal motion, Einstein noticed that there is a third relation between $L$ and $\Delta t$.

$$\left( \frac{L}{\Delta t} \right)^2 = v_{0,x}^2$$

From equipartition theorem, $< v_{0,x}^2 >/ = \frac{kT}{m}$

(we use only one component of velocity)

$$\left( \frac{L}{\Delta t} \right)^2 = \frac{kT}{m}$$

$$D = \frac{L^2}{2\Delta t} \text{ and } \zeta = \frac{2m}{\Delta t}$$

$$D\zeta = kT \text{ Einstein Relation}$$
Einstein Relation

\[ D\varsigma = kT \quad \text{Einstein Relation} \]

- The equation does not depend on mass \( m \).
- Small particles will feel less drag (small \( \varsigma \)) and will diffuse more readily (big \( D \)).
- For a small gas molecule in water, \( D \) is roughly 2000 µm²s⁻¹
- For a typical globular protein (\( R = 3 \) nm) in cytoplasm, \( D \) is roughly 7 µm²s⁻¹
- Both friction (\( \varsigma \)) and diffusion (\( D \)) depend on \( T \) in a complicated way, but their product depend on \( T \) in a simple way.
Diffusion Rules the Subcellular World

How long does it take to move across the bacterial cell?

\[ < r^2 > = 6Dt \quad \text{and} \quad r = 1 \, \mu m \quad (\text{assuming bacteria as a sphere}) \]

\[ D = 100 \, \mu m^2 \, s^{-1} \]

\[ t = 2 \, ms \]

Diffusion time increases by the square of the distance.

Graph showing the relationship between time and length.
Limitations in Vesicle Transport

\[ D = \frac{kT}{6\pi\eta R} \]

for an organelle 500 nm in radius, \( D \approx 0.5 \, \mu m^2 s^{-1} \)

travelling across a nerve cell 1 m in length in 1D,

\[ \frac{\langle r^2 \rangle}{2D} = t = 12 \, \text{days} \]

In reality, it takes much longer than 12 days, because viscosity of cytoplasm is much higher for large particles and the crowding effect slows down diffusion.
Fick's Law

• Suppose that initial distribution of particles is uniform in \( y \) and \( z \) directions, but not in \( x \).
• At every step \( \Delta t \), each particle moves a distance \( L \), either towards right or left.
• \( N(x) \) is the number of particles at position \( x \) (and area \( A \) of the box).
• The net number of particles crossing from left to right:

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

when \( L \to 0 \),

\[
\frac{1}{2} \left( N(x) - N(x + L) \right) = -\frac{1}{2} \left( L \frac{dN}{dx} \right)
\]

concentration of molecules \( c = \frac{N}{V_{\text{box}}} = \frac{N}{A \cdot L} \)
Average rate of crossing a surface per unit area is flux.

\[
j = \frac{1}{A \Delta t} \left( -\frac{L}{2} \frac{dN}{dx} \right) = \frac{1}{A \Delta t} \left( -\frac{L}{2} \frac{dN}{dx} \right)
\]

\[
j = \frac{-L}{2A \Delta t} \left( \frac{d}{dx} c(x) A L \right)
\]

\[
j = \frac{-L^2 A}{2A \Delta t} \frac{dc}{dx}
\]

\[
j = \frac{-L^2}{2 \Delta t} \frac{dc}{dx}
\]

\[
j = -D \frac{dc}{dx} \quad (Fick's Law)
\]

- \(j\) measures the number of particles moving from left to right (+\(x\) direction)
- If there are more particles on the left, \(c\) is decreasing by \(x\), and its negative derivative is positive. There will be net flux of particles towards right.
- Particles will move from densely populated regions to sparsely populated regions to equilibrate their chemical potential (Entropic Forces)
Diffusion Equation

- If there is order in the initial state, diffusion will erase that memory.
- Fick’s Law is useful if concentration gradient is time independent.
- However if the concentration gradient is changing over time due to diffusion of particles, Fick’s Law does not tell much. $N(x,t)$

\[
\frac{d}{dt} N(x, t) = A[j(x) - j(x + L)]
\]

if $L \to 0$, \[ \frac{dN}{dt} = A \left(-L \frac{dj}{dx}\right) \]

\[
\frac{\partial c}{\partial t} = -\frac{dj}{dx} \quad \text{Continuity Equation}
\]

since $j = -D \frac{dc}{dx}$

\[
\frac{\partial c}{\partial t} = D \frac{d^2 c}{dx^2} \quad \text{(Diffusion Equation)}
\]
Diffusion Equation

\[ j = -D \frac{dc}{dx} \]
\[ \frac{\partial c}{\partial t} = D \frac{d^2 c}{dx^2} \]

- Given the initial concentration profile \( c(x,0) \), we can predict the future profile \( c(x,t) \).

