Physics of cell sensing

Boulder lectures, Andrew Mugler, July 2019

Cells are amazing sensors:

- Some cells (rod cells, immune cells, olfactory cells) can sense single molecules
- Amoebae can detect a difference of about 10 molecules from front to back

✡ Are cells as good at sensing as they are ever going to get? What is the limit?

You might worry that you need to know a lot of biology (receptors, internal signaling, mechanics, etc) to answer this. But in fact we will see that we can go a long way with simple models and basic physics.

✡ Ultimately, biological performance is constrained by the physics of molecules in the environment.

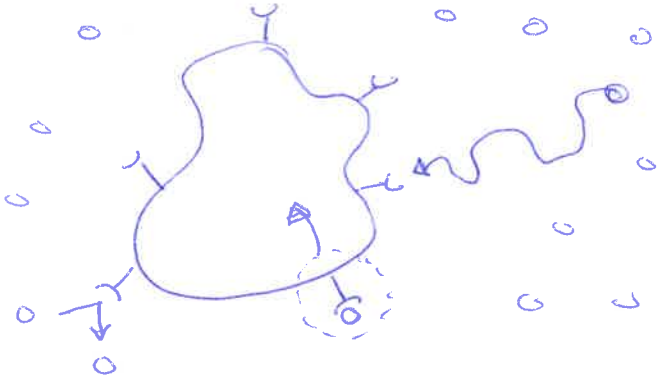
→ I will take a historical approach (1977 → present)

→ We will go deep on some math, but ultimately stay grounded with experiments.

Outline:

- Single cell sensing
  - Uniform concentration — Berg, Purcell, 1977
    - The perfect sink
    - The "perfect instrument"
    - Receptor binding
    - Experiments on bacteria
  - Concentration gradient — Endres, Wingreen, 2008
    - The perfect sink
    - Experiments on amoeba
- Multicellular sensing
  - Experiments on fly embryos — Gregor, Bialek, 2007 →
  - Uniform concentration — My work, et al 2016 →
    - Short-range communication
    - Long-range communication
  - Concentration gradient
    - Short-range communication
    - Experiments on mouse tissue
- Concluding remarks, state of the field, etc.

How does a single cell detect a uniform chemical concentration in its environment?



- Molecules diffuse, bind to receptors
- Receptors change conformation or are internalized
- This leads to further chemical reactions (signal cascade) inside the cell, leading to a response.

Berg + Purcell (1977) considered several simplified models of this to ask: how accurate is the detection process?

(I) Dimensional analysis

- Imagine the "real" background concentration is c_0.
- The cell will detect individual molecules and try to get an estimate, $\hat{c}$.
- There will be error, $\sigma_{\hat{c}}$.
- On what properties should the fractional error, $\sigma_{\hat{c}}/\langle\hat{c}\rangle$, depend?

a. Size of cell → lengthscale, a

b. Amount of molecules → concentration, c_0.

c. How fast the molecules come → diffusion D

d. How long the cell waits → time, T

All of these things should decrease error:

$$\frac{\sigma_{\hat{c}}}{\langle \hat{c} \rangle} \sim \frac{1}{a^x c_0^y D^z T^w}$$

$$[a] = m \,, \quad [c_0] = \frac{1}{m^3} \,, \quad [D] = \frac{m^2}{s} \,, \quad [T] = s$$

need $DT \Rightarrow w = z$

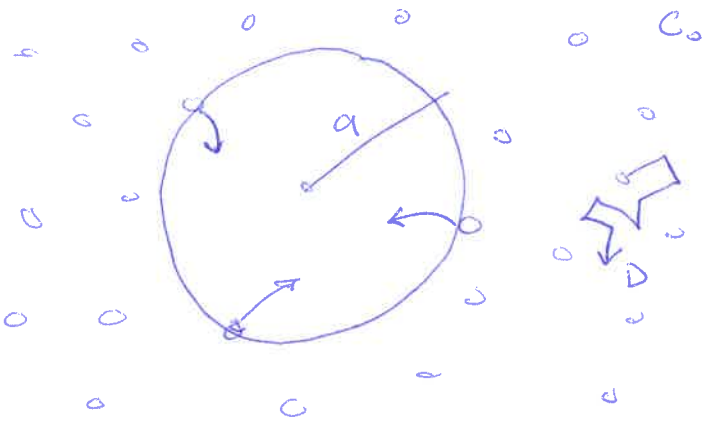
Need $x - 3y + 2z = 0 \Rightarrow x = 3y - 2z$

$$\Rightarrow \boxed{\frac{\sigma_{\hat{c}}}{\langle \hat{c} \rangle} \sim \frac{1}{a^{3y-2z} c_0^y (DT)^z}}$$

for some $y, z \ldots$

(II) The "perfect sink"

Idealize the cell as a sphere that absorbs all molecules that come in contact with it



- In a time T, let the number of molecules absorbed be n_T.

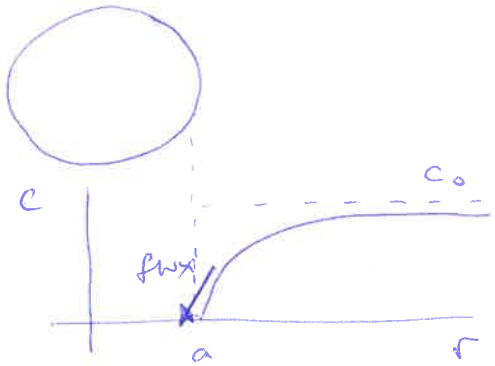
- This number serves as the cell's estimate of c_0,

ie. $n_T \propto \hat{c}$, and $\frac{\sigma_{n_T}}{\bar{n}_T} = \frac{\sigma_{\hat{c}}}{\langle \hat{c} \rangle}$

- The noise σ_{n_T} comes from the fact that diffusion is a Poisson process $\Rightarrow \sigma_{n_T} = \sqrt{\bar{n}_T}$

$$\Rightarrow \frac{\sigma_{\hat{c}}}{\langle \hat{c} \rangle} = \frac{1}{\sqrt{\bar{n}_T}}$$

- So what is $\bar{n}_T$, the mean number of molecules absorbed in time T? We solve the diffusion problem for $c(\vec{x}, t)$: $\dot{c} = D\nabla^2 c$



- We ~~know~~ care only about steady state: $\dot{c} = 0$

- We know $c(r, \theta, \phi) = c(r)$ by symmetry.

$$0 = \nabla^2 c = \frac{1}{r^2}\partial_r\left(r^2 \partial_r c\right) + \text{(0, } \phi \text{ terms)}$$

$$\Rightarrow r^2 \partial_r c = \text{const.} = A \Rightarrow \frac{dc}{dr} = \frac{A}{r^2}$$

$$\Rightarrow c(r) = B - \frac{A}{r}$$

Boundary condition 1: $c(r \gg a) = c_0$

Boundary condition 2: $c(a) = 0$ (perfect absorption.)

- on average, we expect $\bar{n}$ to scale with c_0.

Therefore, we can think of n as, the cell's estimate $\hat{C}$. proportional to

BC 2: $c(a) = B - \frac{A}{a} = 0 \Rightarrow B = \frac{A}{a}$

$$c(r) = \frac{A}{a} - \frac{A}{r} = \frac{A}{a}\left(1 - \frac{a}{r}\right)$$

BC 1: $c(r >> a) = \frac{A}{a} = c_0$

$$\boxed{c(r) = c_0\left(1 - \frac{a}{r}\right)}$$

Inward flux at surface is $j = D\partial_r c|_a$

(# molecules per area per time)

$$j = D\left[+\frac{c_0 a}{r^2}\right]_a = \frac{D c_0}{a}$$

Total # of molecules in time T ($\bar{n}_T$) is:

$$\bar{n}_T = T \times 4\pi a^2 \times j = 4\pi a D c_0 T$$

Thus, $$\boxed{\frac{\sigma_{\hat{c}}}{\langle \hat{c} \rangle} = \frac{1}{\sqrt{4\pi a D c_0 T}}}$$ perfect smk.

☆ Consistent w/ dimensional analysis, with $y = z = \frac{1}{2}$

(III) The "perfect instrument"

Of course, not all receptors internalize the molecules. Some just bind them and release them back into the environment.

Berg + Purcell idealized this as a sphere that is permeable to the molecules but still counts them.

We can first get a rough estimate of the statistics:

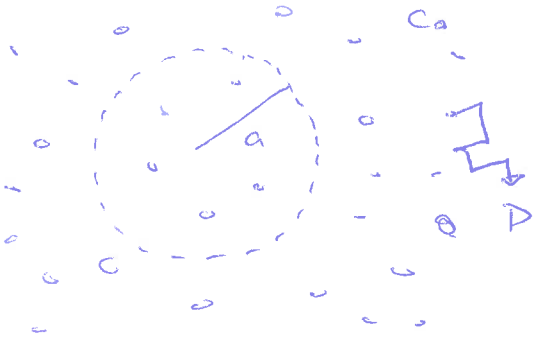
- At any moment the mean # inside is $\bar{n} \sim c_0 a^3$
- This number has Poisson noise: $\sigma_n^2 \sim c_0 a^3$
- But the cell can wait for a new batch of molecules to be "refreshed" by diffusion, the timescale for which is $\sim a^2/D$
- Thus, in a time T, the cell can make $\frac{T}{a^2/D}$ independent measurements, reducing the variance as $\sigma_{\hat{c}}^2 = \frac{c_0 a^3}{T/(a^2/D)} = \frac{c_0 a^5}{DT}$
- Thus, we expect

$$\frac{\sigma_{\hat{c}}}{\langle \hat{c} \rangle} \sim \frac{\sigma_n}{\bar{n}} \sim \sqrt{\frac{c_0 a^5}{DT c_0^2 a^6}} \sim \frac{1}{\sqrt{DT c_0 a}}$$

★ Same scaling! Same physics governs perfect sink and perfect instrument.

→ What is the prefactor? Can we be more exact?

Berg + Purcell idealized this as a "monitor" that is permeable to molecules but still counts them.



- Again we take as our estimator n_T, the # counted in time T, and $\frac{\sigma_\epsilon}{\langle \bar{c} \rangle} = \frac{\sigma_{n_T}}{\bar{n}_T}$

- We will analyze the perfect instrument in detail because it will set up techniques that we will use later for multicellular sensing.

- We cannot use a flux argument as before, since there are fluxes both in and out of the cell

- B+P used the autocorrelation function

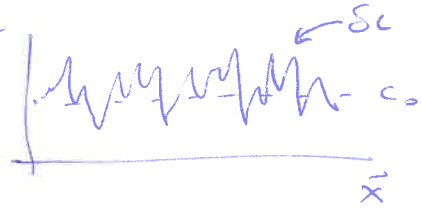
- Here we will use the powerful tool of Langevin dynamics.

The idea is to endow the diffusion equation with a stochastic noise term to account for the actual particulate nature of the molecules:

$$\dot{c} = D\nabla^2 c + \eta$$ ← noise -- we will give its properties later.

