UACM Universidad Autónoma de la Ciudad de México
Nada humano me es ajeno

Maestría en Ciencias
de la complejidad

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Selected topic in Physical Biology

Lectures 4-5

Physics of diffusion and applications in cellular biology

1. Fundamentals
2. Applications to FRAP experiments
3. Receptor binding on a cell's surface
4. Diffusive interactions and diffusion to two receptor-covered cells.

Diffusion (*passive* transport) versus directed motion (this requires *energy*)

We will calculate typical times for passive transport

$$\tau \simeq L^2/D$$

$$L \gg R$$

Diffusion

Directed motion

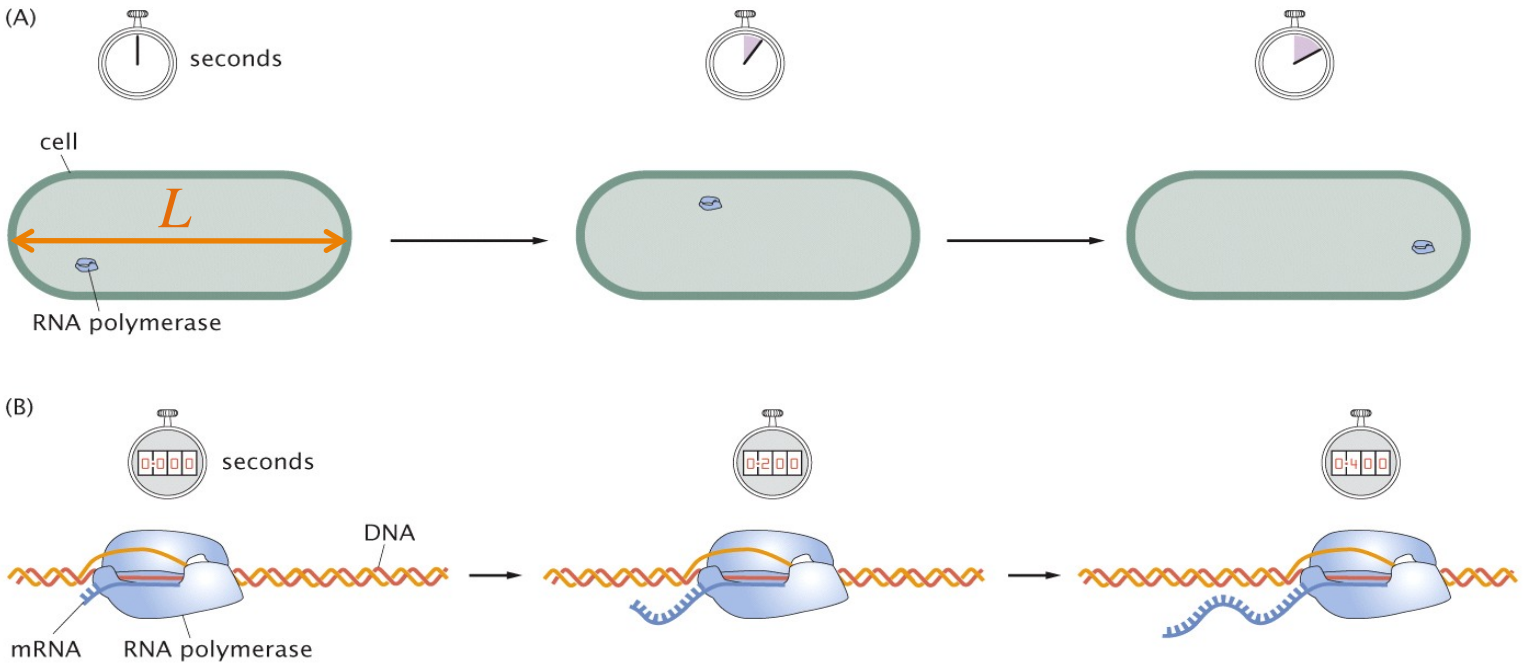


Figure 13.2 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Diffusion time grows quadratically with distance

Diffusion time as a function of the length traveled for a typical value of D (protein in water) of 100 mm/s^2

Transport over macroscopic lengths requires years!

Other mechanisms are required for transport in cells!