- Well mixed uniform solution does not change by time.

\[ \frac{dc}{dx} = 0 = j \quad \frac{d^2 c}{dx^2} = 0 = \frac{\partial c}{\partial t} \]

- Concentration gradient has net flux, but the gradient does not change by time.

- Every second, the number of particles entering the region is equal to the ones leaving.

\[ \frac{dc}{dx} < 0 \quad \frac{d^2 c}{dx^2} = 0 = \frac{\partial c}{\partial t} \]
Fundamental Pulse Equation

• What happens if we introduce $N$ number of particles to $x = 0$ position in pure water.

$$\frac{dc}{dx} = 0 \text{ at } x = 0$$

$$\frac{dc}{dx} < 0 \text{ at } x > 0$$

Net flux of particles on the left towards the left side

$$\frac{dc}{dx} > 0 \text{ at } x < 0$$

Net flux of particles on the right towards the right side

$$\frac{d^2c}{dx^2} < 0, \text{ so } \frac{\partial c}{\partial t} < 0$$

Concentration of particles decreases by time due to diffusion of particles away from 0 position.

• Diffusion finally erases the bump.
Fundamental Pulse Solution

- We expect the variance of the pulse to increase with time.
- Can simple Gaussian be a solution:

\[ c(x, t) = B e^{-x^2/2At} \quad \text{where } \sigma^2 = At \quad \text{and} \quad (A, B \text{ are constants}) \]

No, because the number of particles are fixed

\[ N = \int_{-\infty}^{\infty} dx c(x, t) \]

Amplitude of Gaussian decreases with time.

Indeed, the amplitude of Gaussian is a function of \( \sigma \)

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

because \( \frac{\partial c}{\partial t} = D \frac{d^2 c}{dx^2} \)

\[ c(x, t) = \frac{1}{\sqrt{4\pi Dt}} e^{-x^2/4Dt} \quad \text{in one dimension} \]

\[ \sigma^2 = 2Dt \quad \text{(which satisfies the Brownian Motion)} \]
Example 1

Imagine a long thin glass tube of length L and area A.
One end sits in a bath of pure water and the other end in a solution of ink in water.
Eventually, the system will reach the equilibrium with same ink concentration everywhere.

Prior to that, the system will reach the **quasi-steady state**, where \( c(x) \) is nearly unchanging over time.

\[
\begin{align*}
    c(0) &= c_0 \\
    c(L) &= 0 \\
    \frac{\partial c}{\partial t} &= 0 \text{ steady state}
\end{align*}
\]

\[
\frac{d^2 c}{dx^2} = 0 \text{ graph of } c(x) \text{ is a straight line}
\]

\[
c(x) = c_0 (1 - \frac{x}{L})
\]

**flux of solute** \( j = -D \frac{\Delta c}{L} \) where \( \Delta c = c(L) - c(0) \)
Fluorescence Recovery After Photobleaching (FRAP)

- FRAP denotes an optical technique capable of quantifying the diffusion of fluorescently-labeled biological molecules.
- Diffusion can be in 1-D in long processes (e.g. flagellum), 2-D on membrane proteins in a lipid bilayer or 3-D inside cytoplasm.
- (B) High power laser pulse is sent to photobleach all of the fluorescent probes in certain region.
- (C) Recovery of the fluorescent from the neighboring area is recorded as a function of time.
- (D) The half life of recovery is a function of diffusion constant.
- Recovered signal may be slightly lower than that of the original signal.
One Dimensional Model of FRAP

- Fluorescent molecules diffuse in a thin cylinder (e.g. inside *E.coli*) of length $2L$ ($-L < x < L$).
- Initial concentration of molecules is $c_0$ everywhere.
- After a short intense laser pulse, molecules in interval $-a < x < a$ are photobleached.
- Nonbleached molecules make their way into the box of size $2a$.