- Because of η, the solution c will have fluctuations on top of the uniform background:

$$c(\vec{x}, t) = c_0 + \delta c(\vec{x}, t)$$



- The goal is to go from δc to σ_{n_T}

where $$n_T = \frac{1}{T}\int_0^T dt\, n(t)$$ (time avg.)

and $$n(t) = \int_V d^3x\, c(\vec{x}, t)$$

- Approach: use power spectrum $S_n(\omega)$

$$S_n(\omega) = \int \frac{d\omega'}{2\pi} \langle \delta\tilde{n}^*(\omega')\, \delta\tilde{n}(\omega) \rangle$$

Specifically, $\sigma_{n_T}^2 = \frac{1}{T} S_n(\omega \to 0)$

Proof:

First, we show that the power spectrum and autocorrelation function are related by Fourier transform

$$S_n(\omega) = \int \frac{d\omega'}{2\pi} \langle \delta\tilde{n}^*(\omega') \delta\tilde{n}(\omega) \rangle$$

$$= \int \frac{d\omega'}{2\pi} dt\, dt' \langle \delta n(t) \delta n(t') \rangle e^{i\omega' t'} e^{i\omega t}$$

$\langle \delta n(t) \delta n(t') \rangle = C_n(t-t')$

$\int \frac{d\omega'}{2\pi} e^{i\omega' t'} = \delta(t')$

$$= \int dt\, C(t) e^{i\omega t} \quad \checkmark$$

Inverse: $C(t) = \int \frac{d\omega}{2\pi} S(\omega) e^{-i\omega t}$

Now consider variance:

$$\sigma_{n_T}^2 = \left\langle \frac{1}{T}\int_0^T dt\, \delta n(t) \cdot \frac{1}{T}\int_0^T dt'\, \delta n(t') \right\rangle$$

$$= \frac{1}{T^2}\int_0^T dt\, dt'\, C(t-t')$$

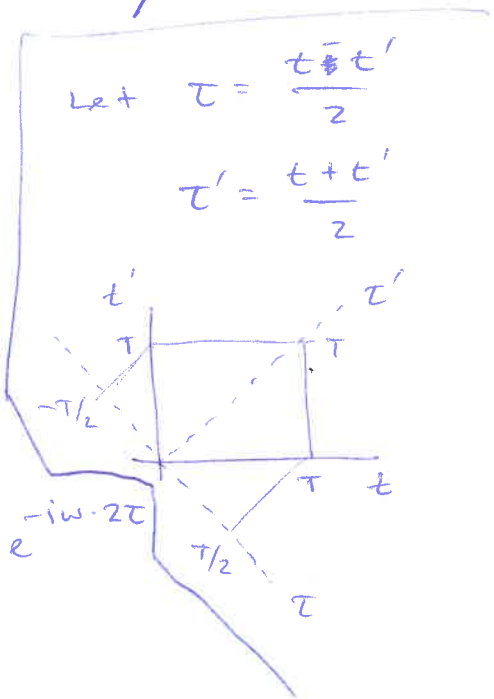
$$= \frac{1}{T^2}\int_{-T/2}^{T/2} d\tau \int_{|\tau|}^{T-|\tau|} d\tau'\, C(2\tau)$$

$$= \frac{1}{T^2}\int_{-T/2}^{T/2} d\tau\, (T-2|\tau|)\, C(2\tau)$$

$$= \frac{1}{T^2}\int_{-T/2}^{T/2} d\tau\, (T-2|\tau|) \int \frac{d\omega}{2\pi} S(\omega) e^{-i\omega\cdot 2\tau}$$

Let $\tau = \frac{t - t'}{2}$

$\tau' = \frac{t + t'}{2}$



Split τ integral at $\tau = 0$, get:

$$\sigma_{n_T}^2 = \frac{1}{T^2} \int \frac{d\omega}{2\pi} S(\omega) \cdot \underbrace{\frac{4\sin^2(\omega T/2)}{\omega^2}}$$

only has support for $\omega T \lesssim 1$

$\Rightarrow$ If $T \gg \omega^{-1}$ for smallest frequency ω,

Then we can approx $S(\omega) \simeq S(0)$ and pull it out.

$$\sigma_{n_T}^2 \simeq \frac{S(0)}{T^2} \int_{-\infty}^{\infty} \frac{d\omega}{2\pi} \cdot \frac{4\sin^2(\omega T/2)}{\omega^2} = \boxed{\frac{S(0)}{T}}$$ after integrating.

✡ Valid if $T \gg$ longest timescale.

So, we need to find $S_n(\omega)$ and take $\omega \to 0$

$$\dot{c} = D\nabla^2 c + \eta$$

$$\partial_t (c_0 + \delta c) = D\nabla^2 (c_0 + \delta c) + \eta$$

$$\dot{\delta c} = D\nabla^2 \delta c + \eta$$

Fourier: $-i\omega \tilde{\delta c} = -Dk^2 \tilde{\delta c} + \tilde{\eta}$

$$\Rightarrow \tilde{\delta c} = \frac{\tilde{\eta}}{Dk^2 - i\omega}$$

$$S_n(\omega) = \int \frac{d\omega'}{2\pi} \langle \tilde{\delta n}^*(\omega') \tilde{\delta n}(\omega) \rangle$$

The reason is because

$$\sigma_{n_T}^2 = \frac{1}{T} S_n(\omega \to 0)$$

if $T \gg$ longest timescale in the process

(to be proven later if time -- see pgs. 8a, 8b)

Mean: $\bar{n}_T = \frac{1}{T}\int_0^T dt\, \bar{n} = \bar{n}$

$$\bar{n} = \int_V d^3x\, \bar{c} = \int_V d^3x\, c_0 = c_0 \cdot \frac{4}{3}\pi a^3$$

Variance:

$$S_n(\omega) = \int \frac{d\omega'}{2\pi} \langle \delta\tilde{n}^*(\omega')\delta\tilde{n}(\omega)\rangle$$

$$\delta\tilde{n}(\omega) = \int dt\, \delta n(t) e^{i\omega t}$$

$$= \int dt \int_V d^3x\, \delta c(\vec{x},t) e^{i\omega t}$$

$$= \int dt \int_V d^3x \int \frac{d\omega'}{2\pi}\frac{d^3k}{(2\pi)^3}\, \delta\tilde{c}(\vec{k},\omega') e^{-i\vec{k}\cdot\vec{x} - i\omega' t} e^{i\omega t}$$

($\int dt$ and $e^{i\omega t}$ combine to give $2\pi\delta(\omega-\omega')$)

$$= \int_V d^3x \int \frac{d^3k}{(2\pi)^3}\, \delta\tilde{c}(\vec{k},\omega) e^{-i\vec{k}\cdot\vec{x}}$$

what is $\delta\tilde{c}$?

$$\dot{c} = D\nabla^2 c + \eta$$

$$\partial_t(c_0 + \delta c) = D\nabla^2(c_0 + \delta c) + \eta$$

$$\dot{\delta c} = D\nabla^2 \delta c + \eta$$

Fourier transform:

$$-i\omega \tilde{\delta c} = -Dk^2 \tilde{\delta c} + \tilde{\eta}$$

$$\tilde{\delta c} = \frac{\tilde{\eta}}{Dk^2 - i\omega}$$

So,

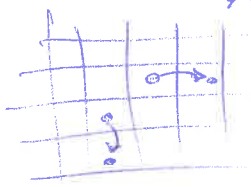
$$S_n(\omega) = \int \frac{d\omega'}{2\pi} \left\langle \int_V d^3x' \int \frac{d^3k'}{(2\pi)^3} \frac{\tilde{\eta}^*(\vec{k}', \omega')}{Dk'^2 + i\omega'} e^{+i\vec{k}'\cdot\vec{x}'} \right.$$
$$\left. \times \int_V d^3x \int \frac{d^3k}{(2\pi)^3} \frac{\tilde{\eta}(\vec{k}, \omega)}{Dk^2 - i\omega} e^{-i\vec{k}\cdot\vec{x}} \right\rangle$$

$$= \int_V d^3x\, d^3x' \int \frac{d\omega'}{2\pi} \frac{d^3k}{(2\pi)^3} \frac{d^3k'}{(2\pi)^3} \frac{e^{-i\vec{k}\cdot\vec{x}} e^{i\vec{k}'\cdot\vec{x}'}}{(Dk^2 - i\omega)(Dk'^2 + i\omega')} \left\langle \tilde{\eta}^*(\vec{k}', \omega') \tilde{\eta}(\vec{k}, \omega) \right\rangle$$

what are statistics of η?

$$\langle \eta(\vec{x}', t') \eta(\vec{x}, t) \rangle = \underbrace{2Dc_0}\ \underbrace{\delta(t - t')}\ \underbrace{\vec{\nabla}_x \cdot \vec{\nabla}_{x'} \delta(\vec{x} - \vec{x}')}$$

"propensity of uniform diffusion" — delta-corr. in time



★ Can derive from lattice & taking spacing to 0...

anti-correlations in space: loss of a molecule at one location = gain of a molecule at the neighboring location

In Fourier space:

$$\langle \tilde{\eta}^*(\vec{k}', \omega') \eta(\vec{k}, \omega) \rangle = 2Dc_0 \cdot 2\pi \delta(\omega - \omega') \cdot (2\pi)^3 k^2 \delta(\vec{k} - \vec{k}')$$

plugging in takes $\vec{k}' \to \vec{k}$, $\omega' \to \omega$.

Taking the $\omega \to 0$ limit, we obtain:

$$S_n(0) = \int_V d^3x\, d^3x' \int \frac{d^3k}{(2\pi)^3} \frac{e^{-i\vec{k}\cdot(\vec{x}-\vec{x}')}}{D^2 k^4} k^2 \cdot 2Dc_0$$

$$= \frac{2c_0}{D} \int_V d^3x\, d^3x' \int \frac{d^3k}{(2\pi)^3} \frac{e^{-i\vec{k}\cdot(\vec{x}-\vec{x}')}}{k^2}$$

just integrals ... evaluate to $\frac{8\pi}{15} a^5$

$$S_n(0) = \frac{16\pi c_0 a^5}{15D}$$

$$\text{So, } \sigma_{n_T}^2 = \frac{16\pi c_0 a^5}{15DT}$$

$$\text{And } \frac{\sigma_{\hat{c}}}{\langle \hat{c} \rangle} = \frac{\sigma_{n_T}}{\bar{n}_T} = \sqrt{\frac{16\pi c_0 a^5}{15DT}} \cdot \frac{q^3}{16\pi^2 c_0^2 a^6}$$

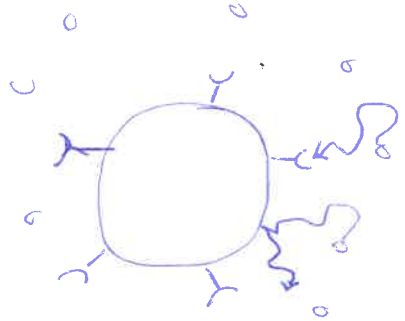
$$= \boxed{\sqrt{\frac{3}{5\pi} \frac{1}{a c_0 DT}}}$$ Perfect instrument.

Error for instrument is $\sqrt{(3/5\pi)/(1/4\pi)} \simeq 1.5$ times larger than that for sink. Why?

✡ Sink does not double-count molecules!

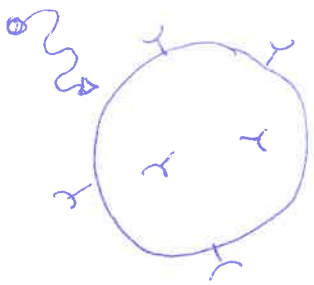
(IV) Receptor binding

In reality, the cell surface is neither permeable nor a perfect sink. Instead, individual receptors cover only a fraction of the surface.

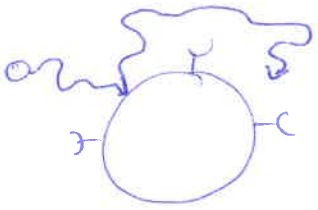


How does this change the sensing process?

