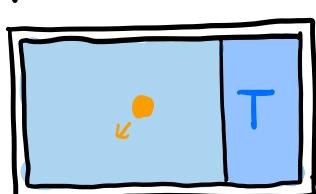
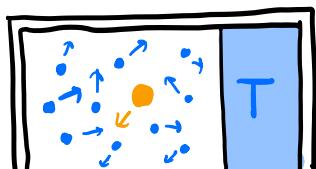


Announcements

- ① Advance copy of notes on Canvas
- ② Optional practice problems for Week 3 posted
- ③ Week 3 reflections due Sat midnight

Last time:

Brownian Motion / Diffusion



Motion under constant thermal collisions:

$$\Delta v = - \frac{\gamma}{m} \cdot v \cdot \Delta t + \Delta v_{\text{random}}$$

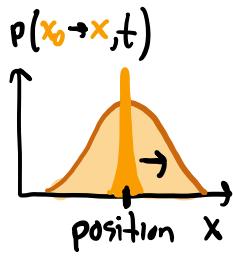
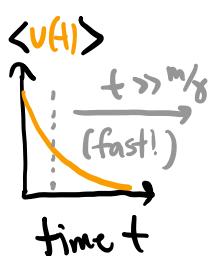
$\underbrace{}_{\text{Effective "Drag"}}$ $\underbrace{}_{\text{Random "kicks"}}$

1. Motion of single particle

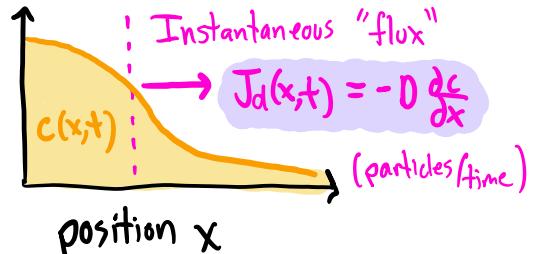
$$p(x \rightarrow x, t) \approx \frac{1}{\sqrt{4\pi D t}} e^{-\frac{(x-x_0)^2}{4Dt}}$$

2. Diffusion of concentration

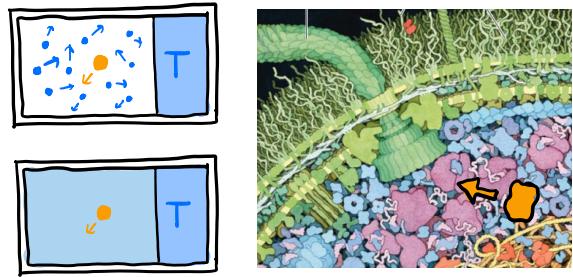
$$\frac{\partial c}{\partial t} = \frac{\partial}{\partial x} \left[D \frac{\partial c}{\partial x} \right]$$



Einstein Rel'n
 $D = kT/\gamma$



* Derived for simple model
but dynamics very general!
(must measure γ or D)



→ e.g. Stokes law: $\gamma = 6\pi\eta a$

* Straightforward to extend to $d=3$ dimensions:

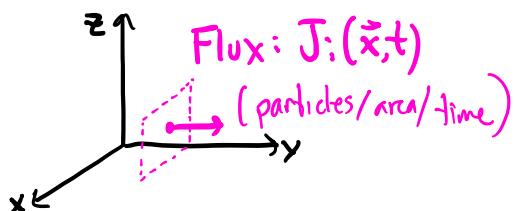
1. Motion of single particle

$$\rho(\vec{x}_0 \rightarrow \vec{x}, t) \approx \prod_{i=1}^d \frac{e^{-\frac{-(x_i - x_{0i})^2}{4Dt}}}{\sqrt{4\pi Dt}}$$

Einstein Relation: $\gamma D = kT$

2. Diffusion of Concentration

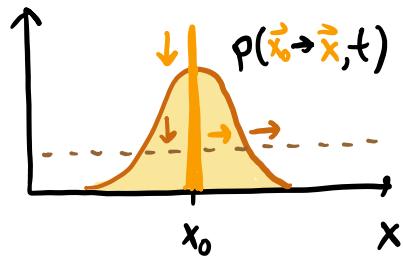
$$\frac{\partial c}{\partial t} = - \sum_{i=1}^d \frac{\partial}{\partial x_i} \left[-D \frac{\partial c}{\partial x_i} \right]$$



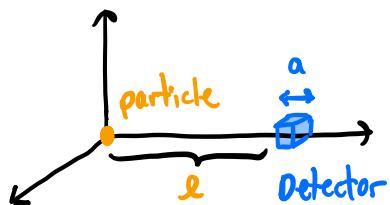
+ Rotational Diffusion ($\langle \dot{\theta}(t)^2 \rangle = 2D_\theta t$), etc.

