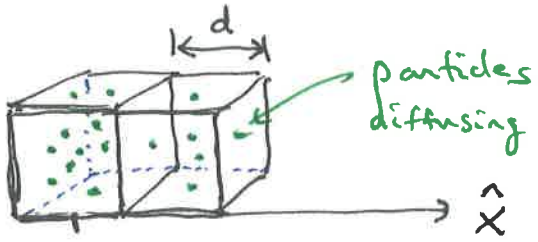
# Simple Diffusion

Consider small voxels of size $d$ in which particles randomly & independently move

$N(x,t)$ = number of particles in cube centered at $x$
(averaged over realizations)




$\vec{J}$ = net number flux = $\frac{\text{Number}}{\text{area} \cdot \text{time}}$ $\left(\frac{\#}{L^2 T}\right)$ across an area with normal along $\vec{J}$

$\vec{J}_\sigma \equiv \frac{\text{amount of "}\sigma\text{"}}{\text{area} \cdot \text{time}}$

$N(x,t)$ changes due to net fluxes through surfaces bounding it:
along surfaces with normal along $\hat{x}$:

$$\frac{dN(x,t)}{dt} = \underbrace{-d^2 J_x(x+d/2)}_{\text{leaving right face}} + \underbrace{d^2 J_x(x-d/2)}_{\text{entering left face}}$$

$J_x \equiv \hat{x}$ component of $\vec{J}$

Taylor expanding:

$$= -d^2\left[J_x(x) + \frac{d}{2}\frac{dJ_x}{dx} + \frac{1}{2}\left(\frac{d}{2}\right)^2 \frac{d^2 J_x}{dx^2} + \dots\right]$$

$$+ d^2\left[J_x(x) - \frac{d}{2}\frac{dJ_x}{dx} + \frac{1}{2}\left(\frac{d}{2}\right)^2 \frac{d^2 J_x}{dx^2} + \dots\right]$$

$$\approx -d^3 \frac{dJ_x}{dx}$$

add up contributions from $\hat{y}$ and $\hat{z}$ directions:

$$\frac{\partial N(\vec{x},t)}{\partial t} = -d^3 \frac{dJ_x}{dx} - d^3 \frac{dJ_y}{dy} - d^3 \frac{dJ_z}{dz} \equiv -d^3 \vec{\nabla}\cdot\vec{J}$$

divide by volume $d^3$:

number density $\frac{\partial n(\vec{x},t)}{\partial t} + \vec{\nabla}\cdot\vec{J} = 0$ ← no birth or death

Conservation law (exact)

Integrating over any volume $\Omega$: $\frac{\partial}{\partial t}\int_\Omega n(\vec{x},t)\, d\vec{x} = \frac{\partial}{\partial t} N(\Omega,t)$ ($d\vec{x} = dx\,dy\,dz$)

$$= -\int_\Omega \vec{\nabla}\cdot\vec{J}\, d\vec{x}$$

$$\equiv -\int \vec{J}\cdot d\vec{S}$$


flux integrated over surface bounding $\Omega$

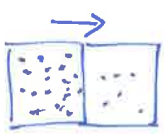
∴ Integral form of conservation $\frac{\partial}{\partial t} N(\Omega,t) = -\int_\Omega \vec{J}\cdot d\vec{S}$

* Now, we need to "close" the conservation equation by relating $\vec{J}(\vec{x})$ to $n(\vec{x},t)$ ⇒ model (approximation)

($n(\vec{x},t)$: vector; $\vec{\nabla}n$: vector)

⇒ Linear response $\vec{J} \propto -\vec{\nabla}n$ (gradient of density)

more particles randomly diffuse to regions with lower density



"Ohms law" "Starling eqn"

"Ficks Law"

$\vec{J} = -\underset{\approx}{D}\vec{\nabla}n$ ($\underset{\approx}{D}$: matrix, e.g.)

$$\underset{\approx}{D} = \begin{pmatrix} D_x & 0 & 0 \\ 0 & D_y & 0 \\ 0 & 0 & D_z \end{pmatrix}$$

anisotropic, different diffusion const. in different directions (layered media)

$D$ has units of $L^2/t$

Addition flux due to convection (fluid flow)

$\vec{v}n$ ← density of particles $\frac{\#}{L^3}$

↓

convection velocity $\frac{L}{T}$ ∴ Total flux: $\vec{J} = -\underset{\approx}{D}\vec{\nabla}n(\vec{x},t) + \vec{v}(\vec{x})n(\vec{x},t)$

$$\frac{\partial n(\vec{x},t)}{\partial t} + \vec{\nabla}\cdot\vec{J} = 0 \Rightarrow \frac{\partial n(\vec{x},t)}{\partial t} + \vec{\nabla}\cdot\left[-\underset{\approx}{D}\nabla n + \vec{v}n\right] = 0$$

* neglect $\vec{\nabla}\cdot\vec{v}$ term

in $\vec{\nabla}\cdot(\vec{v}n) = n\vec{\nabla}\cdot\vec{v}$ (incompressibility) $+ \vec{v}\cdot\vec{\nabla}n$

$$\Rightarrow \boxed{\frac{\partial n(\vec{x},t)}{\partial t} + \vec{v}\cdot\nabla n = D\nabla^2 n}$$

Basic convection-diffusion equation

* also assume constant, isotropic $D$

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In quiet medium, $\vec{v} = 0$, consider dimensional arguments

How long takes to diffuse ~1 cm ?

$D \sim 10^{-5} - 10^{-7}$ cm$^2$/s for typical molecule in water

∴ - time to diffuse 1cm $T \sim \frac{L^2}{D} \sim \frac{(1\text{ cm})^2}{10^{-6}\text{ cm}^2/\text{s}} \sim 10^6\text{ s} \sim 1\text{wk}$

- time to diffuse 1μm $T \sim \frac{(10^{-4}\text{cm})^2}{10^{-6}\text{cm}^2/\text{s}} \sim 10^{-2}\text{ s} \sim 10\text{ms}$