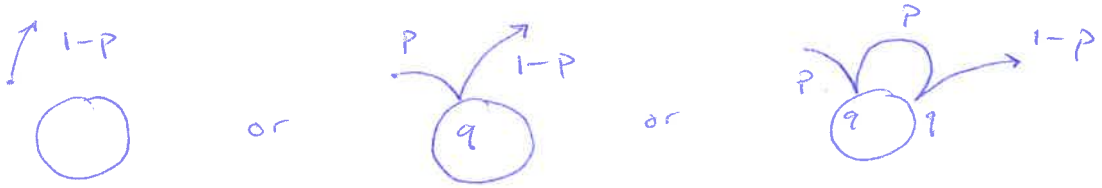
Berg + Purcell considered this question probabilistically, from the perspective of a single diffusing molecule



The molecule hits the cell surface with probability p (with $1-p$ it diffuses away forever). But with probability q, it fails -- it hits part of the surface that is <u>not</u> covered with receptors of that type.



Then, it may bounce off and "try again." Let's count all the ways it could escape forever:



$$P_{esc} = (1-p) + pq(1-p) + (pq)^2(1-p) + \dots$$

$$= (1-p)\sum_{n=0}^{\infty}(pq)^n = (1-p)\cdot\frac{1}{1-pq}$$

So, the probability of actually hitting a receptor is

$$P_{abs} = 1 - P_{esc} = 1 - \frac{1-p}{1-pq} = \frac{p-pq}{1-pq} = \frac{p(1-q)}{1-pq}$$

What are p and q?

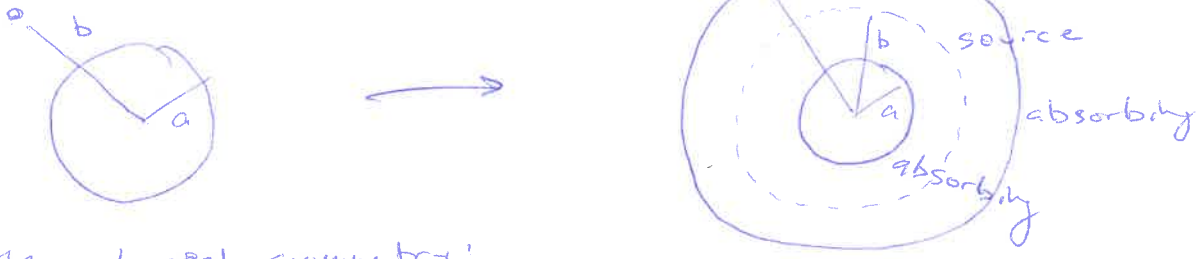
- q is simply the area fraction: call receptor lengthscale s, approximate its cross-section as a circle:

$$q = \frac{\text{area not covered by receptors}}{\text{total area}} = \frac{4\pi a^2 - R\pi s^2}{4\pi a^2}$$

for R receptors.

$$= 1 - \frac{Rs^2}{4a^2}$$

- p can be obtained from a flux argument. Imagine the molecule starts at distance b. The probability of hitting the surface is the ratio of fluxes into an absorbing boundary at $r = a$ and into that or an absorbing boundary at $r = d \to \infty$, given a shell source at $r = b$



With spherical symmetry:

$$c(r) = B - \frac{A}{r}$$

For $a < r < b$:

① $c(a) = 0 = B - \frac{A}{a} \Rightarrow B = \frac{A}{a}$

$$c(r) = A\left(\frac{1}{a} - \frac{1}{r}\right)$$

② $c(b) = c_{max} = A\left(\frac{1}{a} - \frac{1}{b}\right) = A\left(\frac{b-a}{ab}\right) \Rightarrow A = \frac{ab\,c_{max}}{b-a}$

$$c(r) = \frac{ab\,c_{max}}{b-a}\left(\frac{1}{a} - \frac{1}{r}\right)$$

And for $b < r < d$:

$$c(r) = \frac{b d c_{max}}{d-b}\left(\frac{1}{r} - \frac{1}{d}\right)$$

Fluxes:

$$J(a) = 4\pi a^2 \cdot D \left.\frac{\partial c}{\partial r}\right|_a = 4\pi a^2 \cdot D \frac{b c_{max}}{a(b-a)}$$

$$J(d) = -4\pi d^2 \cdot D \left.\frac{\partial c}{\partial r}\right|_d = +4\pi d^2 \cdot D \frac{b c_{max}}{d(d-b)}$$

Ratio:

~~$$P = \lim_{d\to\infty} \frac{4\pi a D b c_{max}(d-b)}{(b-a)\cdot 4\pi d D b c_{max}}$$~~

$$P = \lim_{d\to\infty} \frac{J(a)}{J(a)+J(d)}$$

$$= \lim_{d\to\infty} \frac{a/(b-a)}{a/(b-a) + \underbrace{d/(d-b)}_{\to 1}} = \frac{a}{b-a}\cdot\frac{b-a}{a+b-a} = \boxed{\frac{a}{b}}$$

So, plugging in P, q:

$$P_{abs} = \frac{a}{b}\frac{R_s^2}{4a^2} \Big/ \underbrace{\left[1 - \frac{a}{b}\left(1 - \frac{R_s^2}{4a^2}\right)\right]}$$

$$1 - \frac{a}{b}\frac{4a^2 - R_s^2}{4a^2} = \frac{4ab - 4a^2 + R_s^2}{4ab}$$

$$= \frac{R_s^2}{4ab - 4a^2 + R_s^2}$$

And what of b? For each "bounce" to be independent, molecule must separate itself from the surface a distance on the order of the receptor size:

$$b \sim a + s$$

$$P_{abs} = \frac{Rs^2}{4as + Rs^2} = \boxed{\frac{Rs}{4a + Rs}}$$

Obviously as $R \to \infty$, we recover the perfect sink ($P_{abs} \to 1$).

But how many receptors are needed to make, say, $P_{abs} = \frac{1}{2}$?

$$4a = Rs \Rightarrow R = \frac{4a}{s}.$$

Typically $a \sim 1\,\mu m$, $s \sim 1\,nm \Rightarrow \boxed{R \sim 4{,}000}$ receptors

How much area does this take up?

$$\frac{A_{receptors}}{A_{cell}} = \frac{R \pi s^2}{4\pi a^2} = \frac{4 \cdot 10^3 (1\,nm)^2}{4 (10^3\,nm)^2} = \boxed{0.1\%}$$

Tiny fraction! (Plenty of room for receptors of many types.)

✡ With just a small fraction of the area covered w/ receptors, a realistic model is absorbing almost as much as the perfect sink. Thus, the scaling

$$\frac{\sigma_c}{\langle c \rangle} \sim \frac{1}{\sqrt{a c_0 D T}}$$

should hold pretty well, even for receptors explicitly accounted for.

Experiments on bacteria

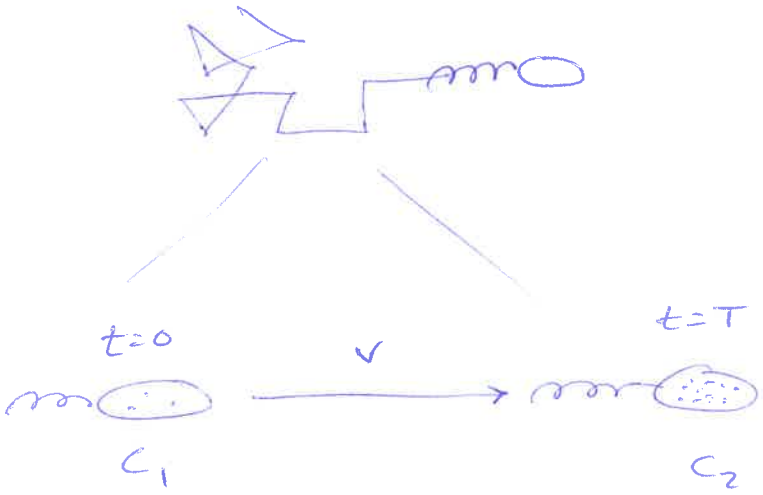
We have considered several models of sensory statistics that set a lower bound on the sensory noise of

$$\frac{\sigma_{\hat{c}}}{\langle \hat{c} \rangle} \sim \frac{1}{\sqrt{a c_0 D T}}.$$

Do cells actually reach this bound?

Berg + Purcell asked this question for *E. coli* bacteria.

E. coli do a run + tumble motion, biased by attractant gradients:



For a run over time T, conc. change is

$$\Delta c = g v T.$$

Berg + Purcell argued that this Δc must be larger than the std. deviation in estimating c, or else the cell is swamped by noise

$$\Delta c > \sigma_{\hat{c}}, \quad \text{or} \quad \frac{\Delta c}{\underbrace{\langle \hat{c} \rangle}_{\sim c_0}} > \frac{\sigma_{\hat{c}}}{\langle \hat{c} \rangle} \sim \frac{1}{\sqrt{a c_0 D T}}$$

$$g v T > \sqrt{\frac{c_0}{aDT}}$$

$$T^{3/2} > \sqrt{\frac{c_0}{aD}} \frac{1}{gv} \quad \rightarrow \quad T > \left[\frac{c_0}{aD g^2 v^2} \right]^{1/3}$$

Typical values from Berg's experiments at the time:

$c_0 \sim 1\,mM$, $g \sim 10\,nM/\mu m$, $a \sim 1\,\mu m$

$v \sim 10\,\mu m/s$, $D \sim 10^3\,\mu m^2/s$

Note $1\,nM \simeq \frac{0.6}{\mu m^3} \sim 1\,\mu m^{-3}$

$$T \gtrsim \left[\frac{10^6}{\mu m^3}\,\frac{1}{1\,\mu m}\,\frac{s}{10^3\,\mu m^2}\left(\frac{\mu m^3 \cdot \mu m}{10}\right)^2\left(\frac{s}{10\,\mu m}\right)^2\right]^{1/3}$$

$$= \left[\frac{10^6}{10^7}\right]^{1/3} s \sim \boxed{0.5\,s}$$

Actual run times are on the order of 1 s.

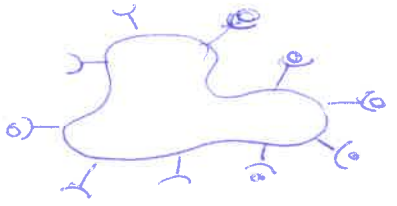
Thus, 1) E. coli "respects" the bound

2) E. coli is very close to the bound, implying optimal sensory machinery.

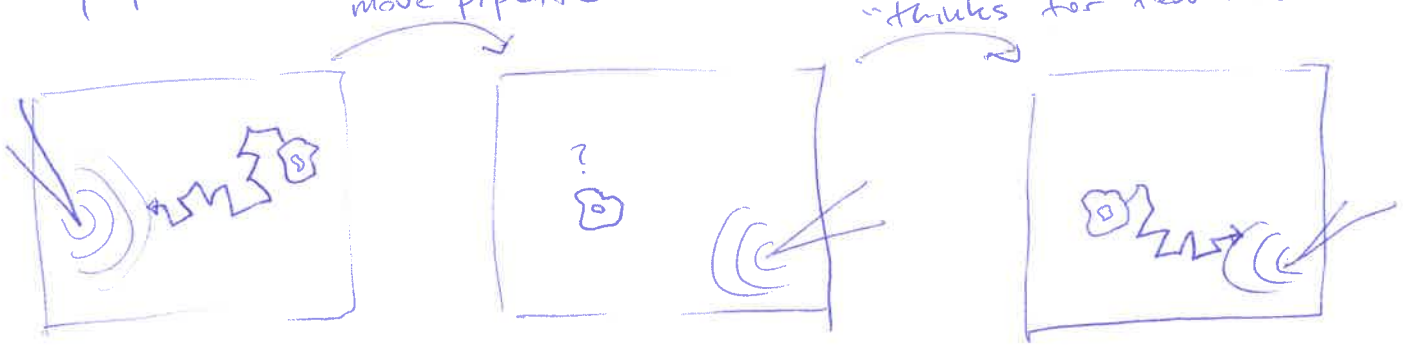
Gradient sensing

E. coli measure gradients by integration many concentration measurements over time while they move.

Bigger cells, such as amoeba can measure gradients by sitting still: they compare bound receptors on each side of the cell body. (They are also ~10 times larger)



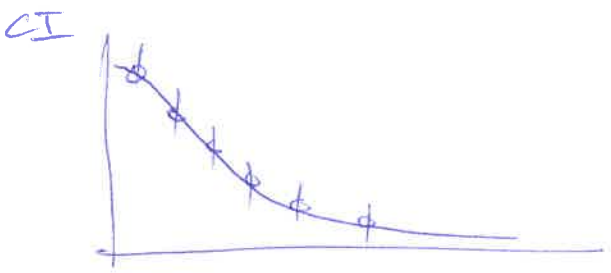
We know this because of cruel experiments w/ a pipette



This is summarized by "chemotactic index"

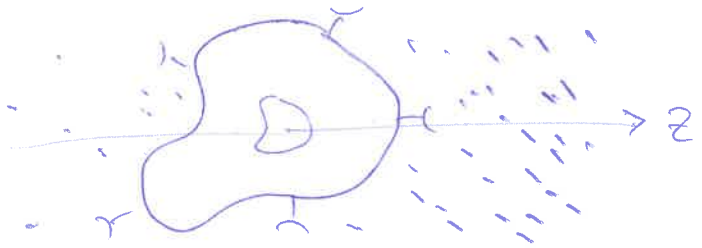
$$CI = \langle \cos\theta \rangle$$

where θ is angle between displacement + "right" dir.