Today: How do we interpret these results?
What constraints do they impose on biology?

Diffusion as concentration equalizer



Today: diffusion as a transport or signaling process



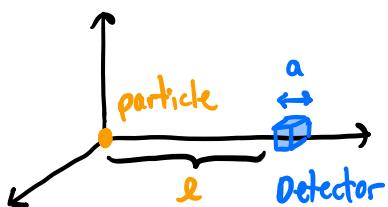
If $a \ll l$:

$$P_{\text{detect}}(t) \propto a^d \cdot \rho(\vec{x}_0 \rightarrow \vec{x}_0 + l \hat{x}, t)$$

$$\Rightarrow P_{\text{detect}}(t) = \frac{a^d}{(4\pi D t)^{d/2}} e^{-\frac{l^2}{4Dt}} \quad (d=1,2,3)$$

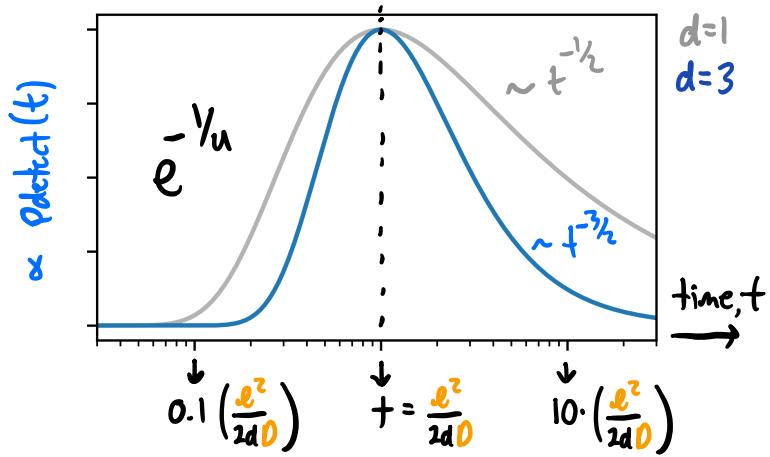
* What does this look like as function of time?

\Rightarrow useful to change variables: $f \equiv \frac{l^2}{D} \cdot u$

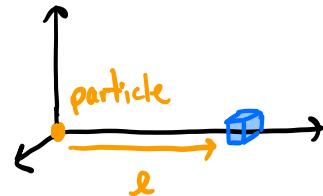


$$P_{\text{detect}}(t = \frac{l^2}{D} u) = \left(\frac{a}{l}\right)^d \cdot \frac{e^{-\frac{1}{4u}}}{(4\pi u)^{d/2}}$$

"Universal" form:



\Rightarrow Diffusion timescale $\tau_d = \ell^2 / D$
 *** required to travel distance ℓ



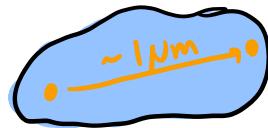
- \Rightarrow increases w/ ℓ (farther distance ✓)
- decreases w/ D (faster thermal motion ✓)
- \Rightarrow but grows as ℓ^2 ! [compare to $\Delta t = \ell / v$]
- \Rightarrow will lead to some counter-intuitive behavior...

Examples of diffusion timescales:

$$\tau_d \sim \frac{e^2}{D}$$

① Diffusion of small molecule

(e.g. glucose / ATP) w/in E. coli cell



$$\Rightarrow \text{measured } D \approx (10 \text{ nm})^2/\text{s}$$

$$\Rightarrow \tau_d = \frac{(1 \text{ nm})^2}{(10 \text{ nm})^2/\text{s}} = \frac{1}{10^2} \text{ s} = 0.01 \text{ s}$$

② Diffusion of protein w/in E. coli Cell $[D \approx (3 \text{ nm})^2/\text{s}]$

$$\Rightarrow \tau_d = \frac{(1 \text{ nm})^2}{(3 \text{ nm})^2/\text{s}} = \frac{1}{9} \text{ s}$$

\Rightarrow But things change quickly if we increase ℓ ...