A) To compute the recovery curve, we need to define boundary conditions:

1) \[ \frac{\partial c}{\partial t} = D \frac{d^2 c}{dx^2} \quad \text{Diffusion Equation} \]

2) \[ c(x, 0) = \begin{cases} c_0 & -L < x < -a \\ 0 & -a < x < a \\ c_0 & a < x < L \end{cases} \quad \text{at } t = 0 \]

3) \[ \frac{\partial c}{\partial x} = 0 \quad \text{at } x = L \text{ and } x = -L \quad \text{no material flows in and out the box} \]

4) \[ c(x, t) = c(-x, t) \quad \text{concentration profile is symmetric} \]
B) Expand the concentration profile in cosine series

\[
c(x, t) = A_0(t) + \sum_{n=1}^{\infty} A_n(t) \cos\left(\frac{x}{L} n\pi\right)
\]

-boundary conditions are met:

1) \( \frac{\partial c}{\partial x} = 0 \) at \( x = L \) and \( x = -L \)  
\[
\sin(n\pi) = 0
\]

2) \( c(x, t) = c(-x, t) \)  
\[
\cos x = \cos(-x)
\]
C) Find $A_n(t)$

\[
\frac{\partial c}{\partial t} = D \frac{d^2 c}{dx^2} \quad \text{and} \quad c(x, t) = A_0(t) + \sum_{n=1}^{\infty} A_n(t) \cos \left( \frac{x}{L} n\pi \right)
\]

\[
\frac{\partial A_0(t)}{\partial t} + \sum_{n=1}^{\infty} \frac{\partial A_n(t)}{\partial t} \cos \left( \frac{x}{L} n\pi \right) = D \sum_{n=1}^{\infty} \left( -A_n(t) \frac{n^2 \pi^2}{L^2} \right) \cos \left( \frac{x}{L} n\pi \right)
\]

Due to orthogonal property of the cosine function for different $n$,

\[
\frac{\partial A_0(t)}{\partial t} = 0
\]

\[
\frac{\partial A_n(t)}{\partial t} = -\frac{Dn^2 \pi^2}{L^2} A_n(t)
\]

\[
A_n(t) = A_n(0) e^{-\frac{Dn^2 \pi^2}{L^2} t}
\]

Therefore \( c(x, t) = A_0(0) + \sum_{n=1}^{\infty} A_n(0) e^{-\frac{Dn^2 \pi^2}{L^2} t} \cos \left( \frac{x}{L} n\pi \right) \)
D) Find $A_n(0)$ at $t = 0$.

$$A_0(0) = \frac{1}{2L} \int_{-L}^{L} c(x, 0) dx = \frac{1}{2L} c_0 2(L - a) = c_0 \frac{L - a}{L}$$

$$A_n(0) = \frac{1}{2L} \int_{-L}^{L} c(x, 0) dx \cos \left( \frac{x}{L} n\pi \right) = -2c_0 \frac{\sin \left( \frac{a}{L} n\pi \right)}{n\pi}$$

E) Put everything together:

$$c(x, t) = c_0 \left[ \frac{L - a}{L} - 2 \sum_{n=1}^{\infty} \frac{\sin \left( \frac{n\pi a}{L} \right)}{n\pi} e^{-\frac{Dn^2 \pi^2}{L^2} t} \cos \left( \frac{n\pi x}{L} \right) \right]$$
when \( t \gg \frac{L^2}{D} \) which is half the diffusion time of molecules in a box of length \( L \)

\[ c = c_0 \left( 1 - \frac{a}{L} \right) \] concentration profile is uniform

The number of fluorescent molecules in the bleached region:

\[ N_f(t) = \int_{-a}^{a} c(x, t) \, dx \]

\[ N_f(t) = c_0 \left( 1 - \frac{a}{L} \right) 2a - 2c_0 L \sum_{n=1}^{\infty} \frac{\sin \left( \frac{n\pi a}{L} \right)}{n^2 \pi^2} e^{-\frac{Dn^2\pi^2}{L^2} t} \left[ \sin \left( \frac{n\pi a}{L} \right) - \sin \left( \frac{-n\pi a}{L} \right) \right] \]

\[ N_f(t) = c_0 \left( 1 - \frac{a}{L} \right) 2a - 4c_0 L \sum_{n=1}^{\infty} \frac{\sin^2 \left( \frac{n\pi a}{L} \right)}{n^2 \pi^2} e^{-\frac{Dn^2\pi^2}{L^2} t} \]

The model predicts that the recovery is fastest when \( a = L/2 \)
Biased Diffusion

- A force $F$ exerted on a particle results in a drift velocity:
  \[ F = \zeta v_{drift} \]

- The movement of particles under the same net $v_{drift}$ would generate a net flux:
  \[ j_F = \frac{1}{A\Delta t} \Delta N \]

  where $\Delta N$ is the number of particles moving under the drift velocity to right.

  \[ \Delta N = cA\Delta t \cdot v_{drift} \]

  \[ j_F = cv_{drift} = c \frac{F}{\zeta} \]

- We can write the total flux due to random diffusion and net movement under the drift velocity:

  \[ j(x) = -D \frac{dc}{dx} + \frac{F}{\zeta} c \]
\[ j(x) = -D \frac{dc}{dx} + \frac{F}{\zeta} c \]

In equilibrium, the net flux vanishes, \( J(x) = 0 \)

\[ D \frac{dc}{dx} = \frac{F}{\zeta} c \]

Nonuniform concentration gradient can be set up by force.