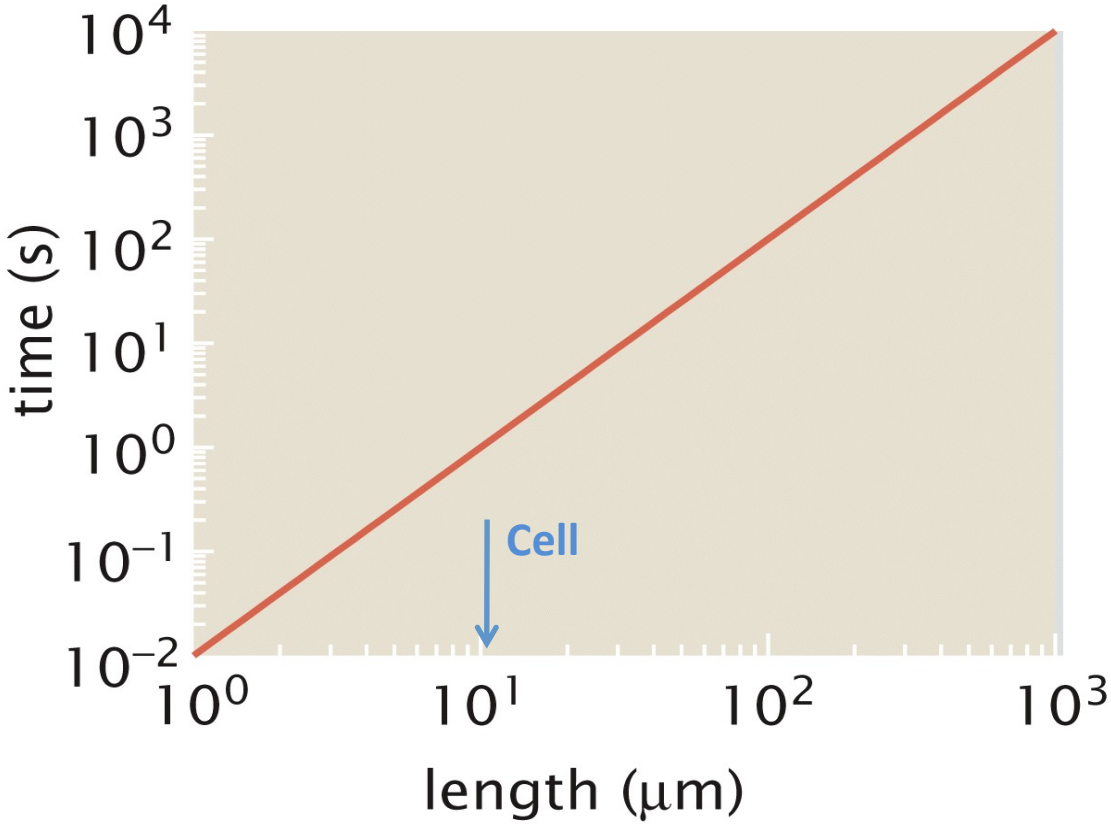


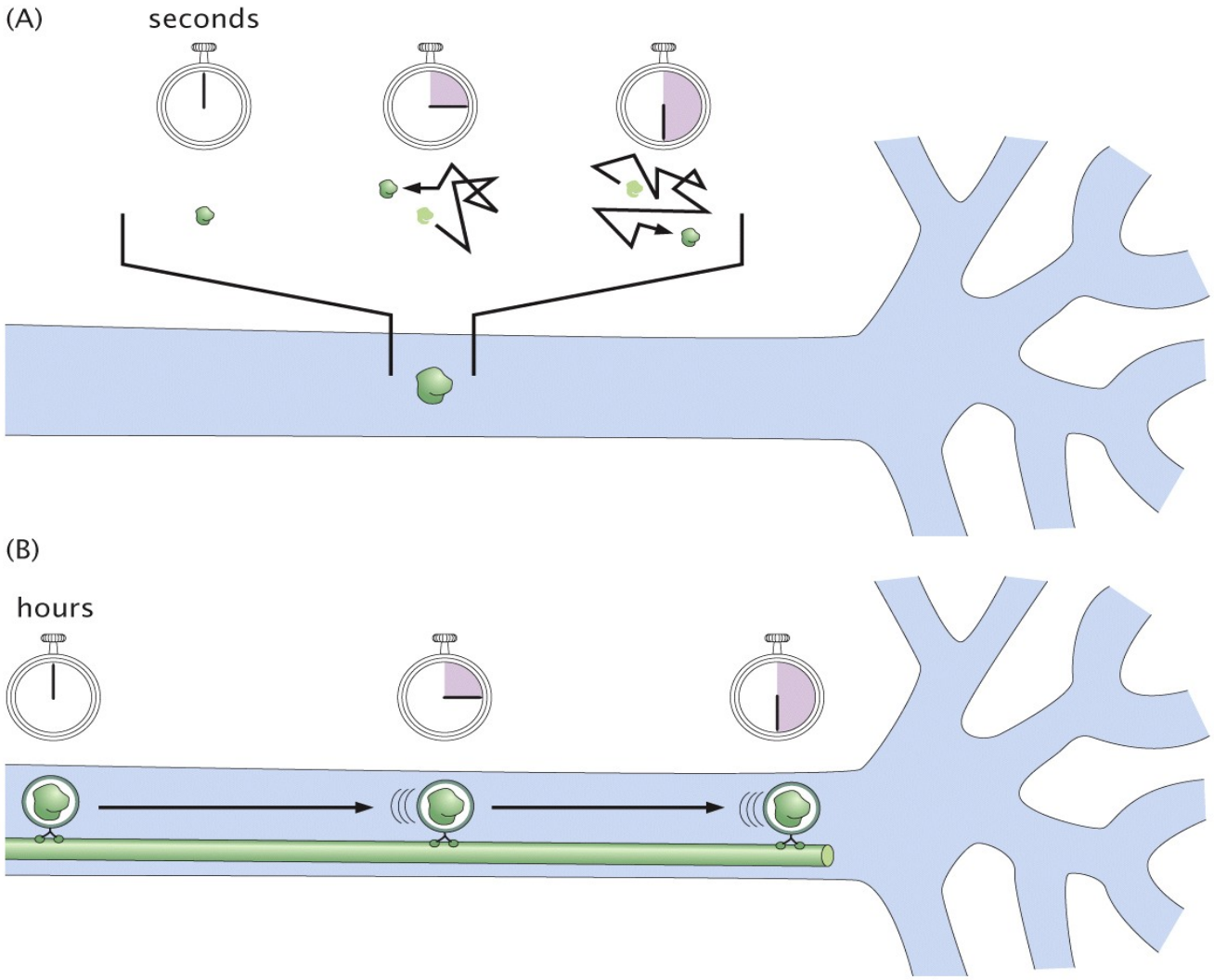
Figure 13.4 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Diffusion is not effective over large cellular distances

A dramatic example: diffusion over one-meter length axons

Passive transport, random jiggling

Directed transport: molecular motors



Imaging and measuring diffusion in the cell: FRAP experiments

Fluorescence Recovery After Photobleaching (FRAP)

After a laser pulse (spot about 1 mm), which quenches the fluorescence of molecules within the illuminated spot, other fluorescent molecules diffuse back in the spot and fluorescence is recovered. By fitting a mathematical model to the recovery curve, the diffusion constant of the molecules can be determined. This technique can be used in vivo!

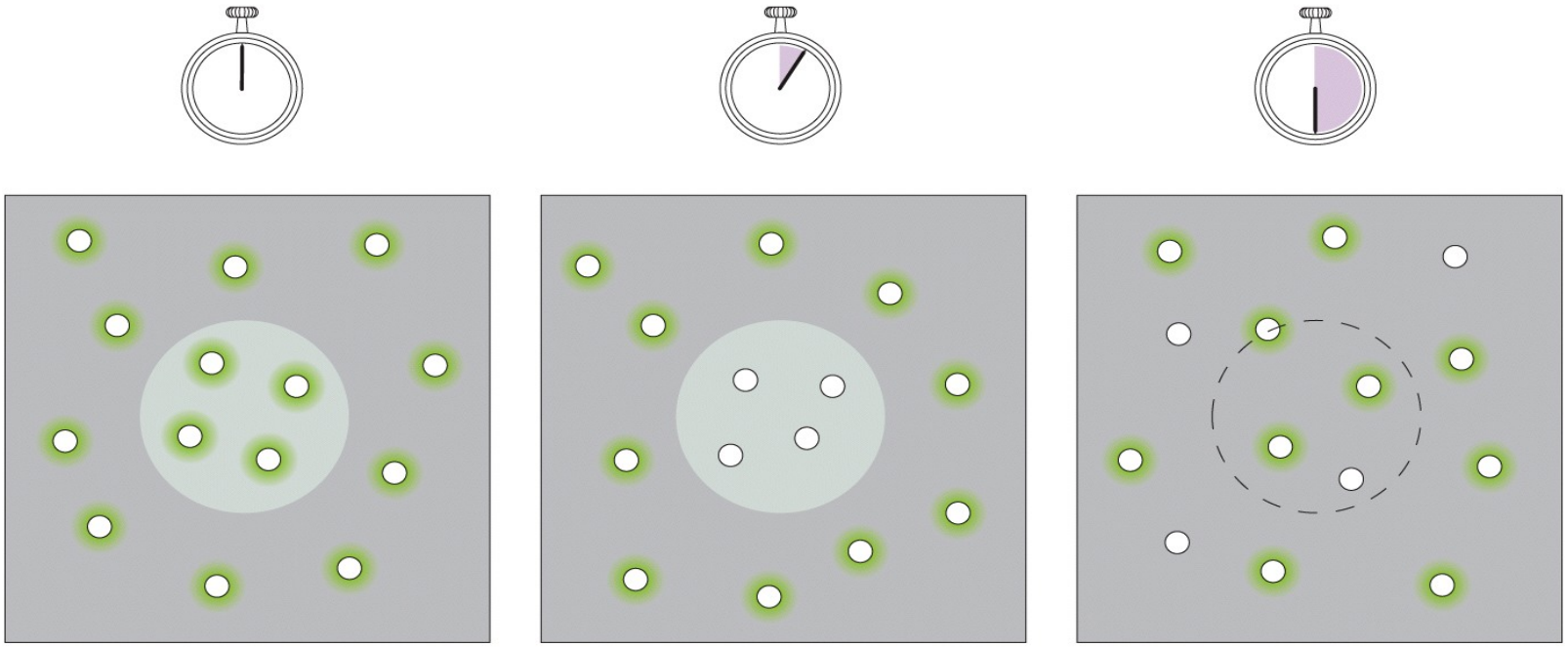
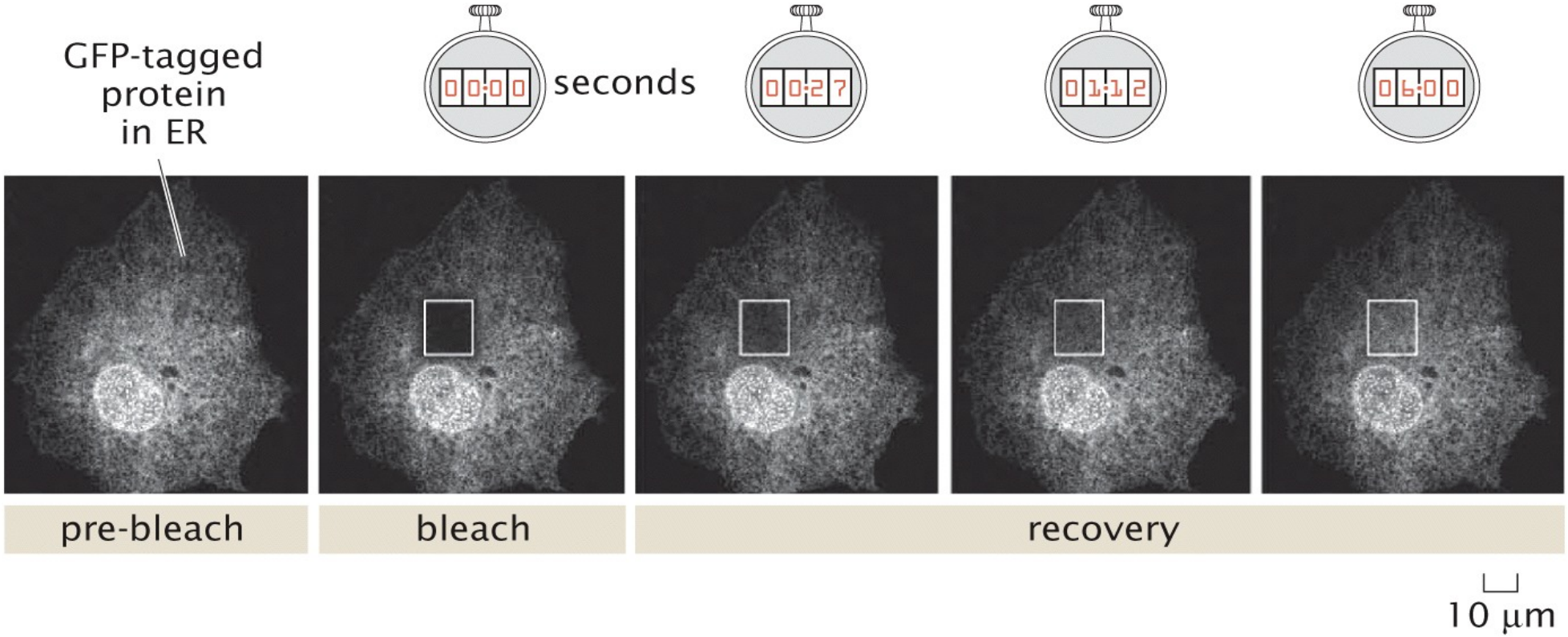


Figure 13.6 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

A true experiment

Fluorescence recovery of a GFP-labeled protein confined to the membrane of the endoplasmic reticulum. The boxed region is photo-bleached at t=0.