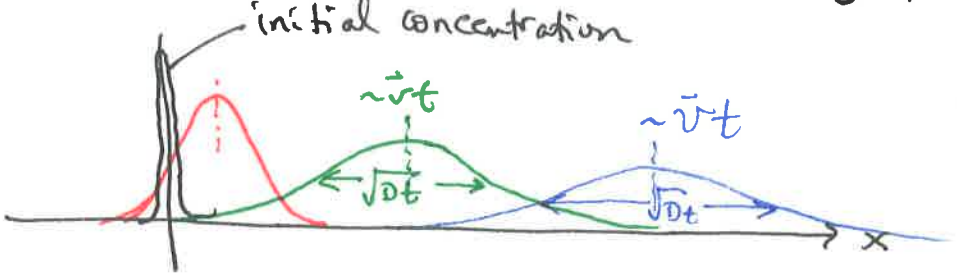
Exact "free-space" solution with "point" initial condition $n(\vec{x}, t=0) = C\,\delta(\vec{x})$:

$$n(\vec{x},t) = \frac{C}{(4\pi D t)^{d/2}} \exp\left[-\frac{|\vec{x}-\vec{v}t|^2}{4Dt}\right]$$

mean position

2. variance

dimensionality of space




spread ~ $\sqrt{Dt}$

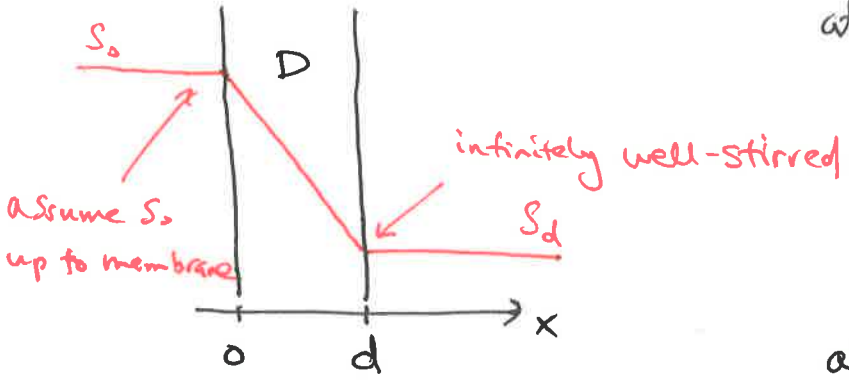
peak position ~ $\vec{v}t$

## Consider steady state

$$\frac{\partial n}{\partial t} = 0 = D\nabla^2 n \Rightarrow \text{Laplace's eqn } \nabla^2 n = 0$$

## Membrane diffusion

diffusion across homogeneous membrane




at steady state, inside membrane,

$$\frac{d^2 S(x)}{dx^2} = 0$$

$$\Rightarrow S(x) = Ax + B$$

at $x=0$, $B = S_0$

at $x=d$, $Ad + S_0 = S_d$

$$\Rightarrow S(x) = \frac{S_d - S_0}{d}x + S_0$$

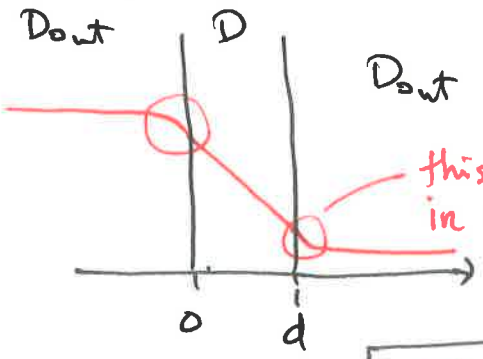
$$\text{flux } J = -D\underbrace{\frac{dS}{dx}}_{\text{constant at each point x (steady state)}} = \frac{D}{d}(S_0 - S_d)$$

$$I = \frac{V}{R} \quad \text{Ohm's law}$$

$$J = \frac{D}{d}(S_0 - S_d)$$

"membr" conductance; "voltages"

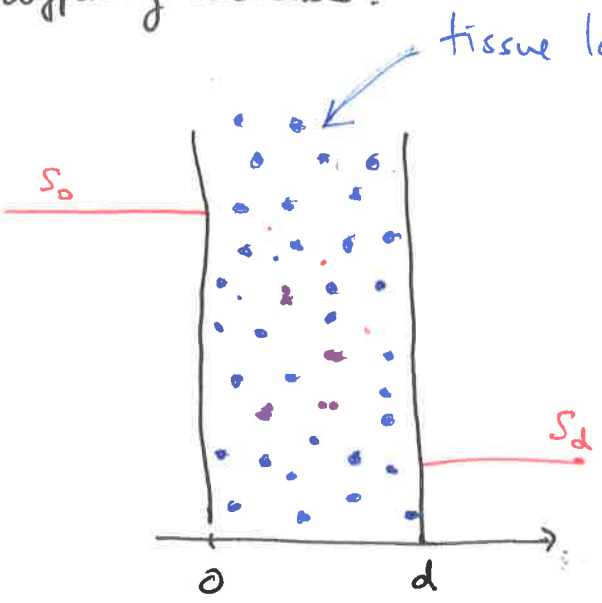
In reality there is diffusion outside the membrane $D_{out}$




Only in $d > 2$

# Facilitated Diffusion

Now consider diffusion mediated by binding to another diffusing molecule:




$S \equiv$ oxygen concentration $[O_2]$

$e \equiv$ myoglobin concentration $[Mb]$

$C \equiv [MbO_2]$ complex

inside membrane:

$$O_2 + Mb \underset{k_-}{\overset{k_+}{\rightleftharpoons}} MbO_2$$

Can myoglobin speed up oxygen transport even though myoglobin-oxygen complex diffuses much more slowly?

* Even though <u>each</u> complex diffuses slowly (much slower than free oxygen), at steady-state, a very high Mb concentration can dramatically load the tissue with oxygen

⇒ gradients are also larger, leading to larger flux.

# Facilitated diffusion

outside tissue $[Mb] = [MbO_2] = 0$

$S = [O_2] = S_0$ or $S_d$

inside tissue:

$$\frac{\partial s}{\partial t} = D_s \frac{\partial^2 s}{\partial x^2} - k_+ s e + k_- c$$

$$\frac{\partial e}{\partial t} = D_e \frac{\partial^2 e}{\partial x^2} - k_+ s e + k_- c$$

$$\frac{\partial c}{\partial t} = D_c \frac{\partial^2 c}{\partial x^2} + k_+ s e - k_- c$$

$c + s \equiv$ total oxygen concentration (complexed + free)

* Mb is large molecule, so $D_e \sim D_c \ll D_s$

* adding eqs: $\frac{\partial s}{\partial t} + \frac{\partial c}{\partial t} = \frac{\partial}{\partial x}\left[D_s \frac{\partial s}{\partial x} + D_c \frac{\partial c}{\partial x}\right]$

$\equiv -J$ (total oxygen flux)

at steady state, $J(x)$ is constant

$$-\int_0^d J\,dx \equiv -dJ = \int_0^d dx \left[D_s \frac{ds}{dx} + D_c \frac{dc}{dx}\right]$$

$$= D_s (S_d - S_0) + D_c (C_d - C_0)$$

$$\therefore \quad J = \frac{D_s}{d}(S_0 - S_d) + \frac{D_c}{d}(C_0 - C_d)$$

$C_0$: concentration just inside membrane

transport from force diffusion

Nondimensionalize $\sigma \equiv \frac{k_+}{k_-} s(x)$, $u(x) = \frac{c(x)}{e_0}$, $x \equiv \xi d$

↑ total initial myoglobin conc.