*using separation of variables, \( \zeta D \frac{dc}{c} = F dx \)*

\[ \zeta D = kT \text{ and } F = -dU/dx \]

\[ \frac{c(x)}{c(0)} = \frac{e^{-U(x)/kT}}{e^{-U(0)/kT}} \]
\[ j(x) = -D \frac{dc}{dx} + \frac{F}{\zeta} \]

Out of equilibrium,

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

\[
\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} - \frac{F}{\zeta} \frac{\partial c}{\partial x} \quad (\text{Nernst – Planck Equation})
\]

- Nernst – Planck Equation describes process that involve both external forcing and diffusion.
Pulse Equation under Bias

You release 1 billion molecules at position \( x = 0 \) in the middle of a narrow tube. The molecules, diffusion constant is 100 \( \mu m^2s^{-1} \). An electric field pulls the molecules to the right with drift velocity of 1 \( \mu m/s \). After 80s, what percentage of molecules will be on the left?

We learned that without bias, \( c(x, t) = \frac{1}{\sqrt{4\pi Dt}} e^{-x^2/4Dt} \) in one dimension.

In the presence of bias, the whole distribution of molecules shift to right

\[
\Delta x = v_{\text{drift}} t
\]

so, if we replace \( x \to x - v_{\text{drift}} t \) on the right hand side of the equation

\[
c(x, t) = \frac{1}{\sqrt{4\pi Dt}} e^{-(x-v_{\text{drift}} t)^2/4Dt}
\]
the number of molecules on the left, $N$:

$$N = 10^9 \int_{-\infty}^{0} c(x, t) dx = 10^9 \int_{-\infty}^{0} \frac{1}{\sqrt{4\pi Dt}} e^{-(x-v_{\text{drift}} t)^2 / 4Dt} dx$$

$$u = x - v_{\text{drift}} t / \sqrt{4Dt}$$

$$du = dx / \sqrt{4Dt}$$

$$x = 0 \Rightarrow u = -v_{\text{drift}} t / \sqrt{4Dt} = -z$$

$$z = \frac{1 \mu m s^{-1} 180 s}{\sqrt{4.100 \mu m^2 s^{-1} 1.80 s}} \approx \frac{80 \mu m}{125 \mu m} = 0.6$$

$$x = -\infty \Rightarrow u = -\infty$$

$$N = \frac{10^9 \sqrt{4Dt}}{\sqrt{4\pi Dt}} \int_{-\infty}^{-z} e^{-u^2} du$$
\[ N = \frac{10^9 \sqrt{4Dt}}{\sqrt{4\pi Dt}} \int_{-\infty}^{-z} e^{-u^2} \, du \]

This integral is equivalent to the complementary error function:

\[ \text{erfc}(z) = \frac{2}{\sqrt{\pi}} \int_z^\infty e^{-u^2} \, du \approx 1 - \frac{2}{\sqrt{\pi}} \left( z - \frac{z^3}{3.1!} + \frac{z^5}{5.2!} + \frac{z^7}{7.3!} \ldots \right) \text{ for small values of } z \]

since the function is symmetric, \( \int_z^\infty e^{-u^2} \, du = \int_{-\infty}^{-z} e^{-u^2} \, du \)

\[ N = \frac{10^9}{\sqrt{\pi}} \int_{-\infty}^{-z} e^{-u^2} \, du \approx \frac{10^9}{\sqrt{\pi}} \left[ \frac{\sqrt{\pi}}{2} - \left( z - \frac{z^3}{3.1!} + \frac{z^5}{5.2!} + \frac{z^7}{7.3!} \ldots \right) \right] \]

\[ N = \frac{10^9}{\sqrt{\pi}} \left[ \frac{\sqrt{\pi}}{2} - 0.53 \right] = 1.9 \times 10^8 \text{ molecules on the left} \]

only 19\% of molecules stay on the left.
The Role of Diffusion in Biological Reactions