J. Ellenberg et al. J. Cell. Biol. 138:1193 (1997)



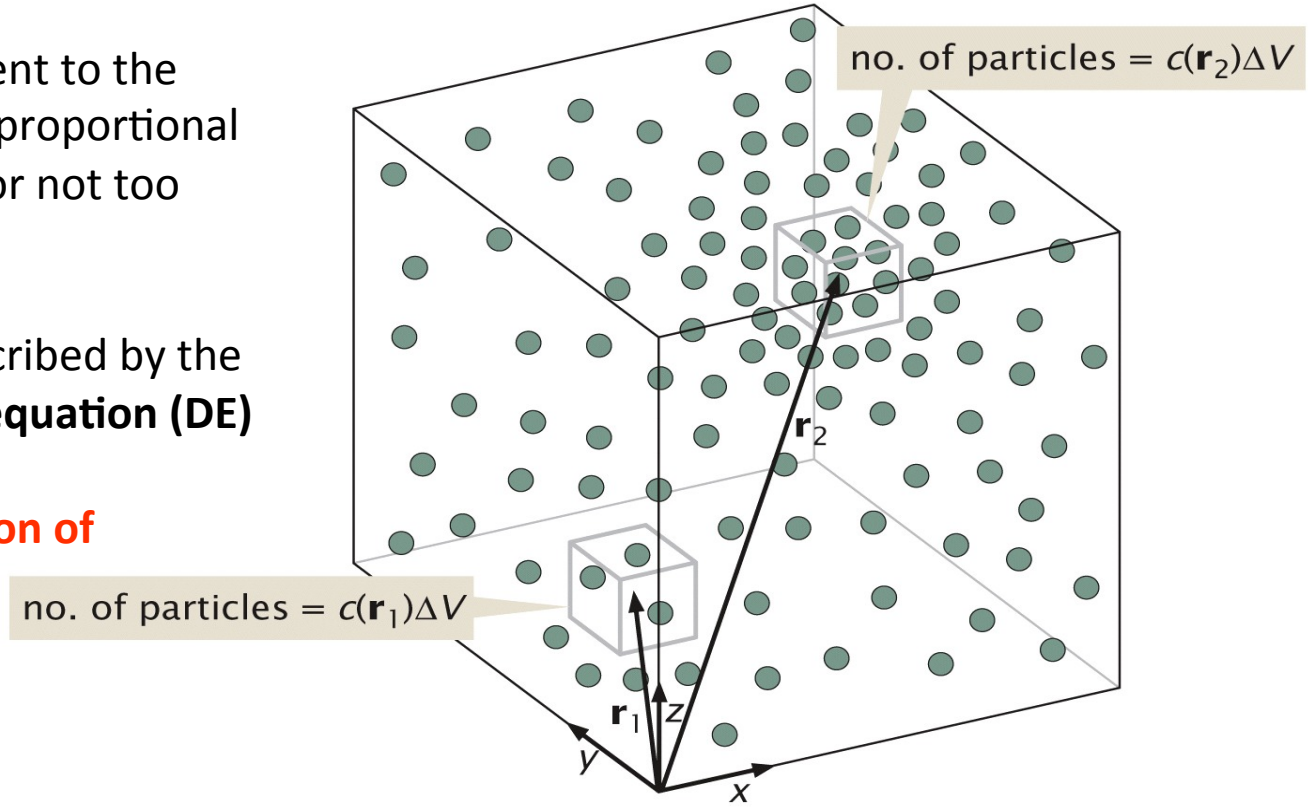
Diffusion is mass transport over distance in the presence of a concentration gradient.

In the regime of linear response theory (the concentration gradient is small), the particle current is proportional to the concentration gradient.

Mathematically this is equivalent to the problem of heat flux, which is proportional to the temperature gradient for not too large temperature differences.

Both processes in fact are described by the same equation, the **diffusion equation (DE)**

The DE describes the relaxation of density fluctuations



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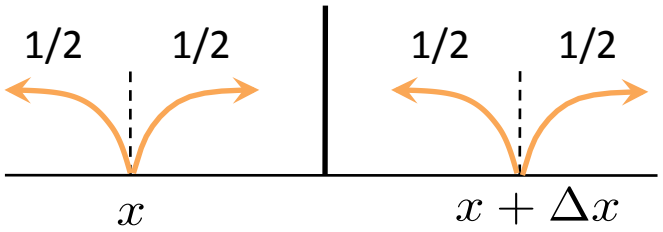
The concentration current: Fick's law

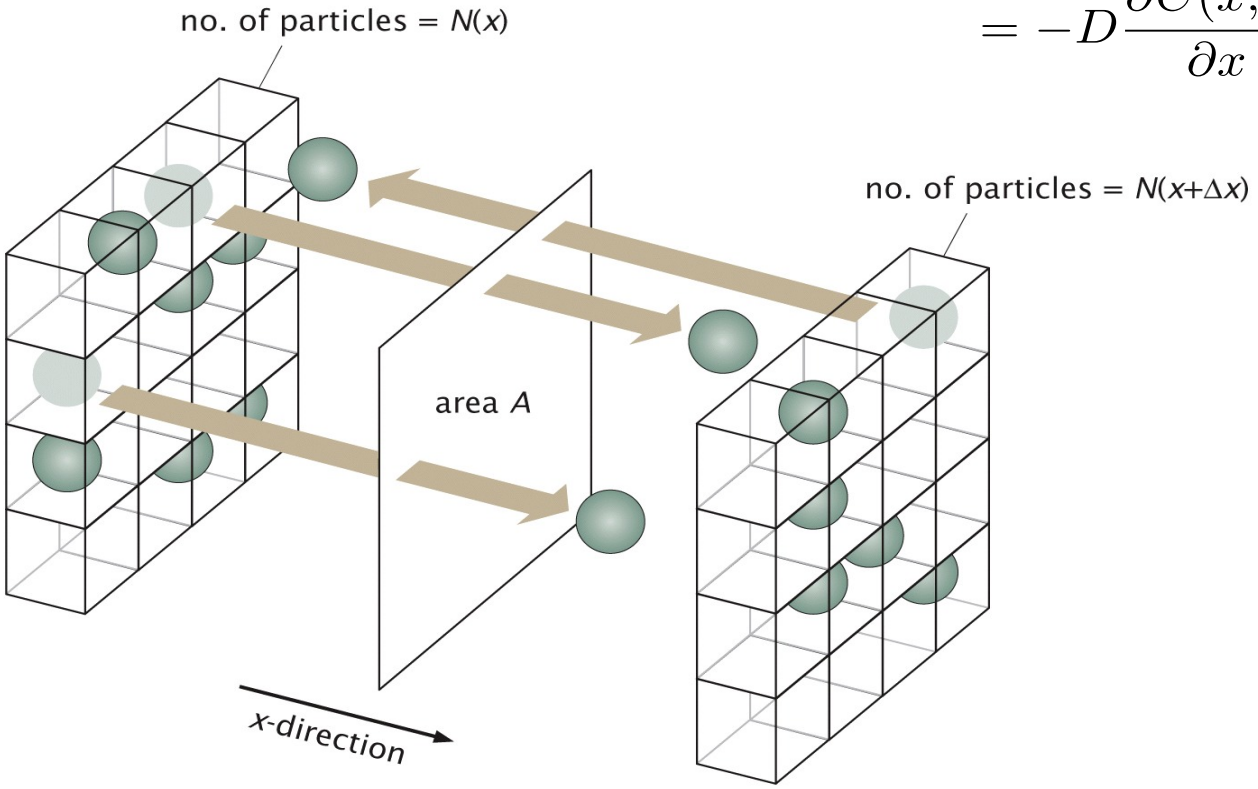


Net number of particles crossing to the right

$$J_x = -\frac{1}{2A\Delta t}\left[N(x+\Delta x) - N(x)\right]$$

$$J_x = -\frac{\Delta x^2}{2A\Delta t}\left[\frac{1}{\Delta x}\left(\frac{N(x+\Delta x)}{A\Delta x} - \frac{N(x)}{A\Delta x}\right)\right]$$