③ Eukaryotic cells \Rightarrow small molecules:

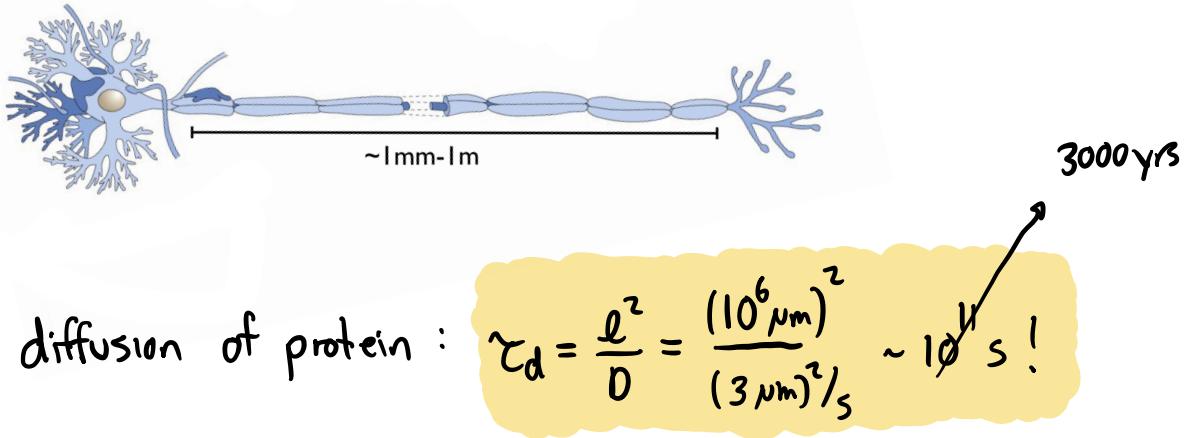
$$\tau_d \sim 1 \text{ s}$$

$(\ell \sim 10 \text{ nm})$

proteins:

$$\tau_d \sim 10 \text{ s}$$

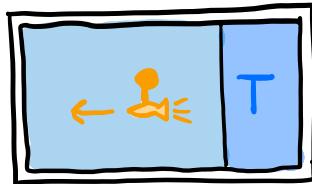
④ Extreme case: human motor neuron:



Problem: most proteins synthesized near nucleus...

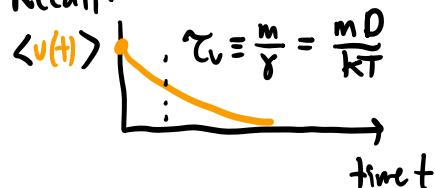
⇒ How does cell transport them across axon?

Answer: needs active transport
(i.e. use energy)



⇒ but not so easy in face of thermal noise ...

Recall:



⇒ initial velocity forgotten after distance:

$$\Delta x \sim v_0 \cdot \tau_v \sim v_0 m D / kT$$

\Rightarrow need to replenish velocity ($v = 0 \rightarrow v = v_0$) every Δx :

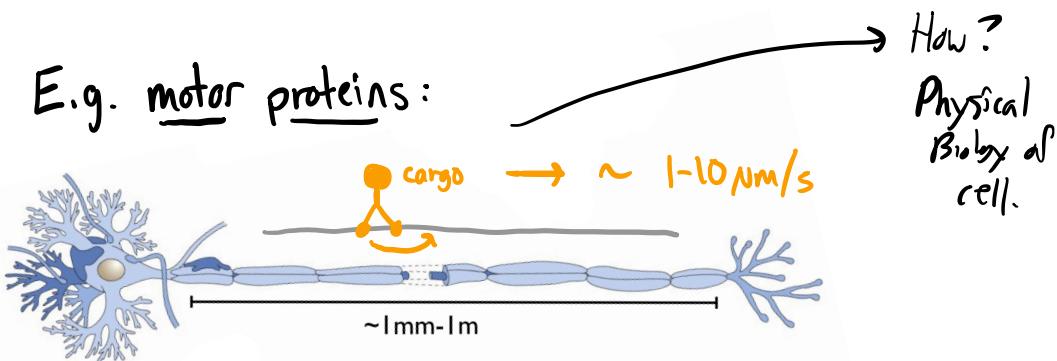
$$\Rightarrow \text{requires energy } \Delta E = \frac{1}{2} m v_0^2 \sim m v_0^2$$

\Rightarrow Energy required per distance:

$$\frac{\Delta E}{\Delta x} \sim \frac{m v_0^2}{\frac{v_0 D}{kT}} = \frac{v_0}{D} kT = \frac{v_0}{20 \cdot D} (70 kT)$$