at steady state,

$$\frac{1}{e_0} D_s \frac{d^2 s}{dx^2} = k_+ s \underbrace{(e_0 - c)}_{e(x)} - k_- c$$

$$\Rightarrow \frac{D_s}{e_0 d^2} \frac{k_-}{k_+} \frac{d^2\sigma}{d\xi^2} + k_- u - k_- \sigma(1-u)$$

$$\Rightarrow \left(\frac{D_s}{e_0 d^2 k_+}\right) \frac{d^2\sigma}{d\xi^2} + u - \sigma(1-u) = 0$$

these are small

Similarly, $\left(\frac{D_c}{d^2 k_-}\right) \frac{d^2 u}{d\xi^2} - u + \sigma(1-u) = 0$

For muscle tissue, $k_+ \sim 1.4 \times 10^{10}\ cm^3/\mu s$, $k_- \sim 11/s$, $d \approx 0.02\ cm$

$e_0 \sim 1.2 \times 10^{-5}\ M/cm^3$, $D_c \sim 4 \times 10^{-7}\ cm^2/s$

$D_s \sim 1.2 \times 10^{-5}\ cm^2/s$

$$\frac{D_s}{e_0 d^2 k_+} \sim 1.5 \times 10^{-7} \equiv \varepsilon_1$$

$$\frac{D_c}{d^2 k_-} \sim 8 \times 10^{-5} \equiv \varepsilon_2$$

$$\varepsilon_1 \frac{d^2\sigma}{d\xi^2} + u - \sigma(1-u) = 0$$

$$\varepsilon_2 \frac{d^2 u}{d\xi^2} - u + \sigma(1-u) = 0$$

$\Rightarrow$ no boundary layers

(boundary conditions are compatible w/ outer solution)

$$\Rightarrow u \approx \frac{\sigma}{1+\sigma}, \quad c \approx \frac{e_0 s}{s + k_-/k_+} \equiv \frac{e_0 s}{s + k}$$

$$\therefore \quad C_b = \frac{e_0 S_b}{S_b + K}, \quad C_d = \frac{e_0 S_d}{S_d + K}$$

Substituting into expression for $J$;

free diffusion flux

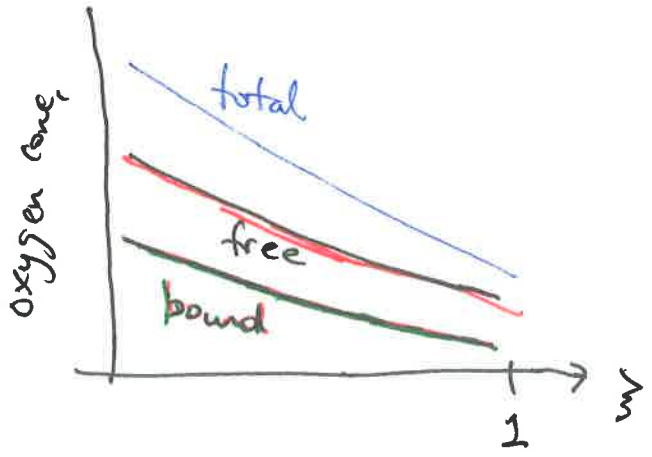
$$J = \frac{D_s}{d}(S_b - S_d) + \frac{D_c}{d} e_0 \left( \frac{S_b}{S_b + K} - \frac{S_d}{S_d + K} \right)$$

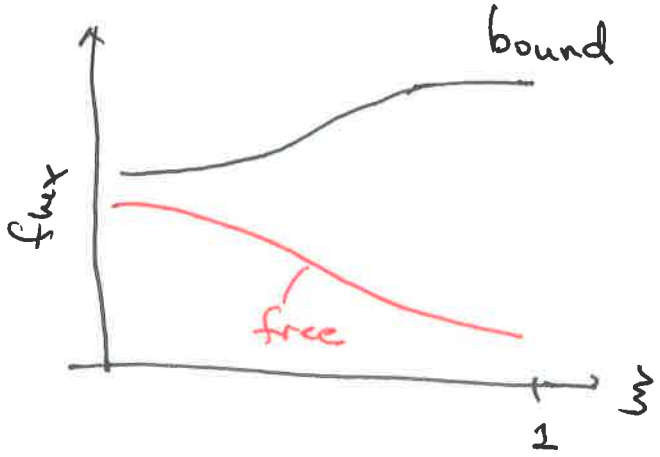
$$= \frac{D_s}{d}(S_b - S_d) \left[ 1 + \frac{D_c}{D_s} \frac{e_0 K}{(S_b + K)(S_d + K)} \right]$$

$$\equiv \frac{D_s}{d}(S_b - S_d)(1 + \mu\rho) \; ; \quad \rho = \frac{D_c}{D_s} \frac{e_0}{K}$$

Can be large if $e_0$ is large

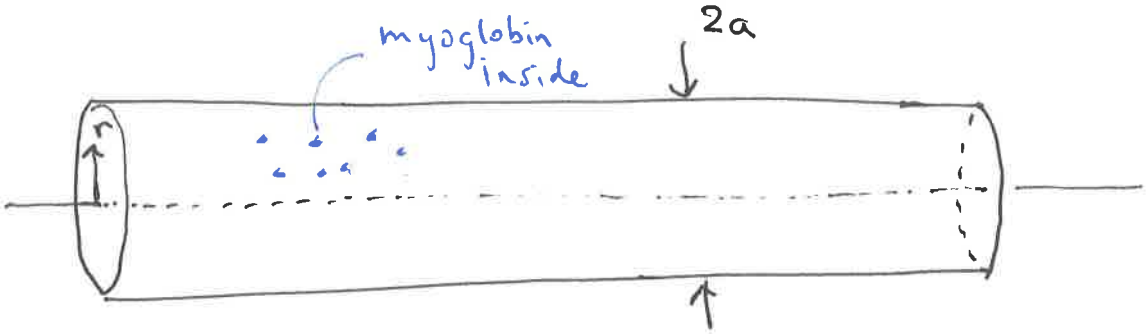
$$\mu \equiv \frac{K^2}{(S_b + K)(S_d + K)}$$



# Facilitated diffusion & oxygen debt

Consider cylindrical muscle fiber:




$s(r=a) \equiv s_a$ (outside $[O_2]$)

no flux of myoglobin outside of fiber,

$$\left.\frac{dc}{dr}\right|_{r=a} = 0$$

Steady-state with 2D cylindrical coordinates

$O_2$ consumption (metabolic) rate

$$\underbrace{D_s \frac{1}{r}\frac{d}{dr}\left(r\frac{ds}{dr}\right)}_{D_s \nabla^2 s} - k_+ s e + k_- c - g = 0$$

we assume $g$ is constant inside cylinder

$$D_c \frac{1}{r}\frac{d}{dr}\left(r\frac{dc}{dr}\right) + k_+ s e - k_- c = 0$$

$s_a \sim 3.5\times10^{-8}$ mol/cm$^3$

$r = ay \quad (0 \le y \le 1), \quad \sigma = \frac{k_+}{k} s, \quad u = \frac{c}{e_0}$

$$\varepsilon_1 \equiv \frac{D_s}{e_0 k_+ a^2} \sim 2\times10^{-4}, \quad \varepsilon_2 \equiv \frac{D_c}{k_- a^2} \sim 1.2\times10^{-3}, \quad \gamma \equiv \frac{g}{e_0 k_-} \sim 3\times10^{-3}$$

$$\varepsilon_1 \frac{1}{y}\frac{d}{dy}\left(y\frac{d\sigma}{dy}\right) - \gamma = \sigma(1-u) - u$$

$$+ \quad \varepsilon_2 \frac{1}{y}\frac{d}{dy}\left(y\frac{du}{dy}\right) = -\sigma(1-u) + u$$

$$\varepsilon_1 \frac{1}{y}\frac{d}{dy}\left(y\frac{d\sigma}{dy}\right) + \varepsilon_2 \frac{1}{y}\frac{d}{dy}\left(y\frac{du}{dy}\right) = \gamma$$

xy: $$\varepsilon_1 \frac{d}{dy}\left(y\frac{d\sigma}{dy}\right) + \varepsilon_2 \frac{d}{dy}\left(y\frac{du}{dy}\right) = \gamma y$$

integrate: $$\varepsilon_1 y\frac{d\sigma}{dy} + \varepsilon_2 y\frac{du}{dy} = \gamma y^2/2 + C_0$$ ← integration const.

/y: $$\varepsilon_1 \frac{d\sigma}{dy} + \varepsilon_2 \frac{du}{dy} = \frac{\gamma y}{2} + \frac{C_0}{y}$$

integrate: $$\varepsilon_1 \sigma + \varepsilon_2 u = \frac{\gamma y^2}{4} + C_0 \ln y + C_1$$

for $r \to 0$ ($y \to 0$) concentrations are bounded, so $C_0 \equiv 0$

at the centerline $\varepsilon_1 \sigma(0) + \varepsilon_2 u(0) = C_1$

∴ "marginal oxygen debt" defined as when $C_1 = 0$,
exactly zero oxygen at the centerline

In this case, $$\varepsilon_1 \sigma + \varepsilon_2 u = \frac{\gamma}{4} y^2$$

We need to relate $\sigma(y)$ and $u(y)$ to each other:

Since $\varepsilon_1, \varepsilon_2, \gamma$ are all small, we assume

$$\sigma(1-u) - u \approx 0$$ (again, no boundary layers, "outer soln" suffices)

$\therefore$ at marginal oxygen debt conditions, $u = \dfrac{\sigma}{1+\sigma}$

$$\Rightarrow u_0 = \frac{\sigma_0}{1+\sigma_0}$$

("$_0$" denoting marginal $O_2$ debt condition)

$$\varepsilon_1 \sigma_0(y) + \varepsilon_2 \frac{\sigma_0(y)}{1+\sigma_0(y)} = \frac{\gamma}{4} y^2$$

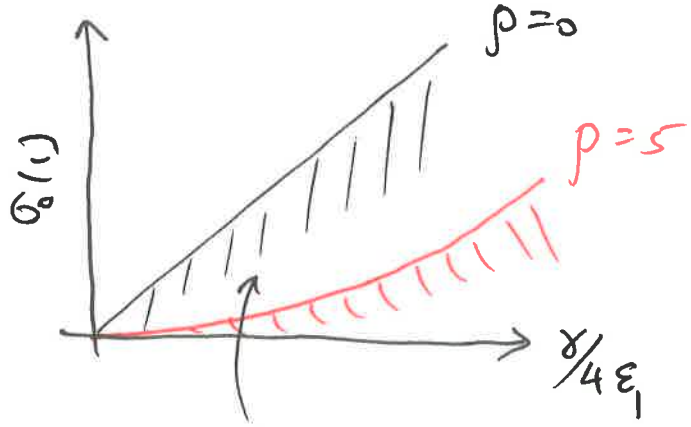
<u>at surface $y=1$</u> :

$$\varepsilon_1 \sigma_0(1) + \varepsilon_2 \left( \frac{\sigma_0(1)}{1+\sigma_0(1)} \right) = \frac{\gamma}{4}$$

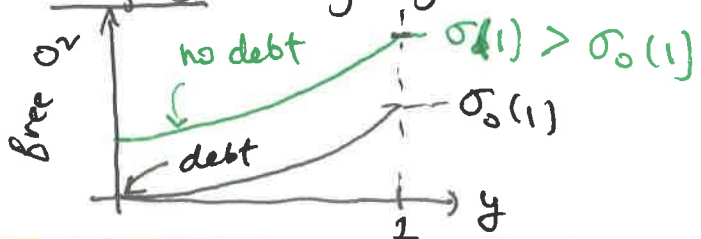
$$\varepsilon_2/\varepsilon_1 = \frac{D_c e_0}{D_g} \frac{k_+}{k_-}$$

$$\sigma_0(1) + \rho \frac{\sigma_0(1)}{1+\sigma_0(1)} = \frac{\gamma}{4\varepsilon_1}$$

$\sigma_0(1)$ is the surface conc. of $[O_2]$ that is just enough to have marginal $O_2$ debt at centerline




<u>for $\rho=5$</u> Any region under these $\rho$ curves leads of $[O_2]$ debt.

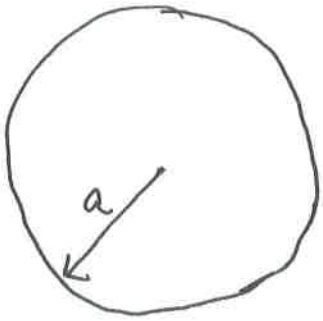


# Chemoreception

Berg & Purcell, Biophysical Journal (1977)

Consider an isolated spherical cell of radius $a$ immersed in an infinite medium of food or signaling molecule

Assume no flow ($\vec{v}=0$) and steady state:




$n(\vec{r})$ = concentration of food

$n(|\vec{r}|\to\infty) \equiv n_\infty$

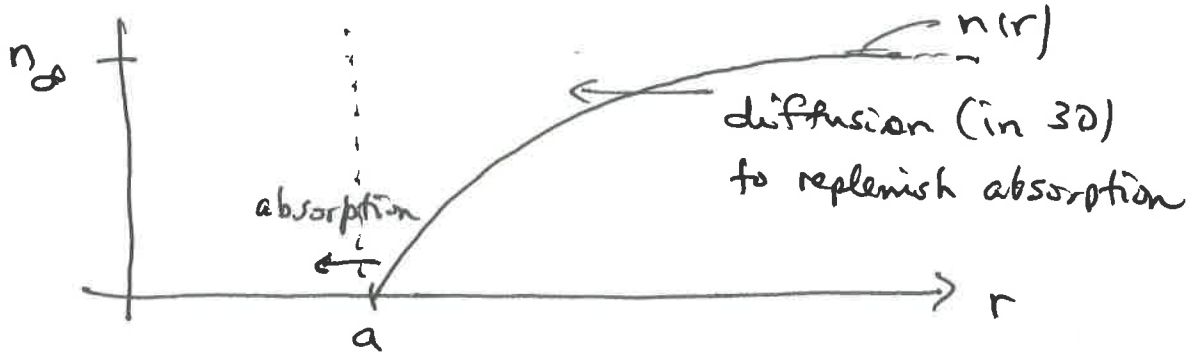
If sphere is perfectly absorbing,

$n(r=a)=0$

$$\nabla^2 n = \frac{\partial^2 n}{\partial r^2} + \frac{2}{r}\frac{\partial n}{\partial r} = 0 \Rightarrow n(r) = \frac{A}{r} + B$$

(spherically symmetric problem)

Applying B.C.s $\boxed{n(r) = n_\infty\left(1 - \frac{a}{r}\right)}$

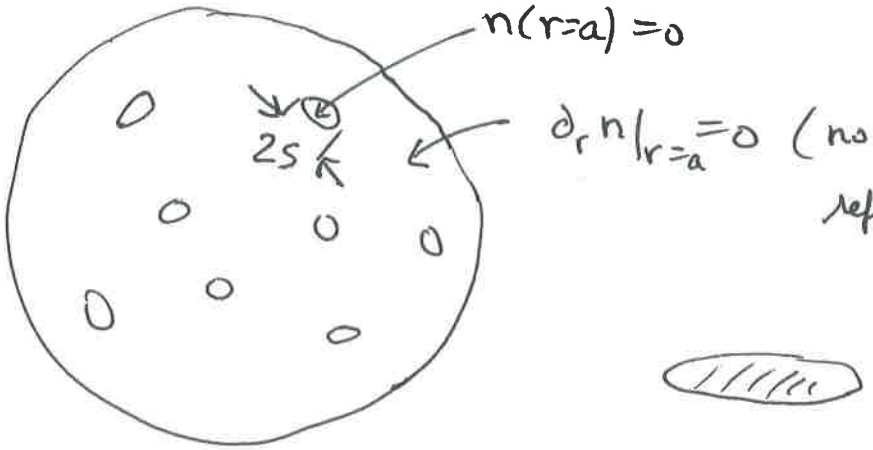


* Uptake rate of spherical, isolated cell:

$$\underbrace{4\pi a^2}_{\text{area}} \underbrace{D\,\partial_r n\big|_{r=a}}_{\text{flux in}} = 4\pi a D n_\infty \equiv J_{max}$$

prop. to $a$, not $a^2$! (one $a$ cancelled by $\partial_r n|_{r=a}$)

* Now consider cells that are covered with small absorbing receptors of radius $s$.




for a single isolated disk, $J_1 = 4Dsn_\infty$

(Solve Laplace's Eqn with an absorbing disk)

Berg & Purcell used an electrostatics analogy to find a "capacitance" of a spherical ball with small conducting patches randomly distributed

$$J = \frac{4\pi D n_\infty a N_s}{N_s + \pi a} \equiv J_{max}\left(\frac{N_s}{N_s + \pi a}\right)$$

reduction in uptake due to mostly reflective surface

Analogy

| Diffusion | Electrostatics |
|---|---|
| $\nabla^2 n = 0$ | $\nabla^2 \phi = 0$ |
| $J = -D\nabla n$ | $\vec{D} = -\varepsilon \nabla \phi$ |
| $J_{tot} = \int \vec{J} \cdot d\vec{s}$ | $Q = \frac{1}{4\pi}\int \vec{D} \cdot d\vec{s}$ (charge) |
| $J_{tot} \Leftrightarrow 4\pi Q$ | |

Charge $Q \equiv \varepsilon \phi_\infty K$ ← Capacitance of medium

$\Rightarrow D n_\infty K$ ← we just have to calculate Capacitance of medium

$J_{TOT} = 4\pi D n_\infty K$ ⇒ many shapes are tabulated, including

$J_1 = 4 D s n_\infty$ for a one-sided disk

$K$ for Wiffle ball (region exterior to) $= \dfrac{a N_s}{N_s + \pi a}$

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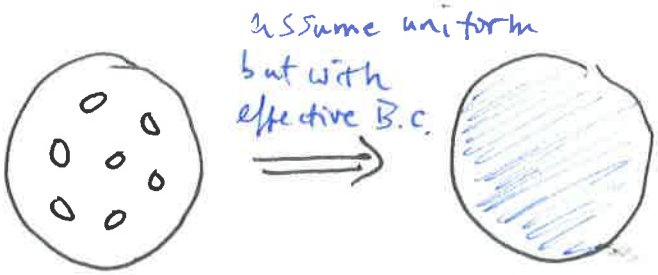
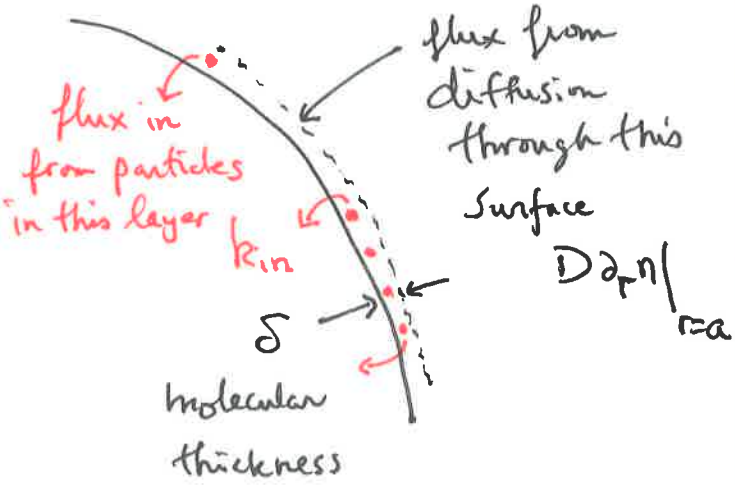
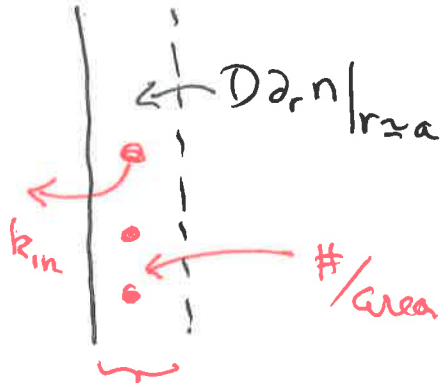
Another approach: effective medium theory (do some sort of averaging)