$$= -D\frac{\partial C(x,t)}{\partial x}$$



$$\lim_{\substack{\Delta x \to 0 \\ \Delta t \to 0}} \left(\frac{\Delta x^2}{2\delta t}\right) \stackrel{\text{def.}}{=} D$$

$$\mathbf{J} = -D\nabla C$$

The diffusion equation results from Fick's law and conservation of mass

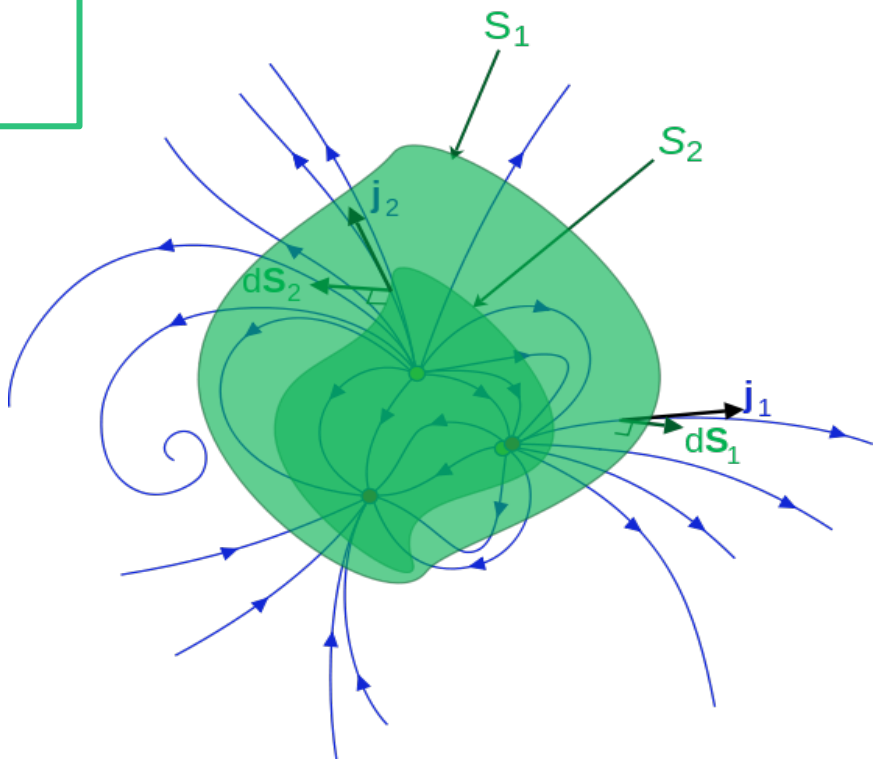
$$\frac{\partial}{\partial t}\left(\int_{V_i} C(\mathbf{x},t)\,d^3\mathbf{x}\right) = -\int_{S_i} \mathbf{J}_i(\mathbf{x},t)\cdot\hat{n}_i\,dS_i = \int_{V_i} \nabla\cdot\mathbf{J}_i(\mathbf{x},t)\,d^3\mathbf{x}$$

$$\begin{cases} \dfrac{\partial C}{\partial t} + \nabla\cdot\mathbf{J} = 0 \\ \mathbf{J} = -D\nabla C \end{cases}$$

Continuity equation

Diffusion equation

$$\frac{\partial C}{\partial t} = D\nabla^2 C$$



Transport equations from microscopic stochastic processes

The space is discretized and we average of microscopic trajectories
k is a *rate*, jump probability per unit time (units of time^{-1})

$$\langle \Delta x(t) \rangle = \left(\frac{t}{\Delta t} \right) \left[a(k\Delta t) + (-a)(k\Delta t) + 0(1 - 2k\delta t) \right] = 0$$

$$\langle \Delta x^2(t) \rangle = \left(\frac{t}{\Delta t} \right) \left[a^2(k\Delta t) + (-a)^2(k\Delta t) + 0^2(1 - 2k\delta t) \right] = 2(ka^2)t$$

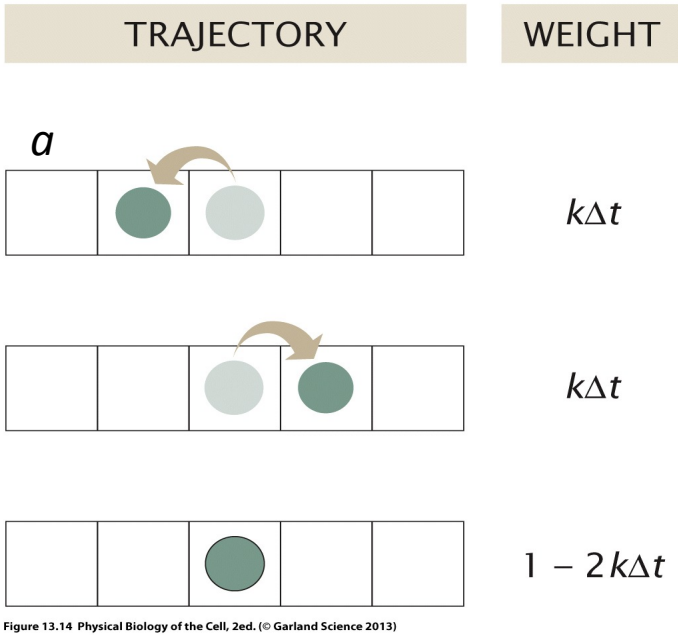


Figure 13.14 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Stay put

$$P(x, t + \Delta t) = (1 - 2k\Delta t)\, P(x, t) + k\Delta t\, P(x - a, t) + k\Delta t\, P(x + a, t)$$

Go left or right

Expand P in Taylor series (l.h.s in time and r.h.s in space) and you will get the diffusion equation with $D = ka^2$

The fundamental solution: the Green function

$$\begin{cases} \dfrac{\partial G}{\partial t} - D\nabla^2 G = 0 \\ G(x, t = t_0 | x_0, t_0) = \delta(x - x_0) \\ \lim\limits_{|x|\to\infty} G(x, t | x_0, t_0) = 0 \end{cases}$$

G is the Green function

Then, by exploiting the linearity of the diffusion equation

$$\begin{cases} \dfrac{\partial P}{\partial t} - D\nabla^2 P = 0 \\ P(x, t = t_0) = P_0(x) \\ \lim\limits_{|x|\to\infty} P(x, t) = 0 \end{cases}$$

has the following solution

$$P(x,t) = \int G(x, t | x_0, t_0) P_0(x_0)\, dx_0$$

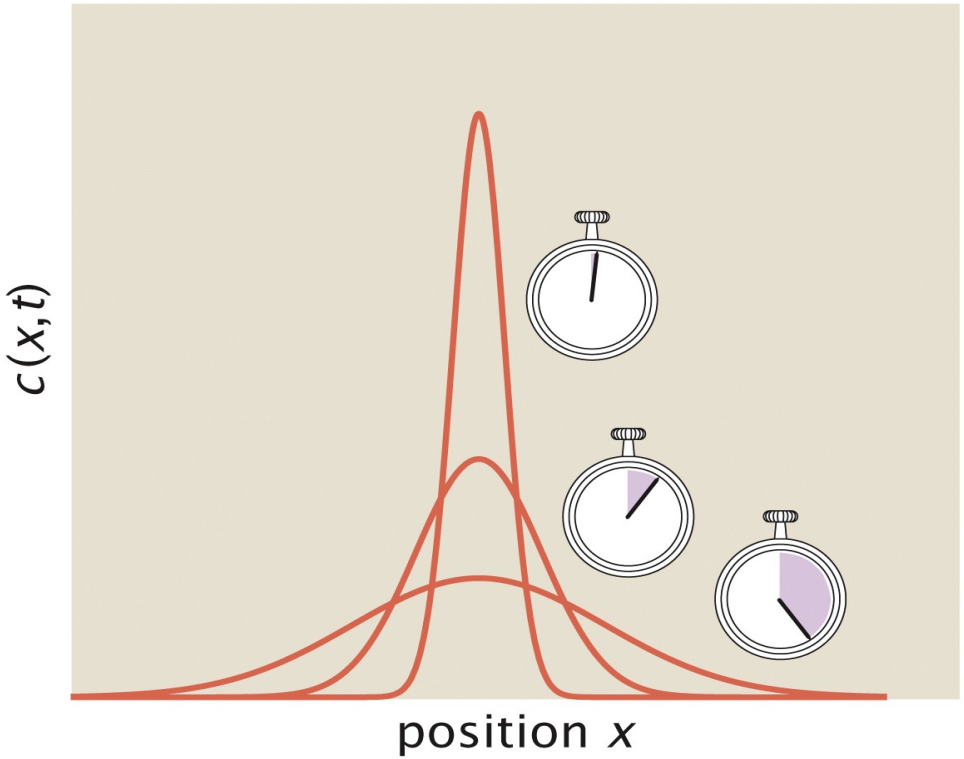


Figure 13.15 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

The fundamental solution: the Green function

Take the Fourier transform of the diffusion equation

$$\frac{\partial \tilde{G}}{\partial t} = -q^2 D\, \tilde{G} \qquad \text{where} \quad \tilde{G}(q,t) = \frac{1}{\sqrt{2\pi}} \int G(x,t|x_0,t_0) e^{-iqx}\, dx$$