Van Haastert + Postma, 2007.

So, what sets the limit to the precision of gradient sensy, and do amoeba reach it?



$$c(\vec{x}) = c_0 + gz$$

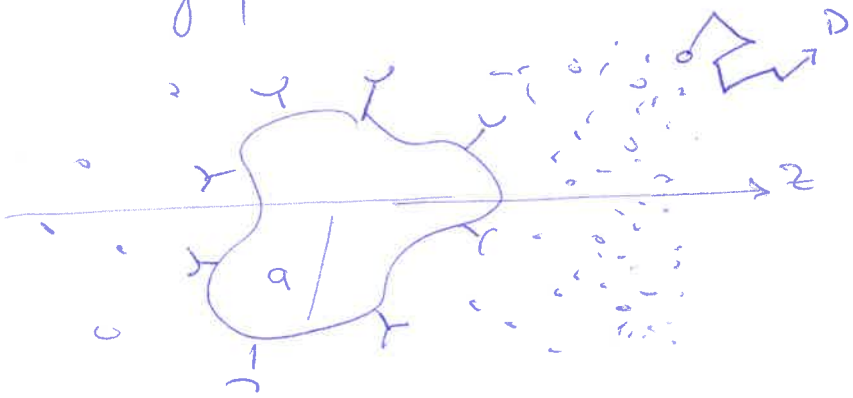
Dimensional analysis:

$$\frac{\sigma_{\hat{g}}}{\langle \hat{g} \rangle} \sim \frac{1}{a^x c_0^y (DT)^v g^w}$$

with

$$x - 3y + 2v - 4w = 0$$

What sets the fundamental limit to gradient sensing precision?



$$c(\vec{x}) = c_0 + gz$$

Dimensional analysis first:

$[a] = m$ $\quad [T] = s$

$[D] = m^2/s$ $\quad [g] = \frac{1}{m^4}$

$[c_0] = \frac{1}{m^3}$

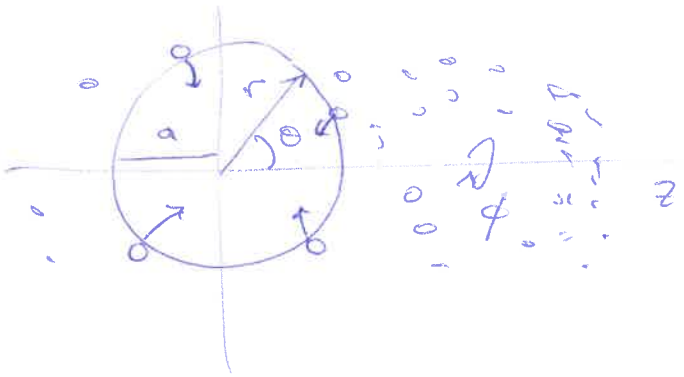
$$\frac{\sigma_{\hat{g}}}{\langle \hat{g} \rangle} \sim \sqrt{\frac{1}{DT} \frac{1}{a^x c_0^y g^z}}$$

as in concentration sensing (?)

and ~~x + y + z + 2 = 0~~

$$x - 3y - 4z + 2 = 0$$

We will consider the "perfect sink" version of this problem, following Endres + Wingreen, 2008.



First we must define a quantity from which the cell can obtain its estimate, $\hat{g}$.

The cell cannot just count molecules anymore, it has to know what direction they came from. From symmetry, this measure need not depend on ϕ. Propose:

$$\alpha = \sum_{i=1}^{n} \cos\theta_i \qquad \text{"anisotropy"}$$

where n = # molecules that arrive in time T.

★ If we find that $\bar{\alpha} \propto g$, then it is a valid choice, i.e. $\dfrac{\sigma_{\hat{g}}}{\langle \hat{g} \rangle} = \dfrac{\sigma_\alpha}{\bar{\alpha}}$

$\bar{\alpha} = \left\langle \sum_{i=1}^{n} \cos\theta_i \right\rangle$. If each molecule independent, then

$= \bar{n} \langle \cos\theta \rangle$

$= \underbrace{\bar{n}}_{\text{T}} \int d\Omega \underbrace{P(\Omega)}_{\text{T}} \cos\theta$ where $d\Omega = \sin\vartheta \, d\theta \, d\phi$

should be able to obtain both from diffusion equation + flux.

$$\dot{c} = D\nabla^2 c = 0 \quad , \text{ where } c(r,\theta,\phi) = c(r,\theta)$$

Boundary conditions:

$$c(a,\theta) = 0 \qquad (1)$$

$$c(r>>a,\theta) = c_0 + gr\cos\theta \qquad (2)$$

General solution: spherical harmonics:

$$c(r,\theta,\phi) = \sum_{l=0}^{\infty} \sum_{m=-l}^{l} R_l(r)\, Y_l^m(\theta,\phi)$$

where $R_l(r) = A_l r^l + B_l r^{-(l+1)}$

Axial symmetry $\Rightarrow m = 0$

and $Y_l^0(\theta) = P_l(\cos\theta)$ Legendre polynomials

$$\therefore c(r,\theta) = \sum_{l=0}^{\infty} \left[A_l r^l + B_l r^{-(l+1)}\right] P_l(\cos\theta)$$

$P_0(x) = 1$

$P_1(x) = x$

$P_2(x) = \frac{1}{2}(3x^2 - 1)$

BC 1:

$$c(a,0) = 0 = \sum_{l=0}^{\infty} \left[A_l a^l + B_l a^{-(l+1)}\right] P_l(\cos\epsilon)$$

0 by orthonormality

$$\Rightarrow B_l = A_l a^{2l+1}$$

$$c(r,\theta) = \sum_{l=0}^{\infty} A_l r^l \left[1 - \left(\frac{a}{r}\right)^{2l+1}\right] P_l(\cos\theta)$$

BC 2:

$$c(r \gg a, \theta) = c_0 + gr\cos\theta$$

$$= \sum_{\ell=0}^{\infty} A_\ell r^\ell P_\ell(\cos\theta)$$

$$= A_0 + A_1 r\cos\theta + \mathcal{O}(\cos^2\theta)$$

$$\Rightarrow A_0 = c_0 \,, \quad A_1 = g \,, \quad A_\ell = 0 \text{ for } \ell \geq 2$$

$$\therefore c(r,\theta) = \underbrace{c_0\left(1 - \frac{a}{r}\right)}_{\text{correct limit for } g \to 0 \ \checkmark} + gr\left[1 - \left(\frac{a}{r}\right)^3\right]\cos\theta$$

Inward flux at surface:

$$j(\theta) = D\,\partial_r c\big|_a = D\frac{c_0}{a} + Dg\cos\theta\left[1 + \frac{2a^3}{a^3}\right]$$

$$\boxed{j(\theta) = \frac{Dc_0}{a} + 3gD\cos\theta}$$

For $\bar{n}$, we don't care where molecules arrive:

$$\bar{n} = Ta^2\int d\Omega\, j(\theta)$$

$$= Ta^2\int_0^{2\pi} d\phi \int_0^{\pi} d\theta \sin\theta \left[\frac{Dc_0}{a} + 3gD\cos\theta\right]$$

$$= Ta^2\left[4\pi\cdot\frac{Dc_0}{a} + 2\pi\int_{-1}^{1} du\, 3gDu\right]$$

$$\boxed{\bar{n} = 4\pi a c_0 DT} \quad \text{(just like } g = 0 \text{ case)}$$

For $P(\Omega)$ we do care : normalized flux

$$P(\Omega) = \frac{j(\theta)}{\int d\Omega' j(\theta')} = \frac{\frac{Dc_0}{a} + 3gD\cos\theta}{\frac{4\pi Dc_0}{a}}$$

$$= \frac{1}{4\pi}\left[1 + \frac{3ga}{c_0}\cos\theta\right]$$

And so,

$$\bar{\alpha} = \bar{n}\int d\Omega\, P(\Omega)\cos\theta$$

$$= 4\pi a c_0 DT \frac{1}{4\pi}\int d\Omega \left[1 + \frac{3ga}{c_0}\cos\theta\right]\cos\theta$$

$$= 2\pi a c_0 DT \int_{-1}^{1} du\, \frac{3ga}{c_0} u^2$$

$$\boxed{\bar{\alpha} = 4\pi a^2 g DT}$$

Note: $\bar{\alpha} \propto g$ ✓ valid meas.

$\bar{\alpha} \neq \bar{\alpha}(c_0)$ Blind. subtraction

What about the noise?

$$\sigma_\alpha^2 = \langle \alpha^2 \rangle - \bar{\alpha}^2$$

$$\langle \alpha^2 \rangle = \left\langle \sum_{i=1}^{n} \sum_{j=1}^{n} \cos\theta_i \cos\theta_j \right\rangle$$

$$= \left\langle \sum_{i=1}^{n} \sum_{j\neq i} \cos\theta_i \cos\theta_j \right\rangle + \left\langle \sum_{i=1}^{n} \cos^2\theta_i \right\rangle$$

$$= \langle n(n-1)\rangle \langle\cos\theta\rangle^2 + \langle n\rangle\langle\cos^2\theta\rangle$$

due to particle independence.

Note: because n is Poissonian,

$$\langle n(n-1)\rangle = \langle n^2\rangle - \bar{n} = \sigma_n^2 + \bar{n}^2 - \bar{n} = \bar{n}^2$$

Thus, $\bar{n}^2 \langle \cos\Theta\rangle^2 = \bar{\alpha}^2$, i.e. these terms cancel

$$\therefore \quad \sigma_\alpha^2 = \bar{n}\langle \cos^2\Theta\rangle$$

$$\langle \cos^2\Theta\rangle = \int d\Omega\, P(\Omega)\cos^2\Theta$$

$$= \frac{1}{4\pi}\int d\Omega \left[1 + \frac{3ga}{c_0}\cos\Theta\right]\cos^2\Theta$$

$$= \frac{2\pi}{4\pi}\int_{-1}^{1} du\, u^2 = \frac{1}{3}$$

$\Rightarrow \boxed{\sigma_\alpha^2 = \frac{\bar{n}}{3}}$

★ Noise does not depend on anisotropy!