- The cell membrane is uniformly decorated by receptor proteins.
- A signaling process depends on the arrival of ligand molecules and attachment to receptors.
- The spherical cell of radius $R$ is introduced into a solution with concentration $c_0$ at the far distance.
- We assume that the cell membrane is a perfect absorber, that concentration of ligand at the surface is 0.
- In a steady-state,

$$\frac{\partial c}{\partial t} = 0 = -\nabla j = D \nabla^2 c$$

in spherical coordinates

$$\nabla^2 c = \frac{1}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial c}{\partial r} \right) = 0$$

$$r^2 \frac{\partial c}{\partial r} = A \text{ (constant)}$$

$$\frac{\partial c}{\partial r} = \frac{A}{r^2} \Rightarrow c(r) = -\frac{A}{r} + B$$
\[ c(r) = -\frac{A}{r} + B \]

To find \( A \) and \( B \), we use the boundary conditions \( c(R) = 0, \ c(\infty) = c_0 \)

\[ c(r) = c_0 (1 - \frac{r}{R}) \]

The flux of particles is

\[ j(r) = -D \frac{\partial c}{\partial r} = -Dc_0 \frac{R}{r^2} \]

The number of particles arriving the cell membrane per unit time:

\[ \frac{dn}{dt} = -j(R)4\pi R^2 = 4\pi DRc_0 \]

4\( \pi DRc_0 \) introduces the upper limit the reaction can occur if it is only limited by diffusion.
The Role of Diffusion in Biological Reactions

• What if the receptors have a finite rate of $k_{on}$ in adsorbing ligands?
• The number of adsorbed ligands per unit time, where M is the number of receptors on the membrane:

$$\frac{dn}{dt} = Mk_{on}c(R)$$

similarly \( \frac{dn}{dt} = -j(R)4\pi R^2 \)

from mass conservation \( j(R)4\pi R^2 = j(r)4\pi r^2 \) where \( j(r) = -D \frac{\partial c}{\partial r} \)

$$Mk_{on}c(R) = D \frac{\partial c}{\partial r} 4\pi r^2$$

$$\int_{c(R)}^{c(r)} dc = \int_{R}^{r} \frac{Mk_{on}c(R)}{4\pi Dr^2} dr$$

$$c(r) - c(R) = \frac{Mk_{on}c(R)}{4\pi D} \left( \frac{1}{R} - \frac{1}{r} \right)$$

when \( r \to \infty \), \( c(R) = \frac{c_0}{1 + \frac{Mk_{on}}{4\pi DR}} \)
\[ c(R) = \frac{c_0}{1 + \frac{Mk_{on}}{4\pi DR}} \]

If \( \frac{Mk_{on}}{4\pi DR} \gg 1 \rightarrow c(R) = 0 \)

*If we have too many receptors with high on rate, we recover the perfect absorber limit*

If \( \frac{Mk_{on}}{4\pi DR} \ll 1 \rightarrow c(R) = c_0 \)

*Inversely, if we have very few receptors with low on rate,*

*Background concentration is not depleted at all.*
Question: How many receptors do we need to achieve the diffusion limit, half of \((4\pi DRc_0)\)?

\[
\frac{4\pi DRc_0}{2} = Mk_{on}c(R) = M \frac{k_{on}c_0}{1 + \frac{Mk_{on}}{4\pi DR}}
\]

\[
\frac{1}{2} = \frac{\beta}{1 + \beta} \text{ where } \beta = \frac{Mk_{on}}{4\pi DR}
\]

\[
\beta = 1 \text{ and therefore } M = \frac{4\pi DR}{k_{on}}
\]

Typical numbers:

\(R = 10 \ \mu m \text{ for eukaryotic cell}\)

\(D = 100 \ \mu m^2 s^{-1} \text{ for small ligands}\)

\(k_{on} = 10 \ \mu M^{-1} s^{-1}\)

therefore, \(M \approx 10^5\) receptors on a cell membrane.

The area of the membrane is roughly 1200 \(\mu m^2\)

The mean spacing between receptors, \(\sqrt{<d^2>} = 100 \ nm\)
Universal Rate for Diffusion Limited Chemical Reactions

We learned that \( \frac{dn}{dt} = 4\pi DRc_0 \) is the diffusion limit.

Assuming that two reacting species are of the same size (same \( D \)), they must be within \( 2R \) distance of each other.

The net diffusion constant for two diffusing particles will be \( 2D \)

using \( D = \frac{kT}{6\pi \eta R} \) and replacing \( R \) with \( 2R \), and \( D \) with \( 2D \)

we obtain \( k_{\text{diff}} = \frac{dn}{dt} = \frac{8kT}{3\eta} \)