$$\tilde{G}(q,t) = \tilde{G}(q,t_0) e^{-Dq^2(t-t_0)}$$

The initial condition corresponds to the particles localized at $x = x_0$

$$G(x, t_0) = \delta(x - x_0) = \frac{1}{2\pi} \int e^{iq(x-x_0)}\, dq$$

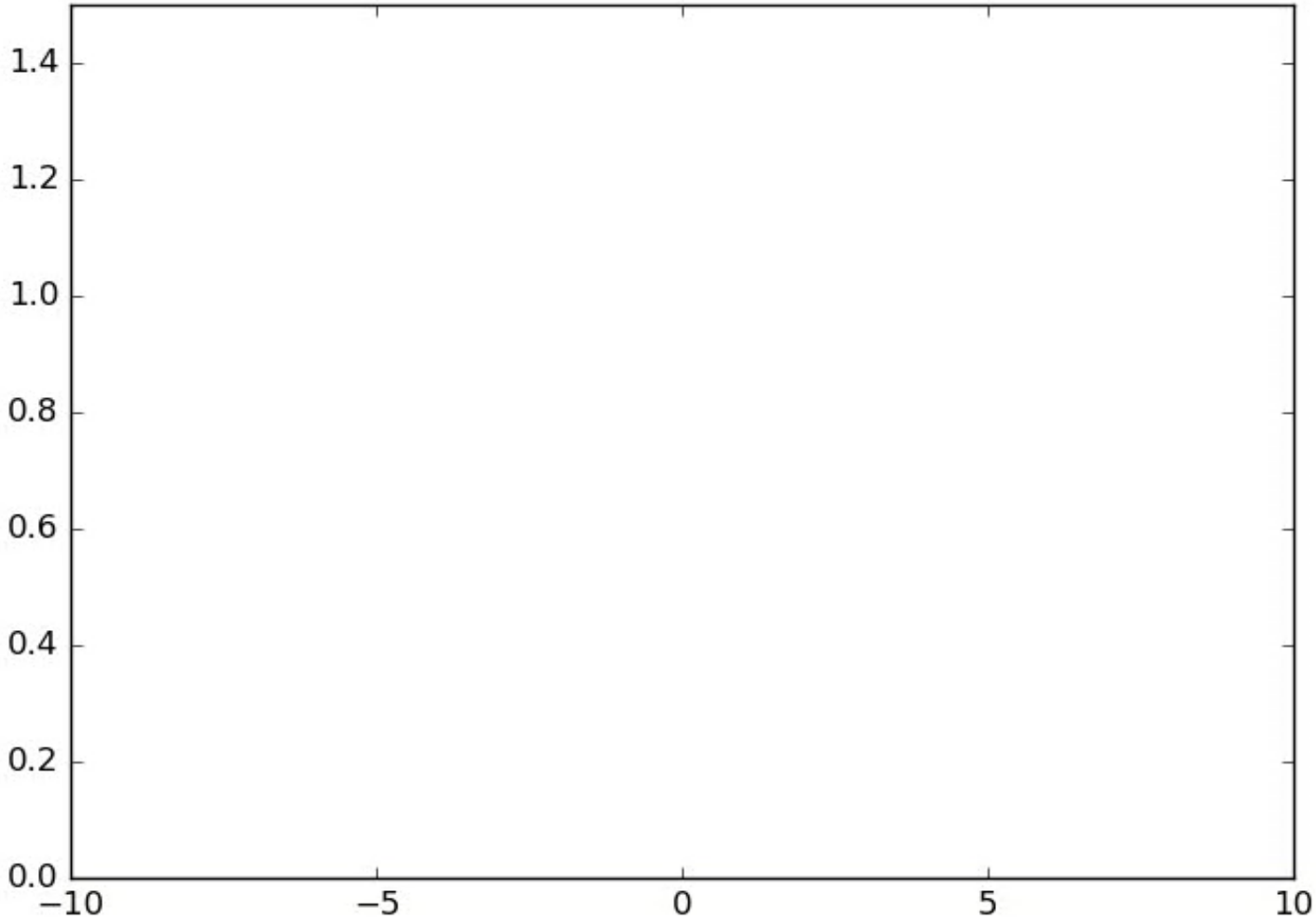
$$= \frac{1}{\sqrt{2\pi}} \int \left[\frac{1}{\sqrt{2\pi}} e^{-iqx_0} \right] e^{iqx}\, dq$$

$$\tilde{G}(q, t_0) = \frac{1}{\sqrt{2\pi}} e^{-iqx_0}$$

We can now take the inverse Fourier transform

$$G(x, t|x_0, t_0) = \frac{1}{2\pi} \int e^{-Dq^2(t-t_0)} e^{iq(x-x_0)}\, dq$$

$$= \frac{1}{\sqrt{4\pi D(t - t_0)}} e^{-(x-x_0)^2/4D(t-t_0)}$$

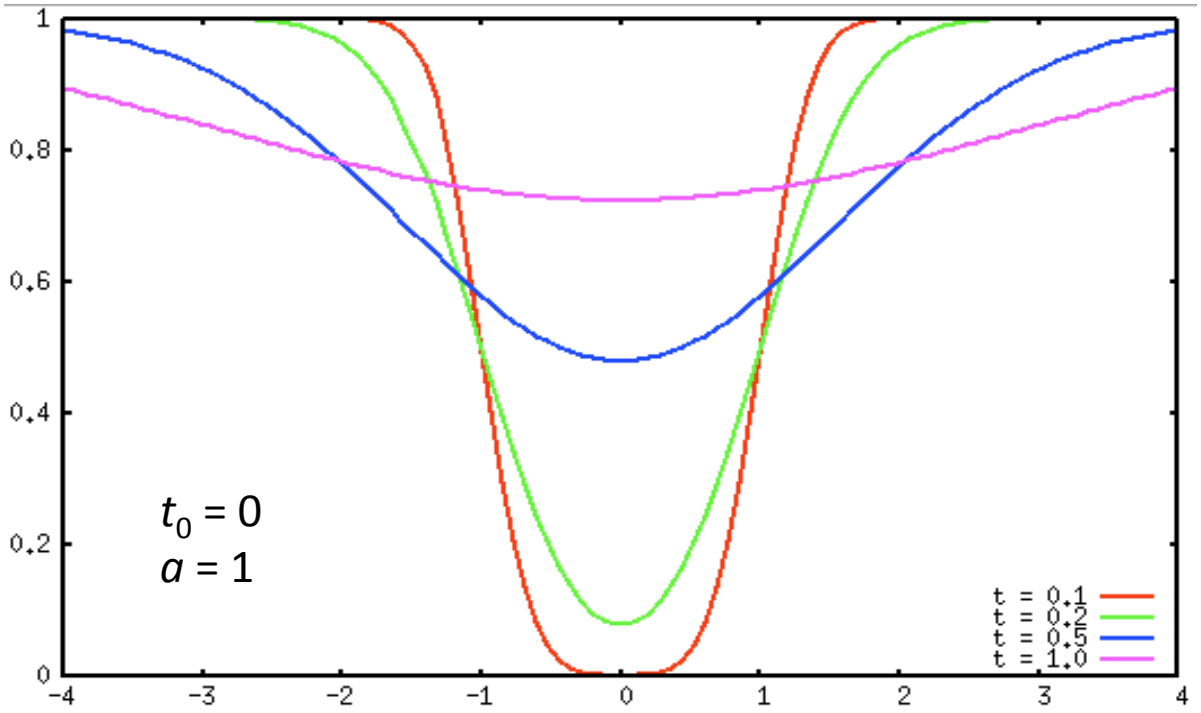

1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
−10
−5
0
5
10

The FRAP recovery curve in 1D

$$P_0(x) = \theta(x-a) + \theta(-x-a)$$

$$P(x,t) = \frac{1}{\sqrt{4\pi D(t-t_0)}}\left[\int_{-\infty}^{-a} e^{-(x-x_0)^2/4D(t-t_0)}\,dx_0 + \int_{a}^{+\infty} e^{-(x-x_0)^2/4D(t-t_0)}\,dx_0\right]$$