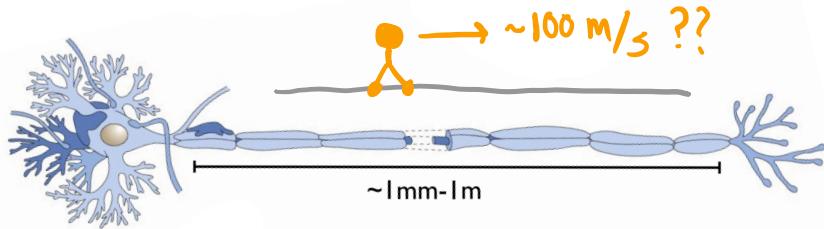
↑ ATP

\Rightarrow Energy costs increase w/ v_0 !



$$\Rightarrow \frac{3 \text{ Nm}}{\text{s}} = \frac{3 \text{ Nm}}{\text{s}} \times \frac{1 \text{ cm}}{10^4 \mu\text{m}} \cdot \frac{10^5 \text{ s}}{\text{day}} \approx 30 \text{ cm/day}$$

Question: what if you wanted to send signal as fast as an action potential?

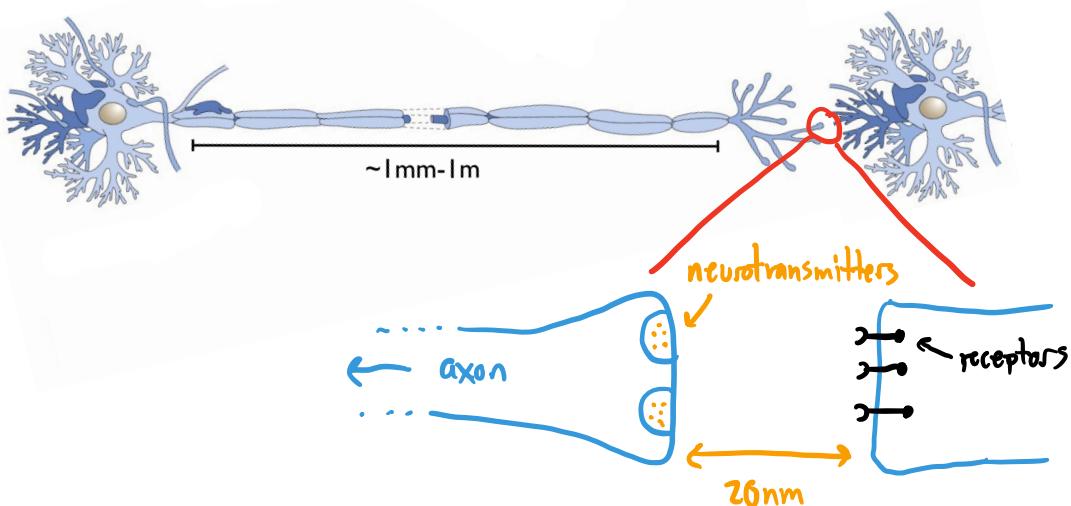


$$\begin{aligned} \text{total ATP required} &= \frac{V_o}{200} \cdot \Delta x = \frac{(100 \text{ m/s}) \cdot 1 \text{ m}}{20 \cdot (3 \mu\text{m})^2 / \text{s}} = 5 \times 10^{11} \text{ ATP} \\ &\quad \downarrow \text{100x larger} \end{aligned}$$

\Rightarrow But typical cells only contain $\sim 5 \times 10^9$ ATPs!

\Rightarrow need some other solution (e.g. bioelectricity)

⑤ Diffusion of neurotransmitters @ synapses

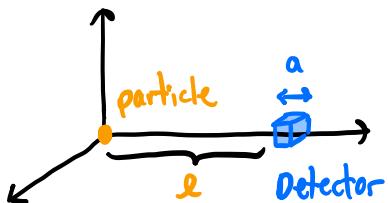


e.g. acetylcholine:
(small molecule) $D \sim (20\text{ nm})^2/\text{s}$

$$\Rightarrow \tau_d \sim \frac{l^2}{D} \sim \frac{(20\text{ nm})^2}{(20\text{ nm})^2/\text{s}} = (10^{-3})^2 \text{ s} = 10^{-6} \text{ s}$$

\Rightarrow actual time is $\sim 10^3 \text{ s}$... what sets this?

Diffusion-to-capture



so far, focused on time required
for signal to travel via diffusion...

