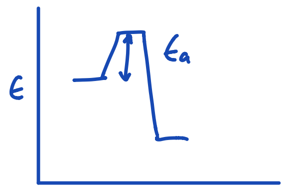
DIFFUSION: 11/25/19

RATES DEPEND ON ENERGY BARRIERS AND COLLISION RATE:

$k = A e^{-E_a/RT}$



WE'VE THOUGHT ABOUT E_a. WHAT ABOUT A?

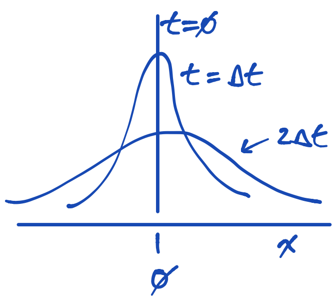
A IS DIFFUSION. HOW OFTEN DO MOLECULES COLLIDE?

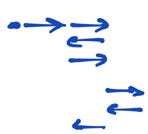
HOW CAN BIOLOGY CONTROL A?

- HIGHER CONCENTRATION PROMOTES MORE COLLISIONS.
- GEOMETRY:

	3D SEARCH SLOWER THAN	2D SLOWER THAN	1D
BIO CONTEXT	FLOATING IN THE CYTOSOL	EMBEDDED IN MEMBRANE	SEARCH ALONG A FILAMENT (DNA, CYTOSKELETON)

CONSIDER A PARTICLE THAT STARTS @ POSITION Ø, 1D:





CHARACTERIZE SPREAD BY THE MEAN SQUARED DISPLACEMENT.

$$MSD(t) = \frac{1}{N}\sum_{1}^{N}(x_n(t) - x_n(0))^2 = \langle (x_n(t)-x_n(0))^2 \rangle_n$$

STARTING POSITION OF PARTICLE "n"

UNITS OF ℓ^2

PARTICLES

POSITION OF PARTICLE "n" AT TIME t

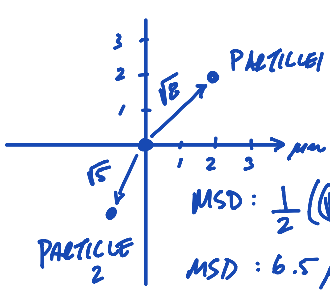
⟨⟩ DENOTES AVERAGE

ROOT-MEAN-SQUARED DISPLACEMENT

$RMS = \sqrt{MSD}$ ← AVERAGE DISTANCE TRAVELED.

UNITS OF ℓ

TWO PARTICLES, 2D:



P1 P2

$MSD: \frac{1}{2}\left((\sqrt{8}-0)^2 + (\sqrt{5}-\varnothing)^2\right)$

$MSD: 6.5\ \mu m^2$

$RMSD: 2.5\ \mu m$ ←

RELATE TO A RATE USING A DIFFUSION COEFFICIENT

$$MSD(t) = 2 \cdot n \times D \cdot t$$

n: NUM DIMENSIONS

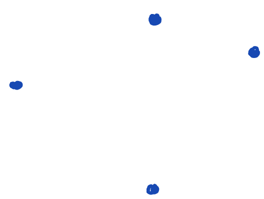
D: HOW FAST

t: HOW LONG

CAN NOW CALCULATE UPPER BOUNDS ON MOLECULAR REACTION RATES:

$A + B \rightarrow AB$

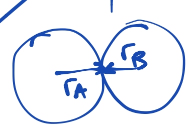
$$\frac{d[AB]}{dt} = k_{coll}[A][B]$$ ← FOR DIFFUSION-LIMITED REACTION, k IS GIVEN BY $k_{collision}$.