$$= 1 + \frac{1}{2}\left[\mathrm{erf}\left(\frac{x-a}{\sqrt{4D(t-t_0)}}\right) - \mathrm{erf}\left(\frac{x+a}{\sqrt{4D(t-t_0)}}\right)\right]$$



$$\mathrm{erf}(x) = \frac{2}{\sqrt{\pi}}\int_0^x e^{-y^2}\,dy$$

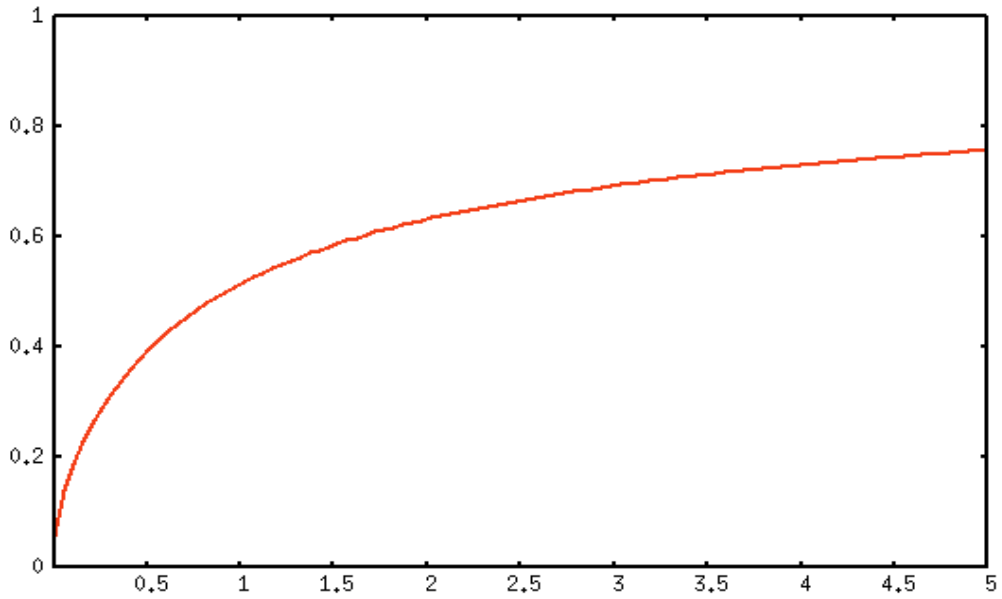
The FRAP recovery curve in 1D

$$\int \operatorname{erf}(x)\,dx = \int \frac{d}{dx}(x)\operatorname{erf}(x)\,dx$$
$$= x\operatorname{erf}(x) - \frac{2}{\sqrt{\pi}}\int x\,e^{-x^2}\,dx$$
$$= x\operatorname{erf}(x) + \frac{1}{\sqrt{\pi}}e^{-x^2}$$

$$f(t) = \frac{1}{2a}\int_{-a}^{a} P(x,t)\,dx$$

$$= 1 + \frac{\sqrt{D(t-t_0)}}{a\sqrt{\pi}}\left(1 - e^{-a^2/D(t-t_0)}\right) - \operatorname{erf}\left(\frac{a}{\sqrt{D(t-t_0)}}\right)$$

f(*t*) is proportional to the measured fluorescence recovery



$$f(t_h) = 1/2 \qquad \xi = \frac{a}{\sqrt{D(t-t_0)}}$$

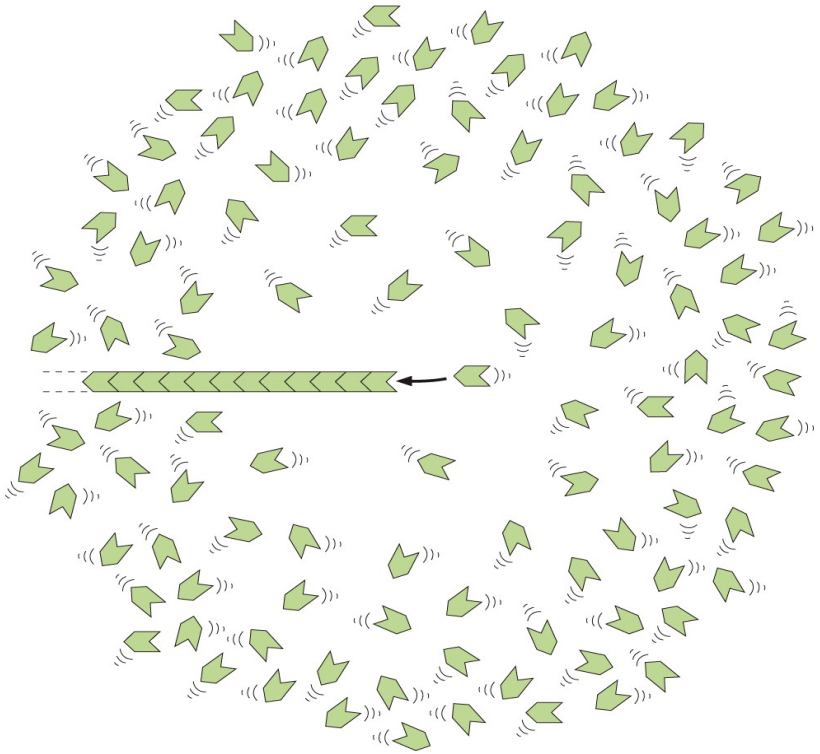
Solve for the non-dimensional half-recovery time

$$1 + \frac{1 - e^{-\xi^2}}{\xi\sqrt{\pi}} - \operatorname{erf}(\xi) = \frac{1}{2}$$

$$\xi \approx 1.0397 \Longrightarrow D = \frac{a^2}{\xi^2 \Delta t_h}$$

Diffusion to capture

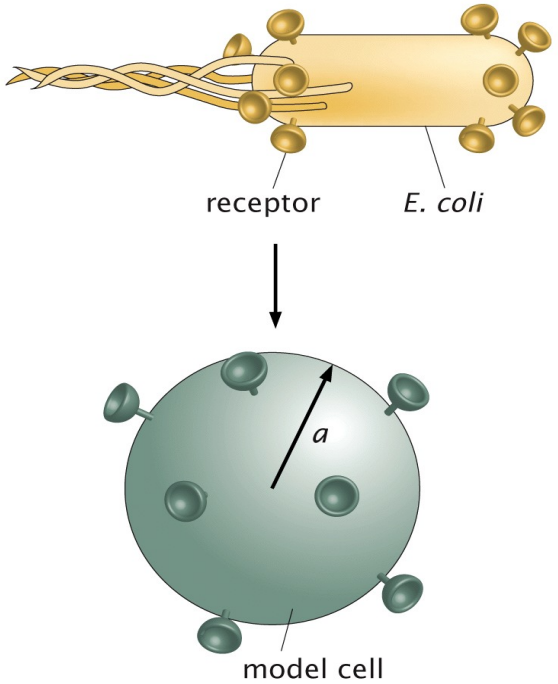
Class of problems where we are interested in the rate at which some diffusing species arrives at a given region of space.



Monomer diffusion to the tip of a growing cytoskeletal filament. Note the **depletion** of monomers in the vicinity of the **absorbing** tip

Chemoreception

The cell surface is decorated with **receptors** that tend to be **clustered** at the cell poles



Modeling the cell signaling Problem: the classical **Smoluchowski rate**

We assume that the cell is a sphere that has receptors uniformly distributed on its surface.

We want to solve for the concentration of the signaling molecules at steady state.