Last thing: cell doesn't know to orient along z direction a priori

$\Rightarrow \sigma_\alpha^2 \to 3\sigma_\alpha^2 = \boxed{\bar{n}}$

Finally,

$$\frac{\sigma_{\hat{g}}}{\langle \hat{g}\rangle} = \frac{\sigma_\alpha}{\bar{\alpha}} = \sqrt{\frac{4\pi a c_0 DT}{\frac{3}{5}(4\pi)^2 a^4 g^2 D^2 T^2}}$$

$$\boxed{\frac{\sigma_{\hat{g}}}{\langle \hat{g}\rangle} = \sqrt{\frac{c_0}{4\pi a^3 g^2 DT}}}$$

Check dimensional analysis:

$x = 3$

$y = -1$ ← !

$u = 1$

$w = 2$

$3 - 3(-1) + 2(1) - 4(2) = 0$ ✓

Why is c_0 on top? Why does having more molecules increase noise?

* Gradient detection is essentially a subtraction computation; the cell is trying to find the difference in molecule numbers between two sides of its body. Although an absolute count is more precise in a high background concentration, a difference is harder to measure on top of a high background.

We can make this argument quantitative with a version of the "perfect instrument"

Assume the cell is estimating the gradient from $\Delta n = n_1 - n_2$

Mean: $\Delta \bar{n} \sim a^3 \Delta c \sim a^3 (a g)$

Noise:

$$\sigma^2_{\Delta n} \sim \sigma^2_{n_1} + \sigma^2_{n_2} \qquad \text{(ignoring cross correlations)}$$

$$\sim \frac{\bar{n}_1 + \bar{n}_2}{T/(a^2/D)} \sim \frac{2 c_0 a^3}{DT/a^2} \sim \frac{c_0 a^5}{DT}$$

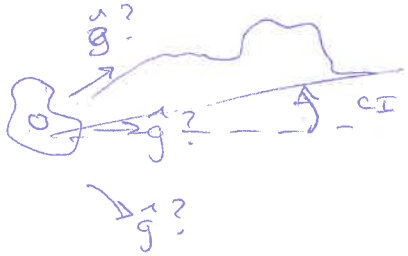
$$\frac{\sigma_{\hat{g}}}{\langle \hat{g} \rangle} \sim \frac{\sigma_{\Delta u}}{\Delta u} \sim \sqrt{\frac{c_0 a^5}{DT \cdot a^8 g^2}} = \boxed{\sqrt{\frac{c_0}{a^3 g^2 DT}}}$$

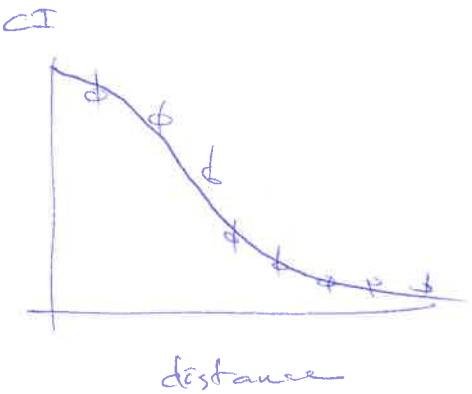
consistent with our calculation.

✱ Analogy from ~~computer~~ "best coding practices":

a small difference between two large numbers is less precise than between two small numbers.

Now that we have our result, we can return to the experimental question: do amoeba reach this bound? Endres + Wingreen related $\sigma_{\hat{g}} / \langle \hat{g} \rangle$ to the chemotactic index (CI), and fit the result to the data of van Haastert and Postma w/ one free parameter: $\boxed{T = 3.2\ s}$





Actual response times are:

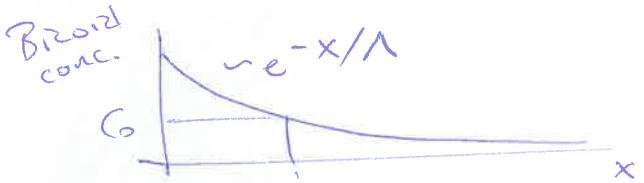
- few seconds (pipette movie)
- 5–10 seconds (fluorence labeling of motility signaling)

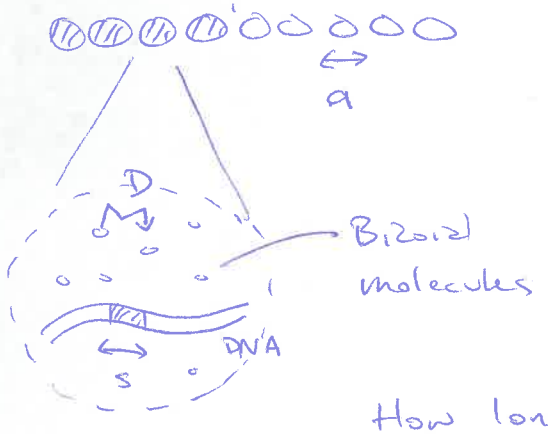
⇒ Amoeba, like E. coli, appear to operate very close to the bound set by molecule counting.

Multicellular sensing

Cells are rarely isolated and usually communicate. Can communication enhance the precision of sensing? This question was raised in the context of a multicellular system where ~~communication~~ sensing with high precision is very important: early embryonic development of a fruit fly (Drosophila).

(Gregor, Bialek, et al 2007 →)





Cells detecty a morphogen (Bicoid) concentration above a threshold $c_0 \sim 5/\mu m^3$ express a gene.

To form a boundary, this process needs a precision of $\sim a/\lambda$

$\simeq \frac{10\ \mu m}{100\ \mu m} = 10\%$.

How long, T, to reach this precision?

$$\frac{\sigma_c}{\langle c \rangle} = \varepsilon \sim \frac{1}{\sqrt{s\, c_0 D T}}$$

where $s \sim 3$ nm is the Bicoid binding site on the DNA, and $D \sim 1\ \mu m^2/s$ (slow in embryo.)

$$T \sim \frac{1}{s c_0 D \varepsilon^2} = \frac{1}{3\cdot 10^{-3}\,\mu m} \cdot \frac{\mu m^3}{5} \cdot \frac{s}{1\,\mu m^2} \frac{1}{(10^{-1})^2} \simeq 7\cdot 10^3$$

$\simeq$ 2 hours.

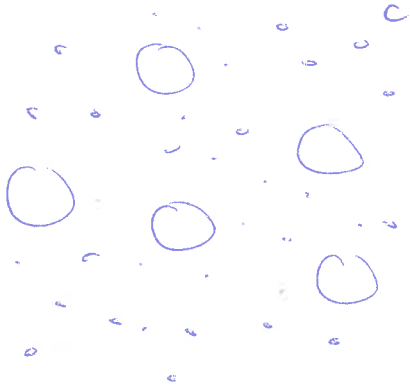
But the problem is that the embryo has only existed for about 2 hours, and the last ~~cell~~ nuclear division cycle only recently occurred!

☆ Possible resolution: nuclei communicate (Gregor, Bialek)

- reduces noise from averaging (good)
- smooths out boundary (bad)

optimal diffusion of communicator molecule? (ten Wolde, 2009)

This raises the more general question: how does cell-cell communication modify the sensory limits?



o = sensed molecule

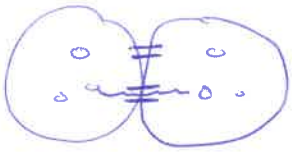
· = communication molecule.

Imagine we have N cells sensing and communicating. ~~How should the~~ A particular cell receives its own sensory information, and that ~~of the~~ communicated by the other cells. How should its estimation error $\sigma_{\hat{c}}/\langle \hat{c} \rangle$ scale?

Guess: $\frac{\sigma_c}{\langle \hat{c} \rangle} \sim \frac{1}{\sqrt{a c_0 D T N}}$ if communication "strong enough"; more weakly with N otherwise (?)

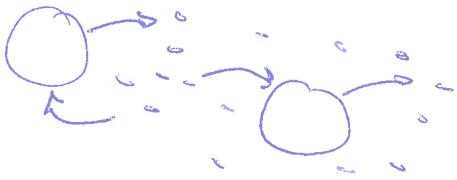
We will answer this question w/ 2 types of communication:

(1) Short-range (juxtacrine)



(epithelial cells, other tissue, etc.)

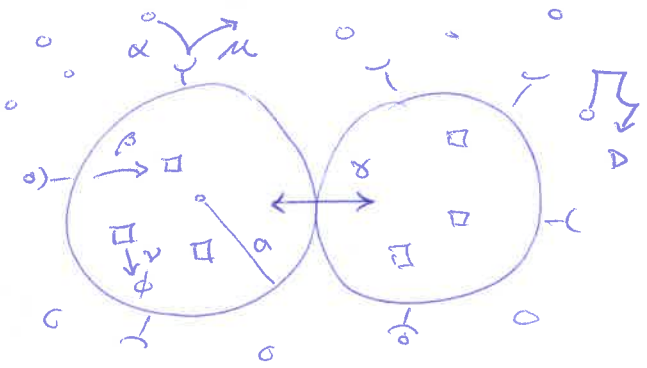
(2) Long-range (autocrine)



(bacteria, amoeba, mammalian cells)

Short range communication

Consider $N = 2$ first:



$\circ = c(\vec{x}, t)$

$\Psi = r_i(t)$

$\square = m_i(t)$ ← communicator and readout.

We will model each cell neither as a sink or monitoring instrument. Rather each will be "infinitely" condensed" at its center location, $\vec{X}_i$.

(Don't worry, we can retain a in the spacing, $|\vec{X}_1 - \vec{X}_2| = 2a$ and as a small-wavelength cutoff $k < k_{max} \sim \frac{1}{a}$ in the Fourier integrals)

The dynamics are then (neglecting receptor saturation)

$$\dot{c} = D\nabla^2 c - \delta(\vec{x}-\vec{x}_1)\dot{r}_1 - \delta(\vec{x}-\vec{x}_2)\dot{r}_2 + \eta$$

$$\dot{r}_{1,2} = \alpha c(\vec{x}_{1,2}, t) - \mu r_{1,2} + \xi_{1,2}$$

$$\dot{m}_{1,2} = \beta r_{1,2} - \nu m_{1,2} + \gamma(m_{2,1} - m_{1,2}) + \chi_{1,2}$$

Langevin noise

Statistics: η, ξ_i, χ_i all zero-mean and obey

$$\langle \eta(\vec{x},t)\eta(\vec{x}',t')\rangle = 2Dc_0\,\delta(t-t')\,\vec{\nabla}_x\cdot\vec{\nabla}_{x'}\,\delta(\vec{x}-\vec{x}') \quad \text{as before}$$

$$\langle \xi_i(t)\,\xi_j(t')\rangle = 2\mu\bar{r}\,\delta(t-t')\,\delta_{ij} \quad \text{where } \bar{r} = \frac{\alpha c_0}{\mu}$$

$$\langle \chi_i(t)\chi_j(t')\rangle = 2\bar{m}\,\delta(t-t')\left[(\nu+\gamma)\delta_{ij} - \gamma(1-\delta_{ij})\right]$$

where $\bar{m} = \frac{\beta\bar{r}}{\nu}$

Rationale: strengths prop. to reaction propensities!

own cell (δ_{ij}):

$\alpha c_0 + \mu\bar{r} = 2\mu\bar{r}$ in steady state

$\beta\bar{r} + \nu\bar{m} + \gamma\bar{m} + \gamma\bar{m} = 2\bar{m}(\nu+\gamma)$ in s.s.

other cell ($1-\delta_{ij}$):

$-\gamma\bar{m} - \gamma\bar{m} = -2\gamma\bar{m}$ anti-correlations from exchange

↑ give away molecules; ↑ get molecules

(Terms like these ultimately become $\vec{\nabla}_x\cdot\vec{\nabla}_{x'}$ in continuum limit for diffusive noise η.)

The system is linear with fully specified statistics.