$\#/_{area}$ at the surface (within $\delta$) $= n(r=a)\cdot\delta$

$\#/L^3 \cdot L \equiv \dfrac{\#}{area}$

Infinitessimal layer, fluxes have to balance in steady-state

$1/T$

$\therefore D\partial_r n|_{r=a} = k_{in}\,\delta\, n(r=a)$

$\equiv k_{in}\, n(r=a)$ ← $L/T$

Using $D\partial_r n(r=a) = k_{in}\, n(r=a)$ on $n(r) = \frac{A}{r} + B$,

we find

$$\boxed{n(r) = n_\infty \left(1 - \frac{k_{in}\, a}{D + k_{in}\, a}\, \frac{a}{r}\right)}$$

How to find $k_{in}$? Set total flux to be that of $N$ independent, isolated disks $NJ_1$

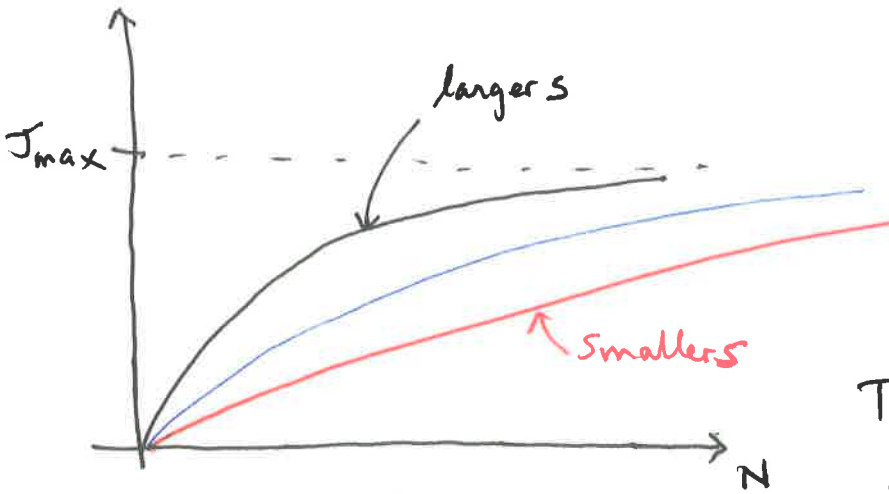
$$4\pi a^2 k_{in}\, n(r=a) = 4\pi a^2 k_{in}\, n_\infty \left(1 - \frac{k_{in} a}{D + k_{in} a}\right)$$

$$= J_1 N = 4 D s\, n_\infty N$$

$$4\pi a^2 k_{in}\, n_\infty \frac{D}{D + k_{in} a} = 4\pi D a\, n_\infty \frac{k_{in} a}{D + k_{in} a} = 4 D s\, n_\infty N$$

$$\Rightarrow k_{in} a = \frac{DNs}{\pi a}$$ use this expression in flux

$$\Rightarrow J = 4\pi a D\, n_\infty \frac{k_{in} a}{D + k_{in} a} = J_{max} \left(\frac{Ns}{Ns + \pi a}\right)$$




Suppose $s \simeq 1\text{nm}$, $a \simeq 1\mu\text{m}$

When does $J = \frac{1}{2} J_{max}$?

$$\frac{Ns}{Ns + \pi a} \simeq \frac{1}{2} \Rightarrow \pi a \simeq Ns$$

$$N \simeq 3100.$$

Total receptor area: $3100\pi s^2 = 10^{-10}\,\text{cm}^2$

$4\pi a^2 = 1.2 \times 10^{-7}\,\text{cm}^2$

If receptors occupy $1/1000$ of cell surface, $J = \frac{1}{2} J_{max}$ !!

Berg & Purcell effect: uniformly spread out receptors are most efficient only need 0.1% of surface in this example to achieve ½ of maximal flux associated with entire surface being absorbing.

Spread out absorbing patches complete least with each other

If all 3100 patches were coalesced into one: $\pi s'^2 = 3100\pi s^2$

Current would reduce from $\frac{J_{max}}{2} \longrightarrow \frac{J_{max}}{\sqrt{3100}}$

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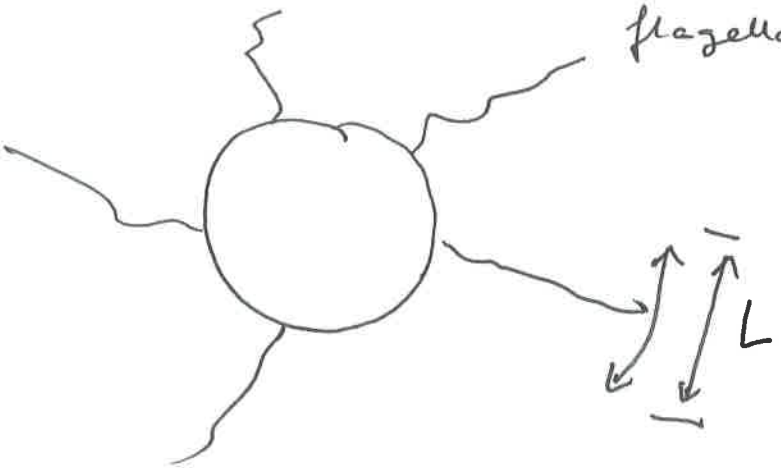
Stirring effects to increase uptake?




flagella move back and forth with velocity $v_s$ over a length scale $L$

typical time scale of beating $\tau_s \sim \frac{L}{v_s}$

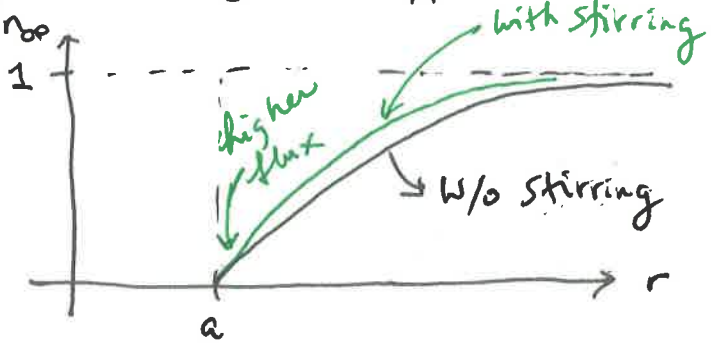
diffusive movement of molecules of distance $L$: $\tau_{diff} \sim \frac{L^2}{D}$