We assume that the concentration has spherical symmetry and far from the cell the ligand concentration has its bulk value c_0

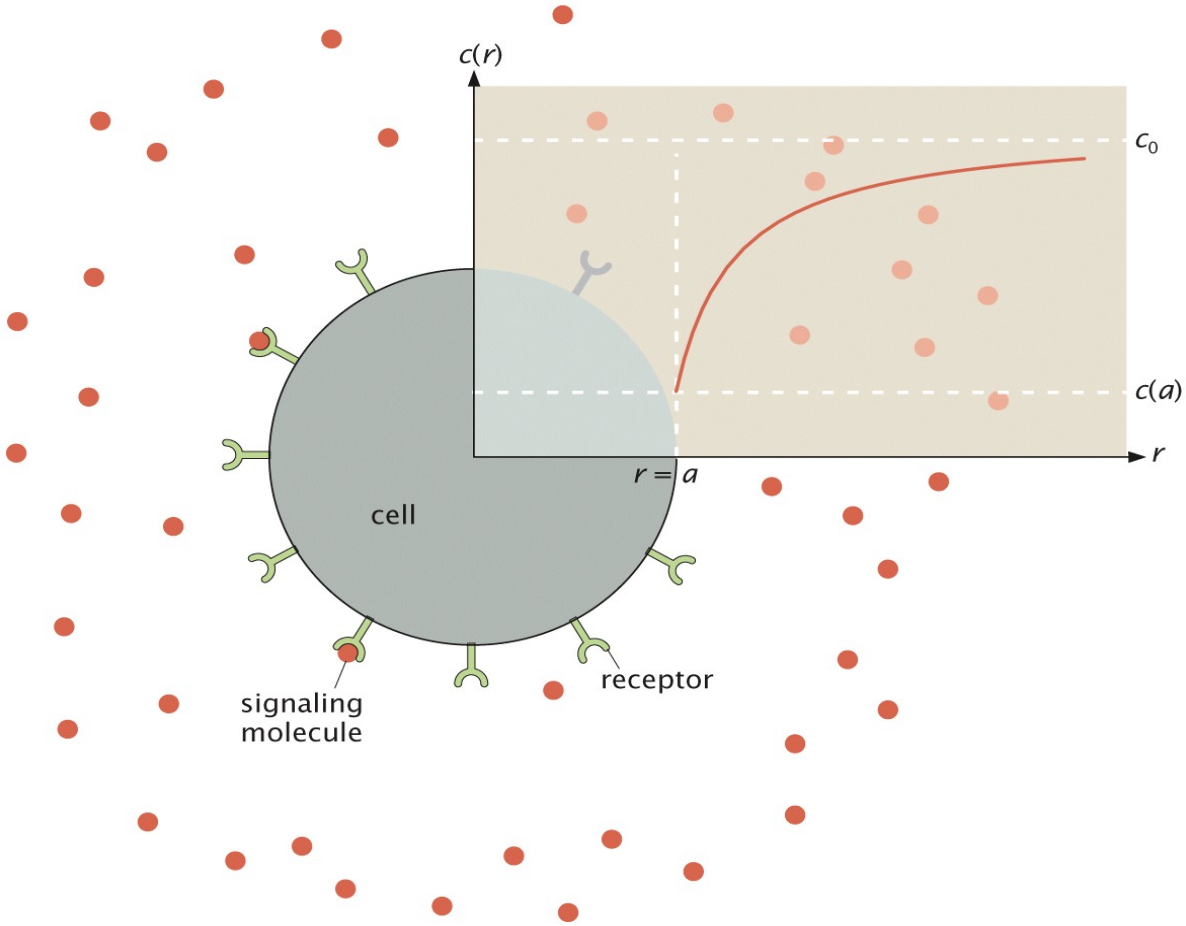


Figure 13.22 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

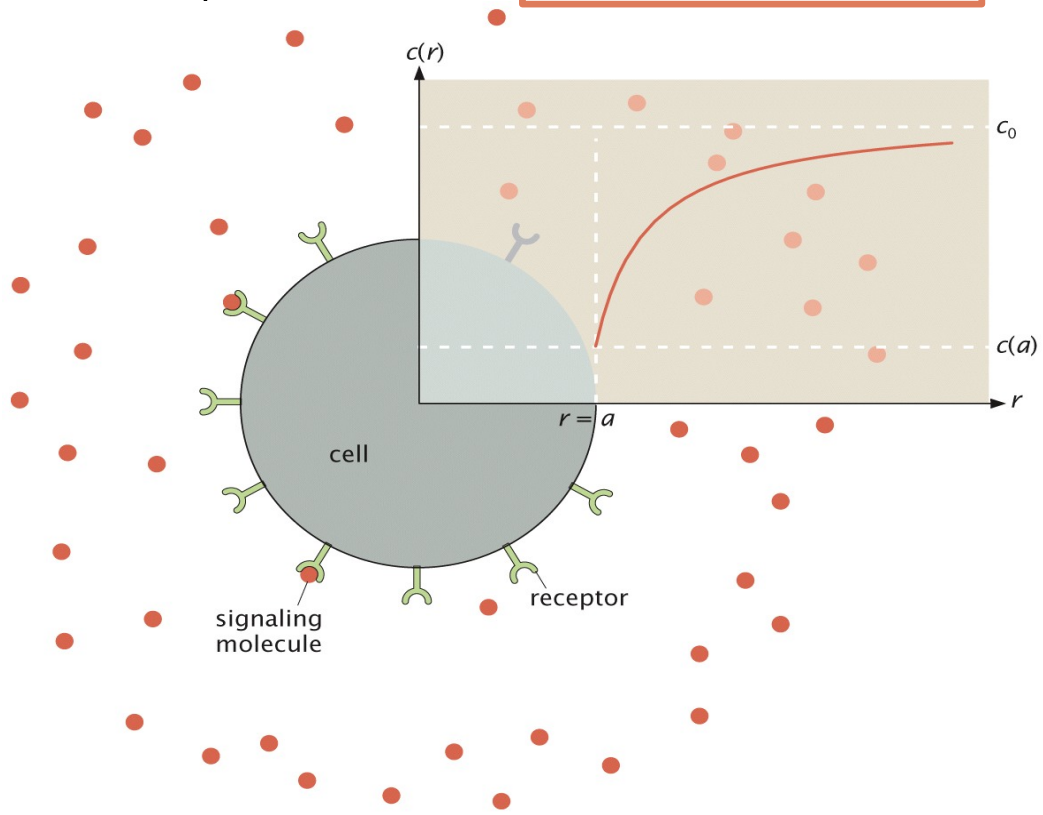
Solving the problem

$$\begin{cases} \nabla^2 c = 0 \\ c(r=a) = 0 \\ \lim_{r\to\infty} c(r) = c_0 \end{cases} \qquad \begin{cases} c(r) = A + \dfrac{B}{r} \\ A = c_0 \qquad B = -c_0\, a \end{cases} \qquad \Longrightarrow \qquad \boxed{c(r) = c_0\left(1 - \frac{a}{r}\right)}$$

$$J_r = -D\frac{\partial c}{\partial r}$$

$$k = -\int_s \mathbf{J}\cdot\hat{n}_r\, dS = 4\pi D a c_0$$

$$\boxed{k_S = 4\pi D a c_0} \qquad \textbf{Smoluchowski rate}$$



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The previous calculations assumes that the rate of (chemical) reactions taking place once the reactant has diffused to the cell surface are **much faster than diffusion**

$$L + R \underset{k_{-1}}{\overset{k_S}{\rightleftarrows}} LR^* \xrightarrow{k_*} B$$

L = Concentration of ligands
R = Concentration of receptors
*LR** = Concentration of encounter complexes
B = Concentration of bound (stabilized) complexes

$$\begin{cases} \dfrac{d[LR^*]}{dt} = k_S[L][R] - (k_{-1} + k_*)[LR^*] \\ \dfrac{d[B]}{dt} = k_*[LR^*] \end{cases}$$

Quasi-equilibrium approximation, [LR*] approximately constant, one gets

$$\frac{d[B]}{dt} = k_{\text{eff}}[L][R]$$

This is the so-called **diffusion-limited** regime, where diffusion (slow) is the *rate-limiting step*

$$k_{\text{eff}} = \frac{k_* k_S}{k_* + k_{-1}} \simeq \begin{cases} k_S & \text{for } k_* \gg k_{-1} \\ < k_S & \text{for } k_* \sim k_{-1} \end{cases}$$

What happens if the **rate of uptake** of receptors (the rate of absorption of our idealized spherical sink) **is not fast enough** to cope with diffusion? How to model this situation?