- IMAGINE PARTICLES EVENLY DISTRIBUTED OVER VOLUME.
- DENSITY IS GIVEN BY [A] AND [B].
- WHAT IS RATE OF COLLISION?

$$k_{coll} = 4\pi(r_A + r_B)(D_A + D_B) \times \underbrace{6.022 \times 10^{20}}_{M^{-1} \cdot cm^{-3}} \quad (M^{-1} s^{-1})$$

$(r_A + r_B)$: cm



$(D_A + D_B)$: RATE OF DIFFUSION BY PARTNERS $(cm^2 \cdot s^{-1})$

RELATE TO PHYSICAL PROPERTIES OF SYSTEM USING STOKES-EINSTEIN:

$$D = \frac{k_B T}{6\pi \eta r}$$

r: RADIUS OF PARTICLE

η: VISCOCITY

(ASIDE: YOU CAN MODEL GEOMETRY IN MUCH MORE SOPHISTICATED WAYS.)

A nucleotide exchange factor (GEF) catalyzes the exchange of GDP and GTP for Ras:

$$Ras \cdot GDP + GTP \rightleftarrows Ras \cdot GTP + GDP.$$

This reaction occurs $\approx$ 300-fold faster when Ras and the GEF are membrane-associated versus free in solution. We are going to explore why this is the case.

The following relationship will help you with this analysis:

$$rms_x = \sqrt{2xDt}$$

where rms is the average root-mean-displacement after time t, x is the dimensionality of the diffusion (1, 2, 3, etc.) and D is the diffusion coefficient.

Some other helpful facts:

- The cell is spherical and has a diameter of 100 μm. This means:

$$volume \approx 500 \times 10^{-15}\ m^3 \quad V = 500\times10^{-15}\ m^3/600{,}000 = 8E{-}19\ m^3/\text{molec}$$

$$area = 314 \times 10^{-10}\ m^2 \quad A = 314\times10^{-10}\ m^2/600{,}000 = 5E{-}14\ m^2/\text{molec}$$

- There are $\approx 300,000$ molecules each of Ras and GEF per cell.

Questions:

1. What are some possible explanations for the observation that the reaction occurs faster on the membrane rather than in solution?
   - LESS SEARCH SPACE
   - HIGHER CONCENTRATION
2. Work the solution case first. The observed diffusion coefficient for each molecule in water is: $D = 10^{-8} cm \cdot s^{-1}$.

   $V = \frac{4}{3}\pi r^3 \quad r = \left(\frac{3 \cdot V}{4 \cdot \pi}\right)^{1/3} = 5.8\ E{-}7\ m$

   (a) What is x? 3 → DIFFUSING IN VOLUME

   (b) What is the distance between two molecules (on average)? $2 \times r = \boxed{1.2 \times 10^{-6}\ m}$

   (c) What is the average time until collision? (You may assume this occurs when the rms distance is 1/2 of the starting value.) COLLIDE @ $0.6 \times 10^{-6}\ m$

   $RMS^2/(2 \cdot 3 \cdot D) = t = \boxed{5.7\ \mu s}$
3. Work the membrane case next. The observed diffusion coefficient for each molecule in a membrane is: $D = 10^{-9} cm \cdot s^{-1}$. (It is slower than water because bulky lipids have to move out of the way).

   $A = \pi r^2 \quad r = \left(\frac{A}{\pi}\right)^{1/2} = 1.3\ E{-}7\ m$

   (a) What is x? 2 → DIFFUSING ON PLANE

   (b) What is the distance between two molecules (on average)? $2 \times r = \boxed{2.6 \times 10^{-7}\ m}$

   (c) What is the average time until collision? (You may assume this occurs when the rms distance is 1/2 of the starting value.) COLLIDE @ $1.3E{-}7\ m$

   $RMS^2/(2 \cdot 2 \cdot D) = \boxed{4.2\ \mu s}$
4. Does the difference in diffusion on the membrane explain the fold speed up? If not, what other factors may be at play?

   NO. MAYBE BEING ON MEMBRANE CAUSES HIGHER FRACTION OF PRODUCTIVE COLLISIONS?