∴ Stirring can only be effective if $\tau_s \ll \tau_{diff}$

$\frac{L}{v_s} \ll \frac{L^2}{D} \Rightarrow v_s \gg \frac{D}{L}$

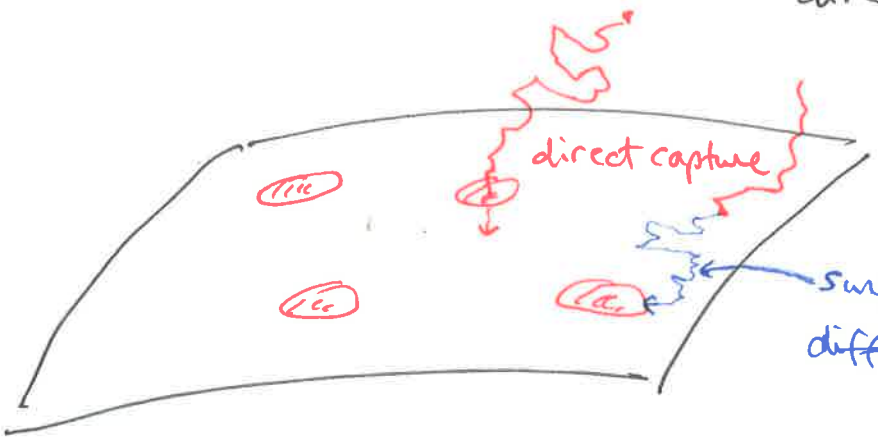
if $L \sim 1\mu m$, $D \sim 10^{-5}\ cm^2/s$

requires $v_s \gg 0.1\ cm/s$ (unrealistic)



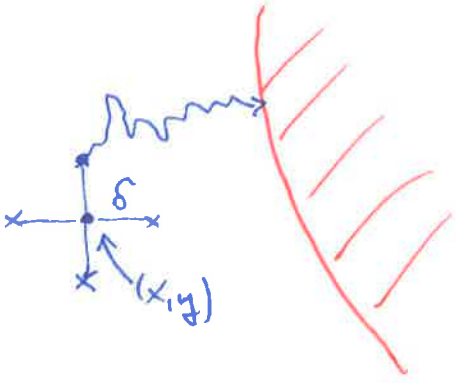
# Two-stage capture ("antenna" effects)

Compare surface diffusion w/ direct diffusion-limited capture




Suppose there is attraction to the non-absorbing surface, surface diffusivity $D_2$ followed by surface diffusion


$T(x,y) \equiv$ average time a surface-absorbed particle takes to bump into path perimeter




$$T(x,y) = \Delta t + \frac{1}{4}\left[T(x+\delta,y) + T(x-\delta,y) + T(x,y+\delta) + T(x,y-\delta)\right]$$

take $\delta \to 0$ but then also $\Delta t \to 0$, but connected through $\frac{\delta^2}{4\Delta t} = D_2$ fixed

Taylor-expanding:

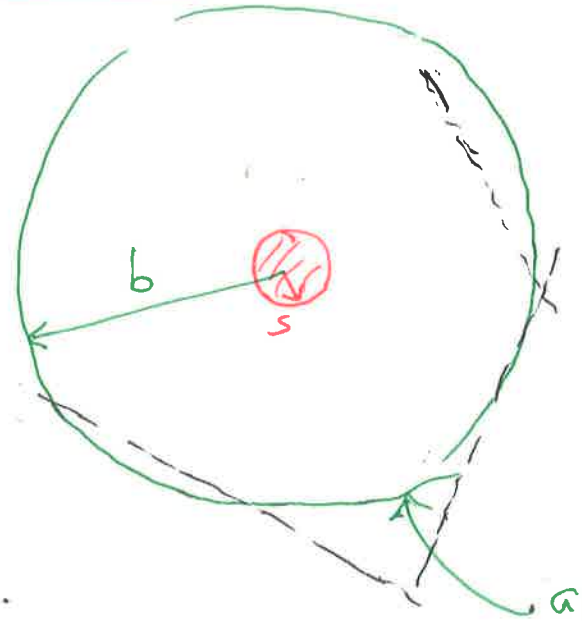
$$T(x,y) = \Delta t + \frac{1}{4}\left[T + \frac{\partial T}{\partial x}\delta + \frac{1}{2}\frac{\partial^2 T}{\partial x^2}\delta^2 + \dots + T - \frac{\partial T}{\partial x}\delta + \frac{1}{2}\frac{\partial^2 T}{\partial x^2}\delta^2 + T + \frac{\partial T}{\partial y}\delta + \frac{1}{2}\delta^2\frac{\partial^2 T}{\partial y^2} + \dots + T - \frac{\partial T}{\partial y}\delta + \frac{1}{2}\frac{\partial^2 T}{\partial y^2}\delta^2\right]$$

$$= \Delta t + T + \frac{1}{4}\delta^2\left(\frac{\partial^2 T}{\partial x^2} + \frac{\partial^2 T}{\partial y^2}\right)$$

$\Rightarrow \quad -\frac{\Delta t}{4\delta^2} = \nabla_\perp^2 T = -\frac{1}{D_2}$ ∴ we need to solve

$\nabla_\perp^2 T(x,y) = -\frac{1}{D_2}$ to find mean absorbing time (from surface diffusion)

## Cell model




Uniform patches → roughly a triangular lattice

approximate Voronoi tesselation by circle of radius b.

Boundary conditions: $T(r=s) = 0$ (no time to reach perimeter)

$\left.\frac{\partial T}{\partial r}\right|_{r=b} = 0$ (reflecting B.C. → transfer to neighboring cell)

$r^2 = x^2+y^2$, solving $\frac{\partial^2 T}{\partial r^2} + \frac{1}{r}\frac{\partial T}{\partial r} = -\frac{1}{D_2}$, $T(r)$ takes the form $Ar^2 + B\ln r + C$ ($A, B, C$ determined by $\frac{1}{D_2}$ and B.C.s)

B.C. $\begin{cases} As^2 + B\ln s + C = 0 \\ 2Ab + \frac{B}{b} = 0 \end{cases}$

$C = \frac{s^2}{4D_2} - \frac{2b^2}{4D_2}\ln s$

Eqn:

$2A - \frac{B}{r^2} + \frac{1}{r}\left(2Ar + \frac{B}{r}\right) = -\frac{1}{D_2}$

$4A = -\frac{1}{D_2}$, $A = -\frac{1}{4D_2}$, $B = \frac{2b^2}{4D_2}$

$$T(r) = \frac{2b^2\ln(r/s) + (s^2 - r^2)}{4D_2}$$

Now, average over the annulus of starting radii r:

$$\langle T \rangle \equiv \frac{2\pi}{\pi(b^2-s^2)} \int_s^b T(r)\, r\, dr$$

$$= \frac{b^4 \ln(b/s)}{2D_2(b^2-s^2)} - \frac{3b^2-s^2}{8D_2} \xrightarrow{b \gg s} \frac{b^2}{2D_2}\left[\ln\left(\frac{b}{s}\right) - \frac{3}{4}\right]$$

$$\pi b^2 N = \text{Surface of cell} = 4\pi a^2 \quad \therefore\ b^2 = \frac{4a^2}{N}$$