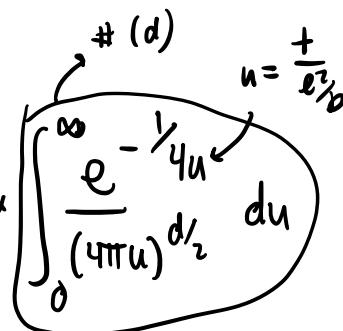
\Rightarrow but physics of diffusion also limits
probability that particle is detected ("captured")

total
probability
of detection

$$\propto \int_0^\infty$$

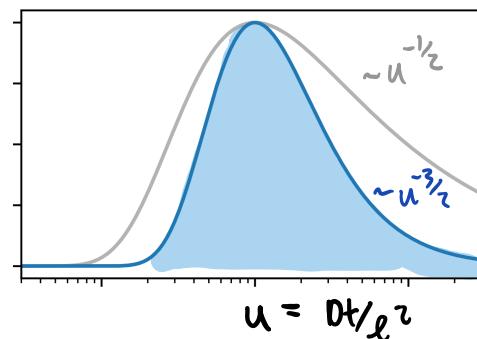
$$P_{\text{detect}}(t) dt$$

$$= \left(\frac{a}{x}\right)^d \frac{x^2}{D} \times \int_0^\infty \frac{e^{-\frac{1}{4}u}}{(4\pi u)^{d/2}} du$$



in 1D: integral diverges $\left(\int_0^\infty \frac{du}{u^{1/2}}\right)$

in 3D: integral converges $\left(\int_0^\infty \frac{du}{u^{3/2}}\right)$
to finite #

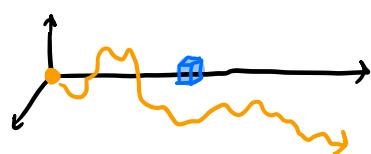


\Rightarrow in 3d, finite chance that particle is never captured!

$$p \sim \frac{a}{x}$$

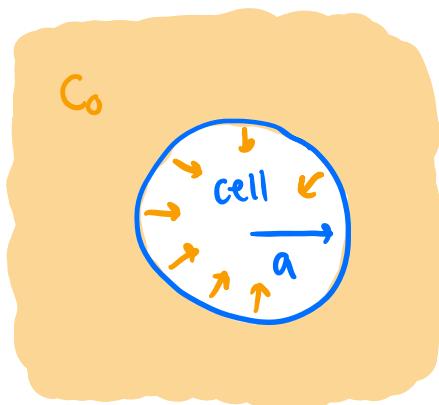
3d

(exact probability worked out
in supplemental note below)



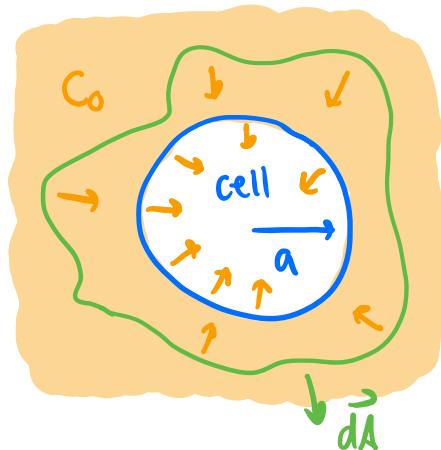
\Rightarrow imposes fundamental limits on rate @ which cells (or other 3d region) can capture particles through diffusion

\Rightarrow can illustrate w/ simple model:



- ① cell is sphere of radius a
- ② in concentration field $c(\vec{x}) \rightarrow C_0$
 $(|\vec{x}| \gg a)$
- ③ Takes up particles @ total rate R (particles/time)

\Rightarrow by conservation of mass, total particles through any other shape containing cell must also be = R



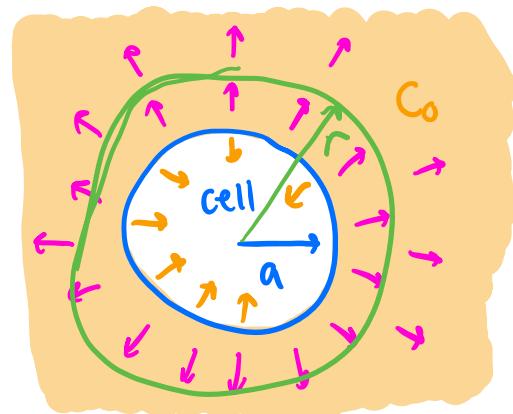
\Rightarrow can express in terms of flux: (particles per area per time)