Therefore we can go to Fourier space (really $k \leftrightarrow 1/a$) and compute $S_m(\omega)$ and $\sigma^2_{m_T} = S_m(0)/T$ for one cell.

The result is, for $\boxed{\upsilon = \gamma/\nu}$:

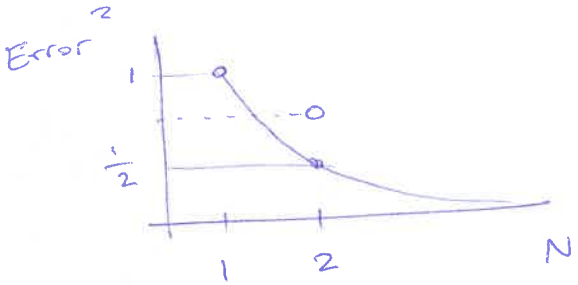
$$\frac{\sigma_{\hat{c}}^2}{\langle \hat{c} \rangle^2} = \frac{\sigma^2_{m_T}}{\bar{m}^2} = \underbrace{\frac{1+3\upsilon+3\upsilon^2}{(1+2\upsilon)^2} \frac{1}{2\pi a c_0 D T}}_{\text{"extrinsic" noise from molecule arrival}} + \underbrace{\frac{1+2\upsilon+2\upsilon^2}{(1+2\upsilon)^2} \frac{2}{\mu T \bar{r}} + \frac{1+\upsilon}{1+2\upsilon} \frac{2}{\nu T \bar{m}}}_{\text{"intrinsic" noise from finite } r, m \text{ numbers}}$$

$$\frac{\sigma^2}{\bar{n}^2} \sim \frac{1}{\bar{n}} \frac{1}{T/\tau} \quad \text{with } \tau \sim \frac{1}{\mu} \quad \text{for Poisson (birth-death) process}$$

Focusing only on extrinsic noise:

$$\frac{\sigma_{\hat{c}}^2}{\langle \hat{c} \rangle^2} = \frac{1}{2\pi a c_0 D T} \times \begin{cases} 1 & \upsilon \ll 1 \quad \text{no communication} \\ 3/4 & \upsilon \gg 1 \quad \text{strong communication} \end{cases}$$

We expected $1/N = \frac{1}{2}$! What gives?

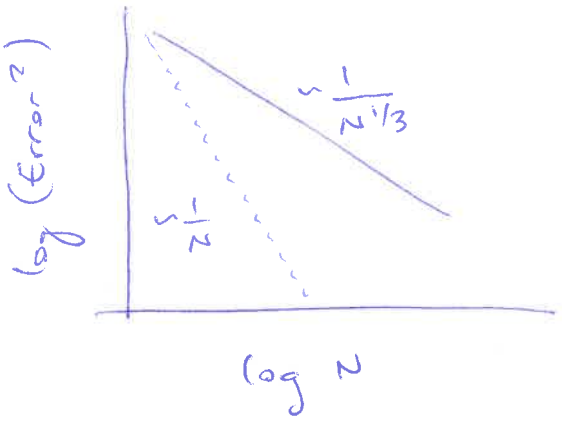


(Cells sample adjacent regions. Molecules counted are not independent.)

Maybe this will resolve itself for $N > 2$.

Can do same math with any N, e.g. w/ cells arranged in a sphere.

Find the following:



much worse than $1/N$!

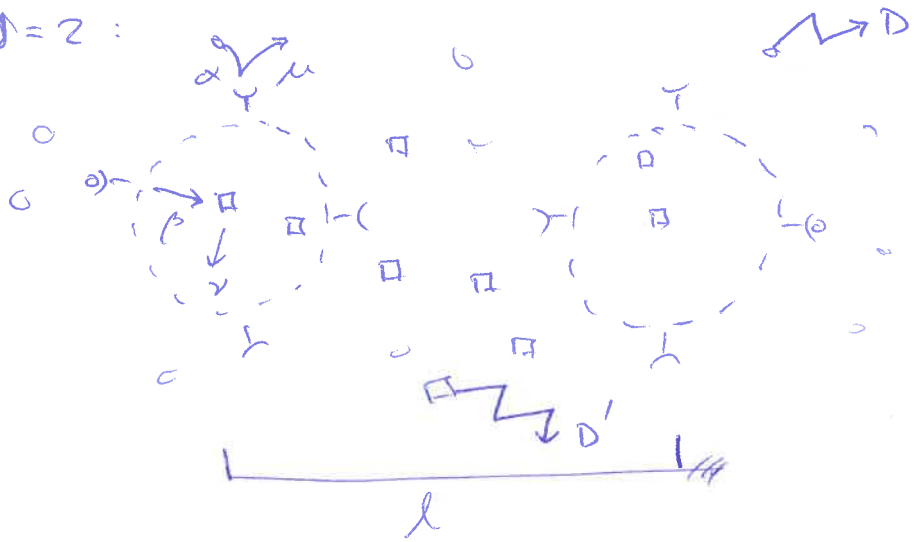
We can understand this intuitively:

the sphere is acting like a "big cell" whose volume is $\sim Na^3$ and lengthscale is $\sim N^{1/3}a$

Thus $\text{Error}^2 \sim \frac{1}{ac_0DT} \rightarrow \frac{1}{N^{1/3}ac_0DT}$

Long-range communication

$N=2$:



Same ~~Brad~~ diffusion / birdy dynamics

$$\dot{c} = D\nabla^2 c - \delta(\vec{x}-\vec{x}_1)\dot{r}_1 - \delta(\vec{x}-\vec{x}_2)\dot{r}_2 + \eta$$

$$\dot{r}_{1,2} = \alpha c(\vec{x}_{1,2}, t) - \mu r_{1,2} + \xi_{1,2}$$

But new dynamics for diffusible communication molecule with concentration ρ

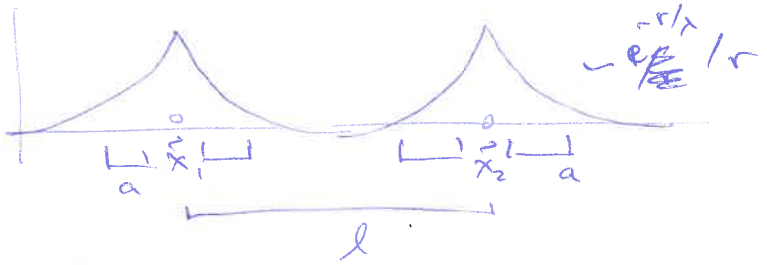
$$\dot{\rho} = D'\nabla^2\rho - \nu\rho + \delta(\vec{x}-\vec{x}_1)(\beta r_1 + \zeta_1) + \delta(\vec{x}-\vec{x}_2)(\beta r_1 + \zeta_2) + \psi$$

$$\langle \zeta_i(t)\zeta_j(t')\rangle = \beta\bar{r}\,\delta(t-t')\,\delta_{ij}$$

$$\langle \psi(\vec{x},t)\psi(\vec{x}',t')\rangle = 2D'\delta(t-t')\,\vec{\nabla}_x\cdot\vec{\nabla}_{x'}\left[\bar{\rho}(\vec{x})\,\delta(\vec{x}-\vec{x}')\right] + \nu\bar{\rho}(\vec{x})\,\delta(t-t')\,\delta(\vec{x}-\vec{x}')$$

where $$\bar{\rho}(\vec{x}) = \frac{\beta\bar{r}}{4\pi D'}\left(\frac{e^{-|\vec{x}-\vec{x}_1|/\lambda}}{|\vec{x}-\vec{x}_1|} + \frac{e^{-|\vec{x}-\vec{x}_2|/\lambda}}{|\vec{x}-\vec{x}_2|}\right)$$

and $\lambda = \sqrt{\frac{D'}{\nu}}$



Note that even if communication is infinitely strong ($\lambda\to\infty$), still $\rho \sim 1/r$ because diffusion is "2D" and cannot fill 3D space.

Define our counting variable N_i the perfect instrument:

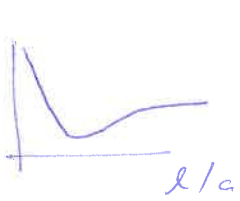
$$m_i(t) = \int_{V_i} d^3x\,\rho(\vec{x},t) \quad \text{for cell } i.$$

Again, use power spectrum to find $\sigma^2_{m_T}$.

In limit $\lambda\to\infty$, and only keeping extrinsic noise, we find

error^2

$$\varepsilon^2 = \frac{\sigma_{m_T}^2}{\bar{m}^2} = \frac{16 + 9(\ell/a)^2}{(2+3\ell/a)^2} \frac{1}{2\pi a c_0 D T}$$



$$= \frac{1}{2\pi a c_0 D T} \times \begin{cases} 1 & \ell \gg a \\ 4/5 & \ell = \ell^* = \frac{8}{3}a \end{cases}$$

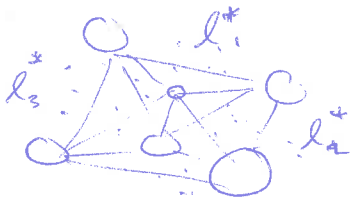
optimal ℓ^* occurs due to tradeoff:

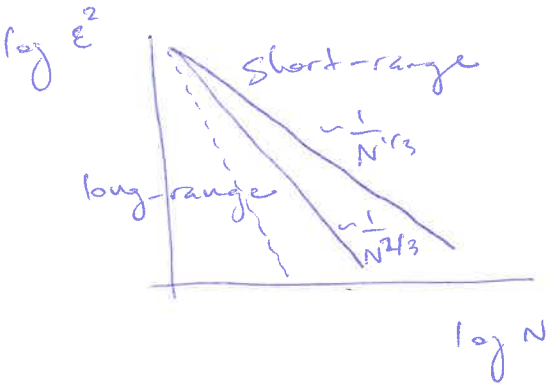
- large ℓ $\Rightarrow$ no communication
- small ℓ $\Rightarrow$ redundant sampling

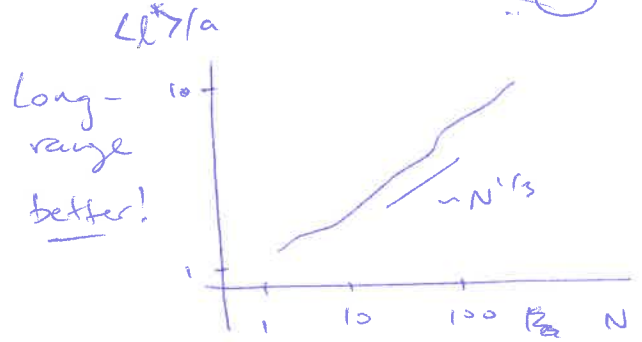
For $N = 2$, ℓ^* is slightly more than a diameter

Noise reduction is similar to short-range (3/4)

what about larger N? One can optimize positions of cells in 3D space. Find:







Long-range better!

Cells become spread out!

Rationale: $V \sim N\ell^{*3} \Rightarrow \varepsilon^2 \sim \frac{1}{N^{1/3}\ell^* c_0 D T} \Rightarrow \ell^* \sim N^{1/3}$

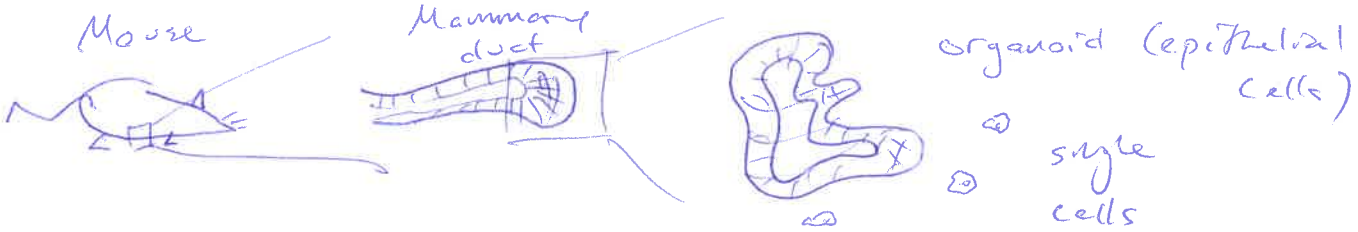
if $\varepsilon^2 \sim \frac{1}{N^{2/3}}$

Note: by $N \sim 100$, $\langle \ell^* \rangle \sim 10a$. Sparse!