(total)

Total uptake rate through perimeters of patches $J_2 = \dfrac{\bar{M}}{\langle T \rangle}$

where $\bar{M}$ is the total number (at steady state) absorbed on cell surface. If $J(\text{bulk}) \ll J_{max}$, $\left(\dfrac{N/s}{Ns + \pi a} \ll 1\right)$

then $\bar{M}$ can be approximated using equilibrium argument

$$\bar{M} \simeq \underbrace{4\pi a^2}_{\text{cell area}}\ \underbrace{d}_{\text{molecular thickness}}\ n_\infty\, e^{E_A/kT}$$

(Surface shell volume)

$E_A$ ← adsorption free energy while "inside" "absorbed" volume $4\pi a^2 d$

Compare $J_2 = \dfrac{4\pi a^2 d\, n_\infty e^{E_A/kT}}{\langle T \rangle}$ with $J \simeq 4NDs\, n_\infty$

---

$J_2$ can be larger than $J$. antenna effect.

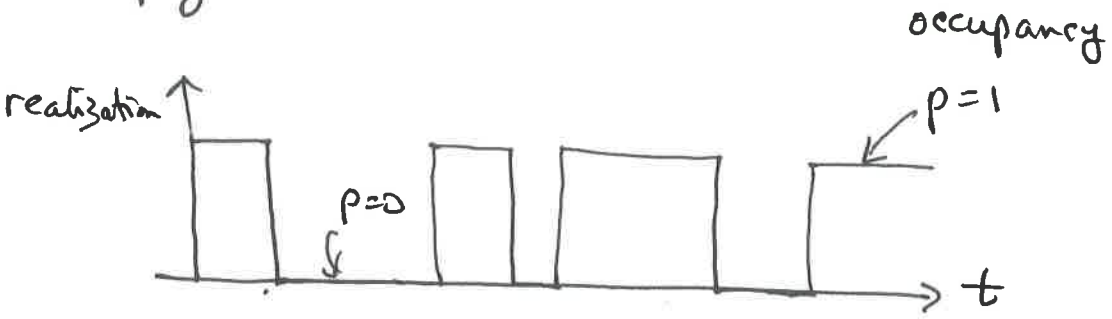
1D-3D

# Single receptor statistics

Cell wants to measure outside molecule concentration $c$

for e.g., chemotaxis

Consider single receptor that can be bound by ligand or empty




define $p(t)$ as the probability of occupancy

$$\dot{p} = k_+ c(1-p) - k_- p$$

$k_+ c(1-p)$: binding rate; $k_- p$: dissociation probability/time (rate)

at steady-state, $\bar{p} = \frac{c}{c+K}$, $K \equiv k_-/k_+$ (mean occupancy is a function of c)

However, a cell can measure occupancy for a finite time $T$,

$$P_T = \frac{1}{T}\int_{t_1}^{t_1+T} p(t')\,dt' \neq \bar{p}$$

measure $P_T$, and infer $c$.

Uncertainty in $c$: $\left(\frac{\delta c}{c}\right)^2 = \frac{1}{c^2}\left(\frac{dc}{d\rho}\right)^2 (\delta\rho)^2$

($\delta c/c$: coeff. of variation in the inferred $c$)

($d\rho$: relate to uncertainty in $\rho$)

Averaging over many measurements

$$\left\langle \left(\frac{\delta c}{c}\right)^2 \right\rangle = \frac{1}{c^2}\left(\frac{d\rho}{dc}\right)^2 \langle \delta\rho^2 \rangle$$

$\langle \delta\rho^2 \rangle = \langle (\rho_T - \bar{\rho})^2 \rangle$ (variation in determining/estimating $\bar{\rho}$)

$G(\tau) \equiv \langle \rho(t)\, \rho(t+\tau) \rangle \equiv$ auto correlation function

$$\langle \rho_T^2 \rangle \equiv \left\langle \frac{1}{T^2} \int_{t_1}^{t_1+T} dt' \int_{t_1}^{t_1+T} dt\ \rho(t')\,\rho(t) \right\rangle$$

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

How to determine $G$? $\rho(t)\,\rho(t+\tau)$ is 1 only if $\rho(t) = 1$ and $\rho(t+\tau) = 1$

otherwise $G = 0$

$\therefore$ # of 1,1's in $N$ measurements $= N G(\tau)$

for $\tau \to \tau + d\tau$, $k_- N G\, d\tau$ is the number of $(1,1) \to (1,0)$

# of $(1,0)$s: $N\bar{\rho} - N G$, in $d\tau$, $k_+ (\bar{\rho} - G) N\, d\tau$

($N\bar{\rho}$: average # of 1; $NG$: # of $(1,1)$)

$\Rightarrow$ # of $(1,0) \xrightarrow[d\tau]{} (1,1)$

since $\bar{p}$ is determined at steady-state $k_+(1-\bar{p}) = k_-\bar{p}$

$$\therefore \quad \frac{dG}{d\tau} = -k_- G + k_-(\bar{p}-G)\frac{\bar{p}}{1-\bar{p}} \qquad \Rightarrow k_+ = \frac{k_-\bar{p}}{1-\bar{p}}$$

$G(0) = \bar{p}$ (pick any initial time after the system has reached steady state)

$$\therefore \quad G(\tau) = \bar{p}^2 + \bar{p}(1-\bar{p})\exp\left[-\frac{k_-|\tau|}{1-\bar{p}}\right]$$

and $\langle p_T^2\rangle - \bar{p}^2 = \frac{2}{T}\cdot\frac{\bar{p}(1-\bar{p})^2}{k_-}$

$$\left\langle\left(\frac{\delta c}{c}\right)^2\right\rangle = \frac{1}{c^2}\left(\frac{c^2}{\bar{p}^2(1-\bar{p})^2}\right)\cdot\frac{2\bar{p}(1-\bar{p})^2}{Tk_-} = \frac{2}{T\bar{p}k_-}$$

Now assume on-rate is to a perfectly absorbing disk of radius $S$:

$$\left.\begin{aligned} k_-\bar{p} &= \underbrace{k_+}_{4DSc}(1-\bar{p}) \end{aligned}\right\} \Rightarrow k_- = 4DSc\left(\frac{1-\bar{p}}{\bar{p}}\right)$$

$$\left\langle\left(\frac{\delta c}{c}\right)^2\right\rangle = \frac{1}{2TDSc(1-\bar{p})}$$

limit of detection of concentration improves for longer $T$, larger $c$, and smaller $\bar{p}$.

Extensions: multiple, correlated receptors, receptor clustering and cooperativity
spatial structure and dynamic $c(\vec{r},t)$