$$\oint \vec{J}(\vec{x}) \cdot \vec{dA} = -R$$

integrate over surface area

\Rightarrow spherical symmetry implies
that $\vec{J}(\vec{x}) = J_r(r) \cdot \hat{r}$

$$\Rightarrow 4\pi r^2 J_r(r) = -R$$



+ Fick's law: $J_r(r) = -D \frac{dc(r)}{dr}$

$$\Rightarrow \frac{dc(r)}{dr} = -\frac{J_r(r)}{D} = \frac{R}{4\pi D r^2}$$

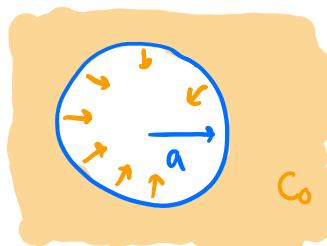
Solution: $c(r) = \text{const} - \frac{R}{4\pi D r} = C_0 - \frac{R}{4\pi D r} = C_0 \left(1 - \frac{R}{4\pi D C_0 r}\right)$

Since $c(r) \geq 0$ for $r \geq a$

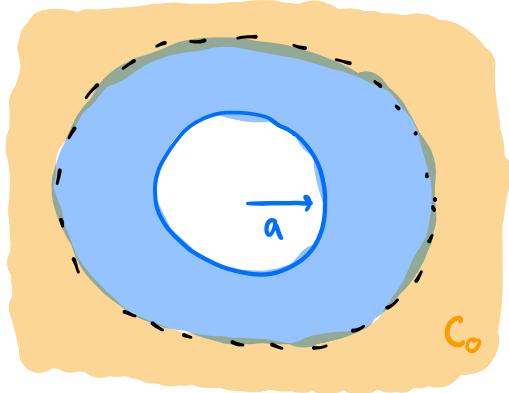
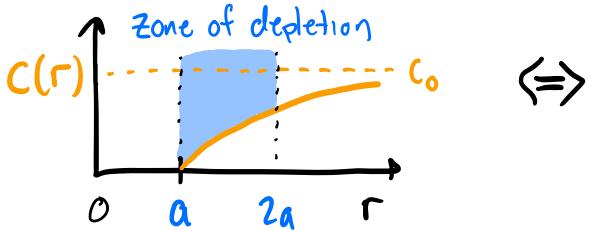
$$\Rightarrow R \leq R_{\max} = 4\pi D a C_0$$

** Universal "speed limit" on capture

of particles via diffusion in 3d



\Rightarrow when $R = R_{\max}$, $C(r) = C_0 \left(1 - \frac{a}{r}\right)$



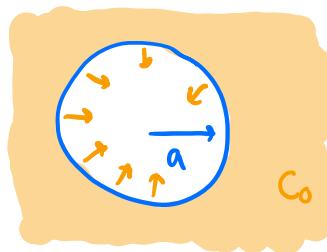
Intuition:

- ① $\sim C_0 a^3$ particles in depletion zone
- ② diffusion time $\sim a^2/D$

$$\Rightarrow R_{\max} = \frac{\text{particles}}{\text{time}} \sim \frac{C_0 a^3}{a^2/D} = D C_0 a$$

\Rightarrow increases w/ C_0, D, a

\Rightarrow but scales linearly in a
(as opposed to surface area $\propto a^2$)



→ 2 alternative derivations
in supplemental notes...

\Rightarrow Lots of applications!

① Limits on cell size / tissue architecture

Question: Could human brain be implemented as single cell w/ same size/shape?



Let's focus on energy requirements:

① Brain needs ~ 300 calories per day

$$R = \frac{300 \text{ cal}}{\text{day}} \cdot \frac{1 \text{ g sugar}}{4 \text{ cal}} \cdot \frac{1 \text{ day}}{10^5 \text{ s}} \sim 10^{-3} \text{ g sugar/s}$$

② How much can import @ speed limit $R_{\max} \sim 4\pi D_a C_o$?



$$① a \sim 20 \text{ cm}$$

$$② D_{\text{sugar}} \sim \frac{(20 \text{ nm})^2}{5} \approx 5 \times 10^{-6} \text{ cm}^2/\text{s}$$

$$③ \text{Blood } C_o - \frac{1 \text{ g sugar}}{L} \sim 10^{-3} \text{ g/cm}^3$$

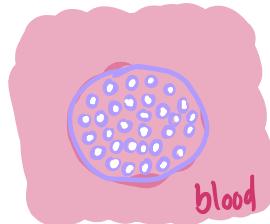
1000x smaller.

$$\Rightarrow R_{\max} \sim 4\pi \times (5 \times 10^{-6} \text{ cm}^2) \times (20 \text{ cm}) \times \left(\frac{10^{-3}}{\text{cm}^3}\right) = 10^{-6} \text{ g sugar/sec.}$$

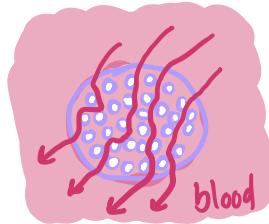
⇒ 3 orders of magnitude too small!