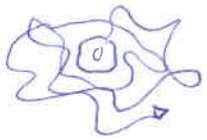
Tumor cells that secrete autocrine factors have been shown to actively spread to reduce noise (PNAS 2014)

Multicellular gradient sensing

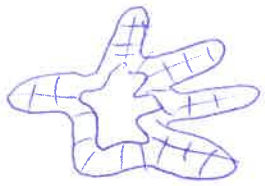
Can cells collectively sense gradients in addition to uniform concentrations? I became interested in this question as a postdoc (w/ Ilya) because our collaborators, the Levchenko lab, had data from mice:



Single cell: biased walk

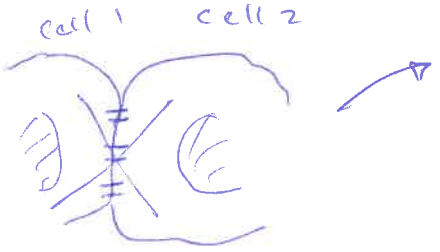


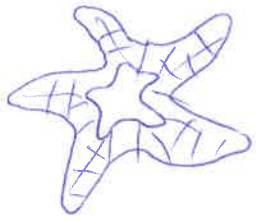
single cell: random walk



organoid: biased branching

★ When we block communication (gap junctions), bias went away!

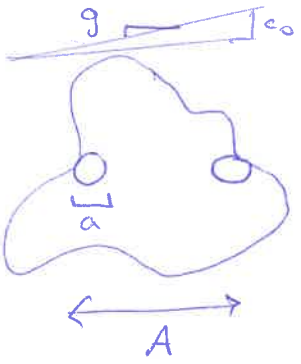




isotropic branching

How can we explain this? First off,

- The organoid is bigger, so it covers more of the gradient.



For gradient sensing (single cell)

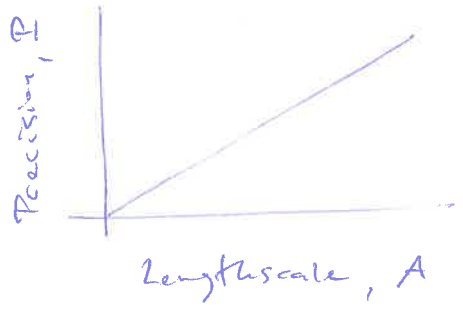
$$\varepsilon^2 \sim \frac{1}{aDT} \frac{c_0}{(ag)^2}$$

↑ compartment size ; ↑ compartment separation

So for the organoid,

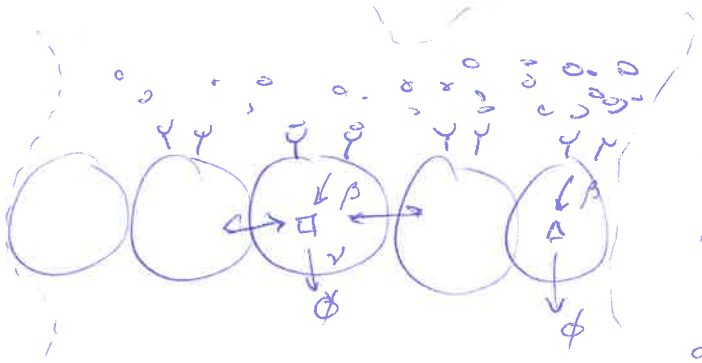
$$\varepsilon^2 \sim \frac{c_0}{aDTg^2A^2}, \text{ or}$$

$$P \equiv \frac{1}{\varepsilon} \sim Ag\sqrt{\frac{aDT}{c_0}}$$



So yes, bigger objects (larger A) should have higher precision P.

★ But we were also interested in the communication mechanism: how can a population share and process gradient information over long distances? Not a trivial task! (How might a chem of people do it?...) Essentially, you have to end up comparing your local measurement with some global measure of others' measurements, i.e. a subtraction.



$c(\vec{x}, t)$

$r_i(t)$

$m_i(t)$ $n_i(t)$

$\sqcap$ Δ

global local (no exchange)

$$\dot{c} = D\nabla^2 c + \sum_{i=1}^{N} \delta(\vec{x} - \vec{x}_i)\, \dot{r}_i + \eta$$

$$\dot{r}_i = \alpha\, c(\vec{x}_i, t) - \mu r_i + \xi_i$$

$$\dot{m}_i = \beta r_i - \nu m_i + \gamma\left(-2m_i + m_{i-1} + m_{i+1}\right) + \chi_i$$

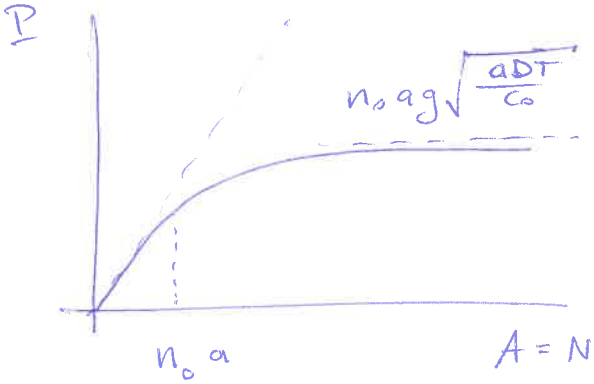
$$\dot{n}_i = \beta r_i - \nu n_i + \chi_i'$$

Key output is $\boxed{\Delta_N = n_N - m_N}$, i.e. difference between local, global in end cell (branching cell)

Then, $\Gamma \equiv \dfrac{\bar{\Delta}_N}{\sigma_{\Delta_N, t}}$

Again, Fourier space, power spectrum, etc.

Find:

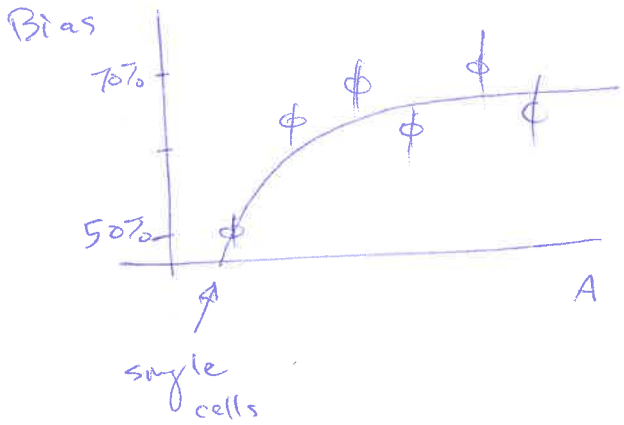


where $n_0 \equiv \sqrt{\gamma/\nu}$

There is an effective size, $n_0 a$, where communication saturates.

✡ Precision only as good as largest communicating subunit.

What do the data show?



One fit parameter:

$n_0 \sim 3$-4 cells

Makes sense:

- approximate width of duct "end bud"

✱ Subsequent experiments also showed Ca^{2+} necessary for bias, and Ca^{2+} pulses traveled ~ few cells up branch.

Thermodynamics of cell sensing

So far we have derived fundamental bounds on sensory precision and outlined some internal mechanisms to reach them, but what is the cost? How much energy must a cell expend to sense accurately?

This is an active topic of current research.

One of the first, now-classic demonstrations that enhancing precision requires driving a system out of equilibrium is kinetic proofreading.

(Hopfield 1974)

Kinetic proofreading : error in discriminatory

$$X + E \underset{b}{\overset{f}{\rightleftharpoons}} C \xrightarrow{v} P$$

Imagine an enzymatic reaction

$$\dot{P} = vC$$

$$\dot{c} = fxe - \underbrace{(v+b)}_{\simeq b} c \simeq 0 \qquad \text{Assume } \{f, b\} >> v$$

$$\Rightarrow \dot{P} = \frac{fxev}{b} = \frac{xev}{K} \qquad K = \frac{b}{f} \text{ dissociation const.}$$

Now imagine an incorrect substrate Y can bind:

$$Y + E \underset{\tilde{b}}{\overset{\tilde{f}}{\rightleftharpoons}} \tilde{C} \xrightarrow{v} \tilde{P} \qquad \Rightarrow \dot{\tilde{P}} = \frac{yev}{\tilde{K}}, \quad \tilde{K} = \frac{\tilde{b}}{\tilde{f}}$$

$$\text{Error } \varepsilon = \frac{\#\text{ fail}}{\text{total}} \simeq \frac{\#\text{ fail/time}}{\#\text{ success/time}} = \frac{\dot{\tilde{P}}}{\dot{P}} = \frac{yK}{x\tilde{K}}$$

If equal amts of X, Y, $\boxed{\varepsilon = \frac{K}{\tilde{K}}}$ Affinity determines discrimination.

Now imagine additional reaction step:

$$X + E \underset{b}{\overset{f}{\rightleftharpoons}} C \xrightarrow{w} C^* \xrightarrow{v} P \qquad (C \xrightarrow{b} E)$$

$$\dot{c}^* = wc - (b+v)c^* \simeq 0$$

$$\dot{P} = vc^* = \frac{vwc}{b} = \frac{vw}{b}\frac{fxe}{b}$$

Incorrect: $\dot{\tilde{P}} = \frac{vw\tilde{f}ye}{\tilde{b}^2}$

$$\varepsilon = \frac{\tilde{\dot{P}}}{\dot{P}} = \frac{\tilde{f}}{f}\,\frac{\gamma}{\chi}\,\frac{\tilde{b}^2}{b^2} = \left(\frac{K}{\tilde{K}}\right)^2 \quad \text{if} \quad \begin{matrix}\chi = \gamma \\ \tilde{f} = f\end{matrix} \quad \text{(e.g. diffusion-limited)}$$

★ Extra "checkpoint" reduces error.

This would not have worked if extra step was a reversible, equilibrium reaction: detailed balance requires equal fluxes:

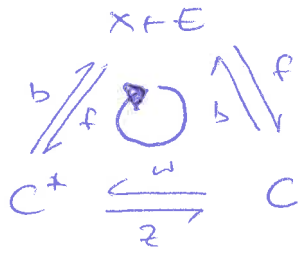
$$X + E \underset{b}{\overset{f}{\rightleftharpoons}} C \underset{z}{\overset{w}{\rightleftharpoons}} C^*$$

f (C → C*), b (C* → C)

$$\left.\begin{aligned} fxe &= bc \\ wc &= zc^* \\ fxe &= bc^* \end{aligned}\right\} \quad c = c^* \Rightarrow \dot{P} = \nu c^* = \underline{\nu c}$$

just as without the step.

★ We can view nonequilibrium driving as flux cycle in reaction space:



Irreversible reactions are the extreme case ↻.

Let's try to demonstrate that precision requires energy dissipation in the context of cell sensing. This follows the work of Mehta + Schwab (2012) and the ten Wolde group (2014).