⇒ what do organisms do instead??

⇒ multicellularity?



⇒ need active transport
(e.g. blood circulation)

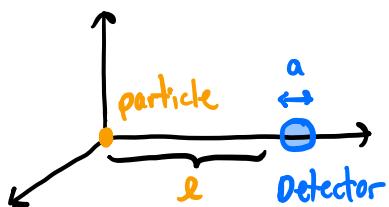


Supplemental Note: Diffusion hitting probability in 3d

To gain intuition for the speed limit $R_{\max} = 4\pi D a C_0$, will be helpful to explicitly calculate probability that single particle diffuses to region distance l away.

Will do this in two ways:

① Integrating $P_{\text{detect}}(t)$ over time.



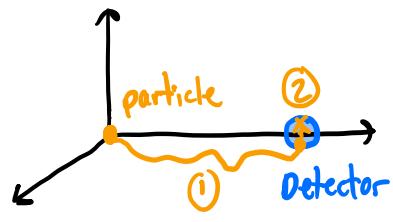
\Rightarrow In limit of low detection rate, we argued above that

$$P(\text{detect}) = \int P_{\text{detect}}(t) dt \propto \frac{a^3}{0l}$$

\Rightarrow can break detection into two stages:

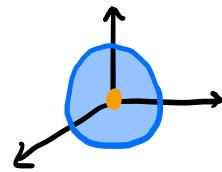
① particle reaches detector region

② particle is detected
after entering detector region



$$\Rightarrow \rho(\text{detect}) = \rho(\text{detect} | \text{reaches detector}) \rho(\text{reaches detector})$$

\Rightarrow we can calculate
by considering related
detection problem:



$$\rho(\text{detect} | \text{reaches detector}) \propto \int_{\text{detector}} dx dy dz dt \frac{1}{(4\pi D t)^{3/2}} e^{-\frac{x^2 + y^2 + z^2}{4Dt}}$$

$$\propto \int_0^a 4\pi r^2 dr \int_0^\infty dt \frac{1}{(4\pi D t)^{3/2}} e^{-\frac{r^2}{4Dt}}$$

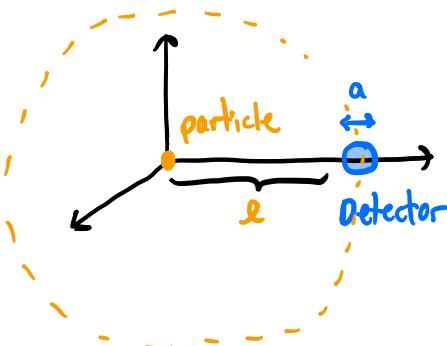
$$\Rightarrow \text{change of variables: } r = av, t = \frac{a^2}{D} u$$

$$p(\text{detect} \mid \text{reaches detector}) \propto \frac{a^2}{D} \cdot \underbrace{\left[\int_0^1 4\pi v^2 dv \int_0^\infty \frac{du}{(4\pi u)^{3/2}} e^{-v^2/4u} \right]}_{\text{just a constant}}$$

Combining these results, we have:

$$p(\text{reaches detector}) \propto \frac{p(\text{detect})}{p(\text{detect} \mid \text{reaches detector})} \propto \frac{\frac{a^3}{Dl}}{\frac{a^2/D}{D}} \propto \frac{a}{l}$$

$$\Rightarrow \text{Hitting probability} \propto \frac{a}{l}$$



Note: scales like ratio of

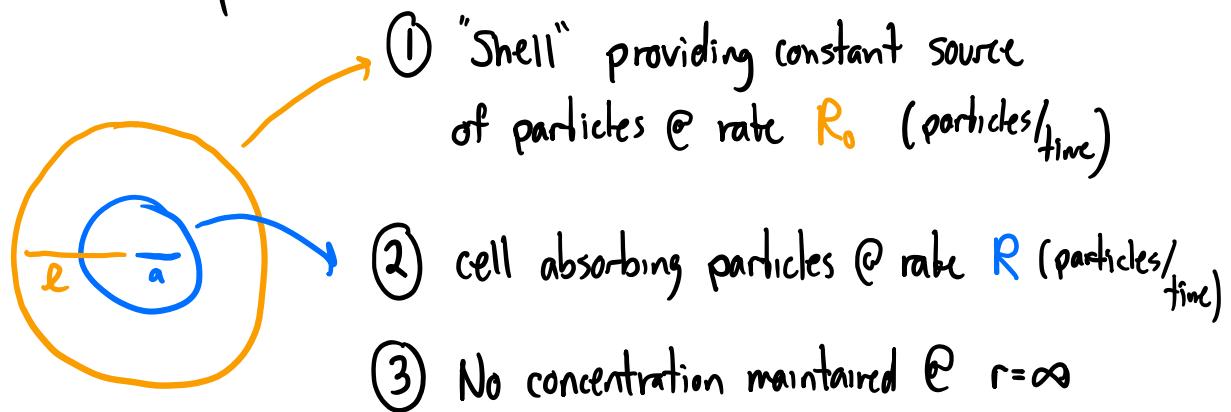
linear dimensions (a, l)

rather than ratio of surface areas ($\propto a^2, l^2$)

② Solving diffusion equation

we can also derive this result exactly
using a variant of the "Gauss's law"
approach we used to calculate $R_{\max} = 4\pi D a C_0 \dots$

Basic setup :



Solution : $\rho(\text{captured}) \equiv \frac{R}{R_0} \leq \frac{R_{\max}}{R_0} = \frac{a}{l}$

(exercise for reader — Hint: consider flux through spheres inside + outside shell)

Heuristic derivation of limit to capture rate

⇒ we can use the hitting probability above to obtain a "heuristic" derivation of $R_{\max} \sim D a c_0$
(valid in the limit of low concentrations)

① A volume of radius ℓ contains $\sim c_0 \ell^3$ particles

⇒ closest particle to detector has $\ell^* \sim c_0^{-\frac{1}{3}}$

② This particle has probability $\sim \frac{a}{\ell^*}$
of hitting our detector

③ Will reach detector on timescale $\sim \frac{\ell^{*2}}{D}$

$$\Rightarrow R_{\max} \sim \frac{1 \text{ particle} \cdot \frac{a}{\ell^*}}{\frac{\ell^{*2}}{D}} \sim \frac{D a}{\ell^{*3}} \sim D a c_0 \quad \checkmark$$

⇒ shows that linear scaling of R_{\max} emerges from linear scaling of hitting probability in 3D

\Rightarrow technically, this argument only applies for short times...

\Rightarrow @ longer times, total # of captured particles is

$$N(t) \sim \int_0^{\Theta(\sqrt{Dt})} 4\pi r^2 dr \cdot c_0 \cdot \frac{a}{r}$$

maximum radius that can reach detector in time t

total # of particles in shell @ distance r

probability that reaches detector

$$\Rightarrow R_{\max} \approx \frac{N(t)}{t} \sim \frac{D \cdot a \cdot c_0 \cdot t}{t} \sim D \cdot a \cdot c_0 \quad \checkmark$$

\Rightarrow this argument shows why limits on capture rate only exist for $d \geq 3$

[Hint: try setting $\rho_{hit}=1$ in integral above]

Limits to capture rate via dimensional analysis

we can also obtain the maximum capture rate almost "for free" using dimensional analysis.

\Rightarrow capture rate R has units of particles/time.

\Rightarrow if a maximum capture rate exists,
we know it can only depend on:

① detector size a [units: length]

② diffusion constant D [units: length²/time]

③ external concentration C_0 [units: particles/length³]

\Rightarrow the only way to combine these 3 quantities to obtain same units as R is $R_{\max} \propto D \cdot a \cdot C_0$ ✓

\Rightarrow shows that linear scaling in a is tied to length² units of diffusion constant D

\Rightarrow however, this argument doesn't give much insight into the role of 3D space.

\Rightarrow e.g. same dimensional analysis can be done for $d=1, 2$:

$$\Rightarrow d=1: R_{\max} \propto D_{C_0} / a \quad / \quad d=2: R_{\max} \propto D_{C_0}$$

\Rightarrow but in both cases we know that $R_{\max} = \infty$!

\Rightarrow shows that existence of finite R_{\max} was crucial assumption, which is hard to obtain from dimensional analysis alone...