★ We can summarize what we have done in the context of concentration sensing as follows:

n molecules

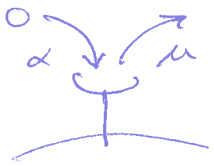
$\bar{n} \propto c_0$

$$\varepsilon^2 \equiv \frac{\sigma_{n_T}^2}{\bar{n}^2} \sim \frac{\sigma_n^2/(T/\tau)}{\bar{n}^2} = \frac{1}{\bar{n}}\frac{\tau}{T}$$

and $\tau \sim a^2/D$, $\bar{n} \sim a^3 c_0$

$$\Rightarrow \varepsilon^2 \sim \frac{1}{a c_0 D T}$$

Consider a single receptor. The logic is the same, except now the binding probability $\bar{b}$ is not strictly proportional to c_0:



$$\bar{b} = \frac{\alpha c_0}{\alpha c_0 + \mu}$$

$$\delta b = \left(\frac{d\bar{b}}{dc}\right)_{c_0} \delta c \quad \text{(Error propagation)}$$

$$\sigma_{b_T}^2 = \left(\frac{d\bar{b}}{dc}\right)_{c_0}^2 \sigma_{c_T}^2$$

$$\Rightarrow \varepsilon^2 = \frac{\sigma_{c_T}^2}{c_0^2} = \frac{\sigma_{b_T}^2}{\bar{b}^2}\left[\frac{\bar{b}/c_0}{(d\bar{b}/dc)_{c_0}}\right]^2$$

Transformation factor — one if measure $\propto c_0$

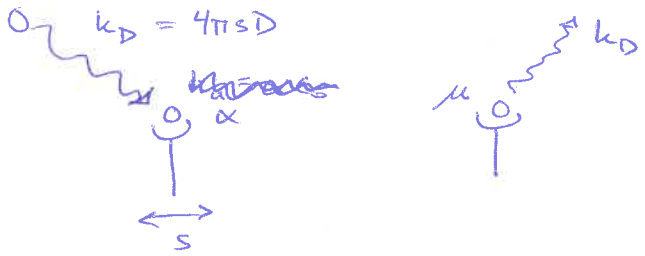
Here, $\left(\frac{d\bar{b}}{dc}\right)_{c_0} = \frac{\bar{b}(1-\bar{b})}{c_0}$, $\sigma_{b_T}^2 \propto \frac{\sigma_b^2}{T/\tau} = \frac{\bar{b}(1-\bar{b})}{T}\tau$

(binomial w/ $N=1$ receptor)

$\Rightarrow \varepsilon^2 \propto \frac{\tau}{T\bar{b}(1-\bar{b})}$ What is τ?

The autocorrelation time for any switching process is one over the sum of the switching rates:

$$\tau = \frac{1}{k_{on}c_0 + k_{off}}$$



Here, k_{on} & k_{off} each involve two processes:

Binding:

1. Diffusing to receptor, k_D
2. Binding if in contact, α

Unbinding:

1. Detachment, μ
2. Diffusing into bulk, k_D

$$\frac{1}{k_{on}} = \frac{1}{\alpha} + \frac{1}{k_D}$$

$$\frac{1}{k_{off}} = \frac{1}{\mu} + \frac{K_{eq}}{k_D}$$

Times add.

$k_D = 4\pi s D$, $K_{eq} = \frac{\alpha}{\mu}$

$$\Rightarrow \tau = \frac{\alpha + k_D}{k_D(\alpha c_0 + \mu)} = \bar{b}\left[\frac{1}{4\pi s D c_0} + \frac{1}{\alpha c_0}\right].$$

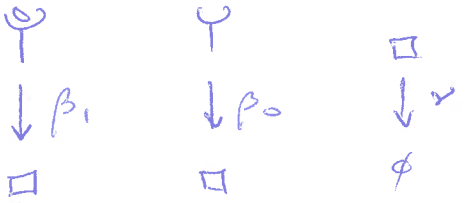
$$\varepsilon^2 \sim \frac{1}{4\pi s D c_0 T(1-\bar{b})} + \frac{1}{\underbrace{\alpha c_0}\,\underbrace{T(1-\bar{b})}}$$

$\mu\bar{b}$

Or, $$\varepsilon^2 \sim \underbrace{\frac{1}{4\pi s D c_0 T (1-\bar{b})}}_{\text{extrinsic (Berg-Purcell)}} + \underbrace{\frac{1}{\mu T \bar{b}}}_{\text{intrinsic (receptor kinetics)}}$$

Now, receptor binding/unbinding is an equilibrium process, so the cell need not expend energy yet.

But almost always the cell wants to do something internal with the receptor state, like produce or activate signaling molecules:



$$\dot{m} = \beta_1 b + \beta_0 (1-b) - \nu m + \eta$$

$$\langle \eta(t)\eta(t') \rangle = 2\nu\bar{m}\,\delta(t-t')$$

$\square = m(t)$ $\quad = \Delta$

Note: $$\bar{m} = \frac{(\beta_1 - \beta_0)\bar{b} + \beta_0}{\nu} = \frac{\bar{b}\Delta + \beta_0}{\nu}$$

and $$\bar{b} = \frac{\alpha c_0}{\alpha c_0 + \mu} \quad \text{so} \quad \bar{m} \neq c_0$$

$$\Rightarrow \varepsilon^2 = \frac{\sigma_{m_T}^2}{\bar{m}^2} \left[\frac{\bar{m}/c_0}{(d\bar{m}/dc)_{c_0}} \right]^2 \quad \text{where} \quad \sigma_{m_T}^2 = \frac{S_m(0)}{T}$$

Fourier, power spectrum, etc:

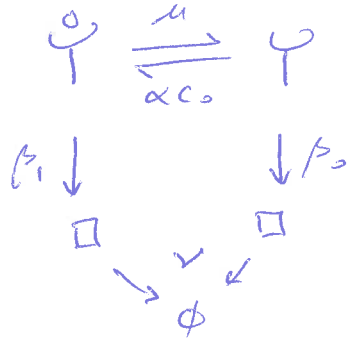
$$\varepsilon^2 \sim \underbrace{\frac{1}{4\pi s D c_0 T (1-\bar{b})}}_{\text{extrinsic}} + \underbrace{\frac{1}{\mu T \bar{b}}}_{\text{receptor}} + \underbrace{\frac{1}{\nu T \bar{m}} \left[\frac{\bar{m}}{\bar{b}(1-\bar{b})} \frac{\nu}{\Delta} \right]^2}_{\text{signaling molecule}}$$

Note: if

1. Receptor always bound ($\bar{b}=1$)
2. Receptor never bound ($\bar{b}=0$)
3. m produced indiscriminately ($\Delta=0$)

} then $\varepsilon^2 \to \infty$ no sensing

What about energetics?



reversible ⇒ equilibrium

irreversible ⇒ non-equilibrium

How much energy dissipated?

Dissipation in reaction networks is given by the entropy production rate:

$$\dot{s} = \sum_{\vec{n}\vec{n}'} P_{\vec{n}} k_{\vec{n}\vec{n}'} \log \frac{k_{\vec{n}\vec{n}'}}{k_{\vec{n}'\vec{n}}}$$

for states $\vec{n}$ and transition ~~rates~~ propensities k

In our problem we have states

$b = 0, 1$

$m = 0, 1, 2, 3, \ldots$

and joint probability

P_{bm}

Transitions are:

$b=0,\ m \to m+1$ $\quad \beta_0$

$b=1,\ m \to m+1$ $\quad \beta_1$

$b=0,\ m \to m-1$ $\quad \nu m$

$b=1,\ m \to m-1$ $\quad \nu m$

$b=0 \to 1,\ m$ $\quad \alpha c_0$

$b=1 \to 0,\ m$ $\quad \mu$

$$\dot{S} = \sum_m \Big[P_{0m} \beta_0 \log \frac{\beta_0}{\nu(m+1)} + P_{1m} \beta_1 \log \frac{\beta_1}{\nu(m+1)}$$

$$+ P_{0m} \nu m \log \frac{\nu m}{\beta_0} + P_{1m} \nu m \log \frac{\nu m}{\beta_1}$$

$$+ P_{0m} \alpha c_0 \log \frac{\alpha c_0}{\mu} + P_{1m} \mu \log \frac{\mu}{\alpha c_0} \Big]$$

Last 2 terms, sum over m:

$$\Big[p(b=0)\, \alpha c_0 \overline{\in} p(b=1)\, \mu \Big] \log \frac{\alpha c_0}{\mu}$$

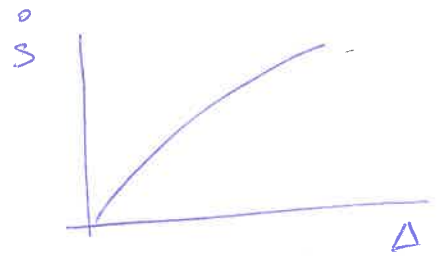
Receptor is in equilibrium $\Rightarrow$ detailed balance

requires $\dfrac{p(b=0)}{p(b=1)} = \dfrac{\mu}{\alpha c_0}$ $\Rightarrow$ these terms vanish

$$\dot{S} = \sum_{bm} P_{bm} \Big[\beta_b \log \frac{\beta_b}{\nu(m+1)} + \nu m \log \frac{\nu m}{\beta_b} \Big]$$

↑ get from master eq. @ steady state.

$\dot{S}$ is a complicated expression but it has important limits:

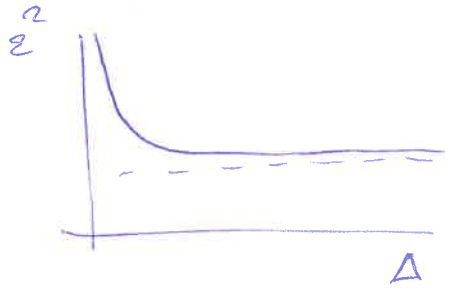


$\dot{S} \to 0$ as $\Delta \to 0$

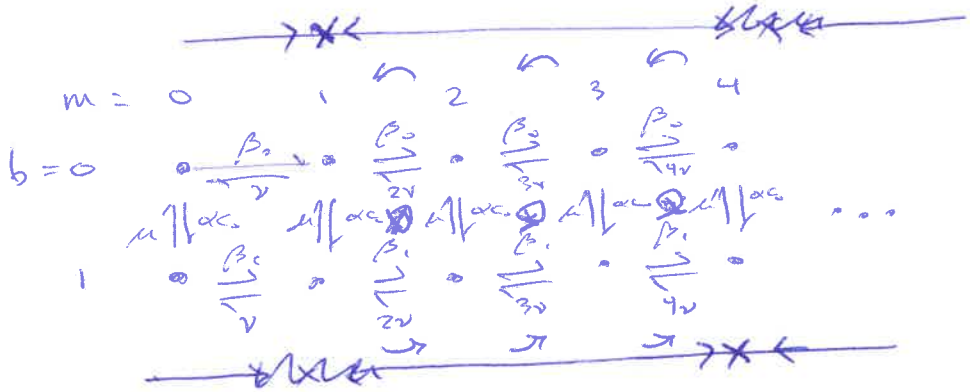
And recall

$\varepsilon^2 \to \infty$ as $\Delta \to 0$

$\Rightarrow$ Sensing requires dissipation



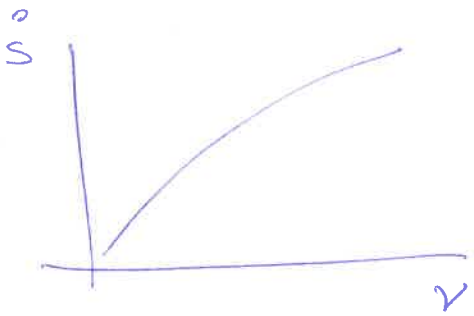
Visually, state space is:



flux cycles are generated between $m = \frac{\beta_0}{\nu}, \frac{\beta_1}{\nu}$

Taking $\Delta = \beta_1 - \beta_0 \to 0$ removes them!

Another limit:



$\dot{S} \to 0$ as $\nu \to 0$

(m & e never degrades)

This is Landauer's principle:

Dissipation results from "erasing" memory.