The intrinsic (chemical reaction rate *k** should enter the picture). It does so in the framework of our continuous model through what the chemists call ***radiation boundary conditions***, the mathematicians ***Robin boundary conditions***

$$\begin{cases} \nabla^2 c = 0 \\ \left(4\pi D a^2 \dfrac{\partial c}{\partial r} - k_* c\right)_{r=a} = 0 \\ \lim\limits_{r\to\infty} c(r) = c_0 \end{cases}$$

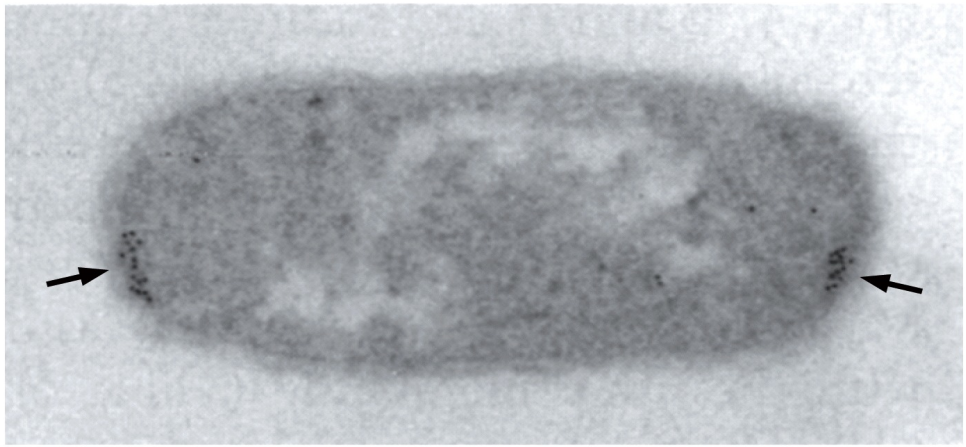
$$\begin{cases} c(r) = A + \dfrac{B}{r} \\ A = c_0 \quad h = \dfrac{k_*}{4\pi D a} \\ B = -c_0 \left(\dfrac{h}{1+h}\right) \dfrac{a}{r} \end{cases}$$

$$k = \frac{k_S k_*}{k_* + 4\pi D a} \qquad k_S = 4\pi D a c_0$$

$$c(r) = c_0 \left[1 - \frac{a}{r}\left(\frac{k_*}{k_* + 4\pi D a}\right)\right]$$

Real receptors are not always uniformly distributed

Localization of chemotaxis receptors in E. Coli as shown by immunogold labeling in a thin-section electron micrograph. Receptors appear **clustered** at each pole of the cell



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High-resolution fluorescence image of E. Coli chemotaxis receptors. Many small clusters are evident along the sides of the bacterium as well as the two major ones at the poles.

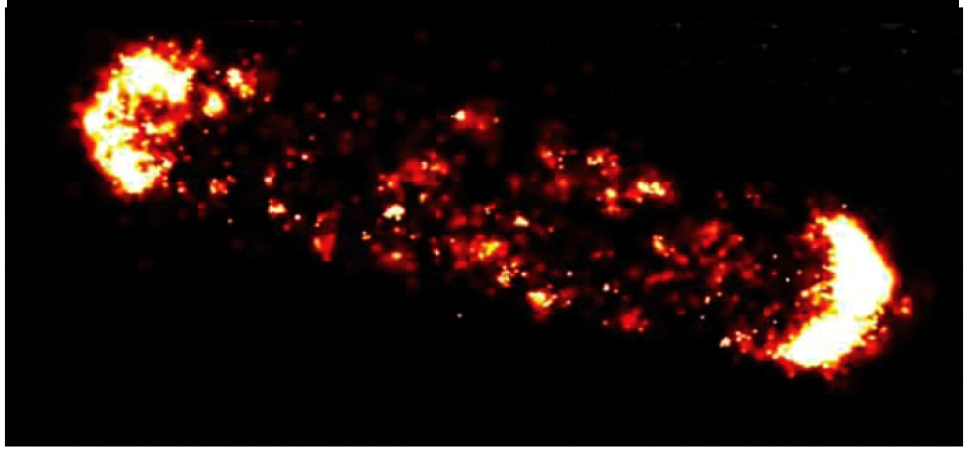


Figure 13.23b Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Some receptors appear to be arranged on lattice-like structures

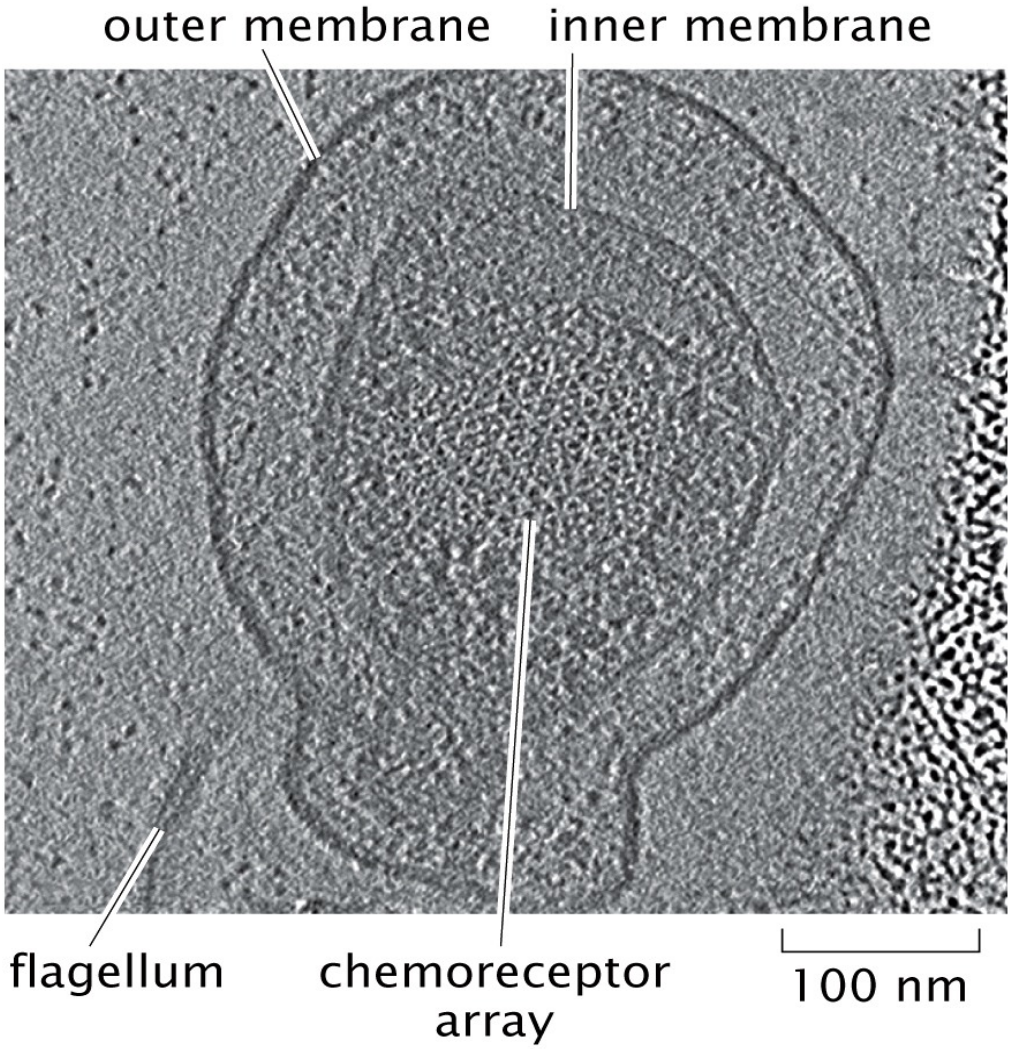
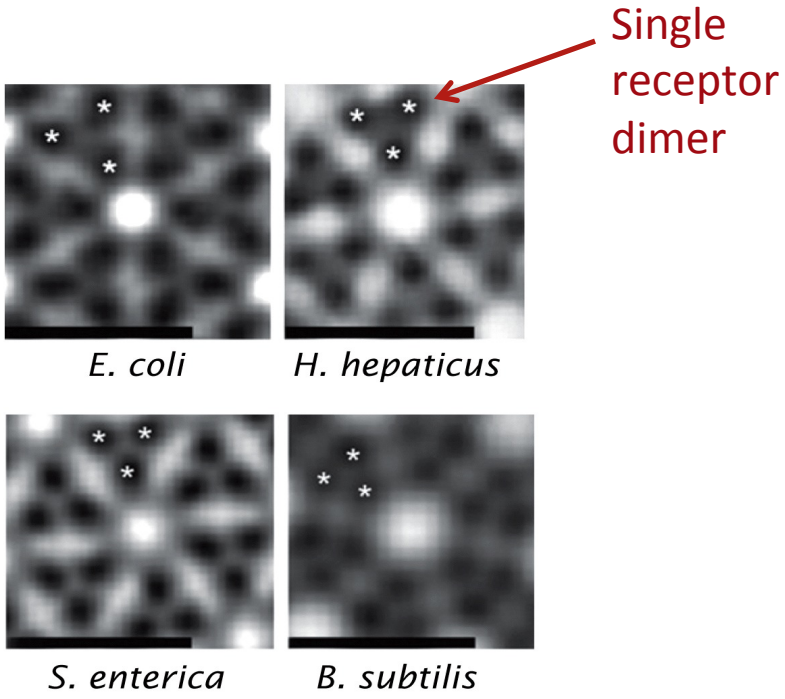


Figure 13.23c Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Cryo-electron microscopy showing a tomographic slice through the pole of Salmonella Enterica. It becomes apparent at this resolution that **receptors are packed into regular hexagonal arrays**



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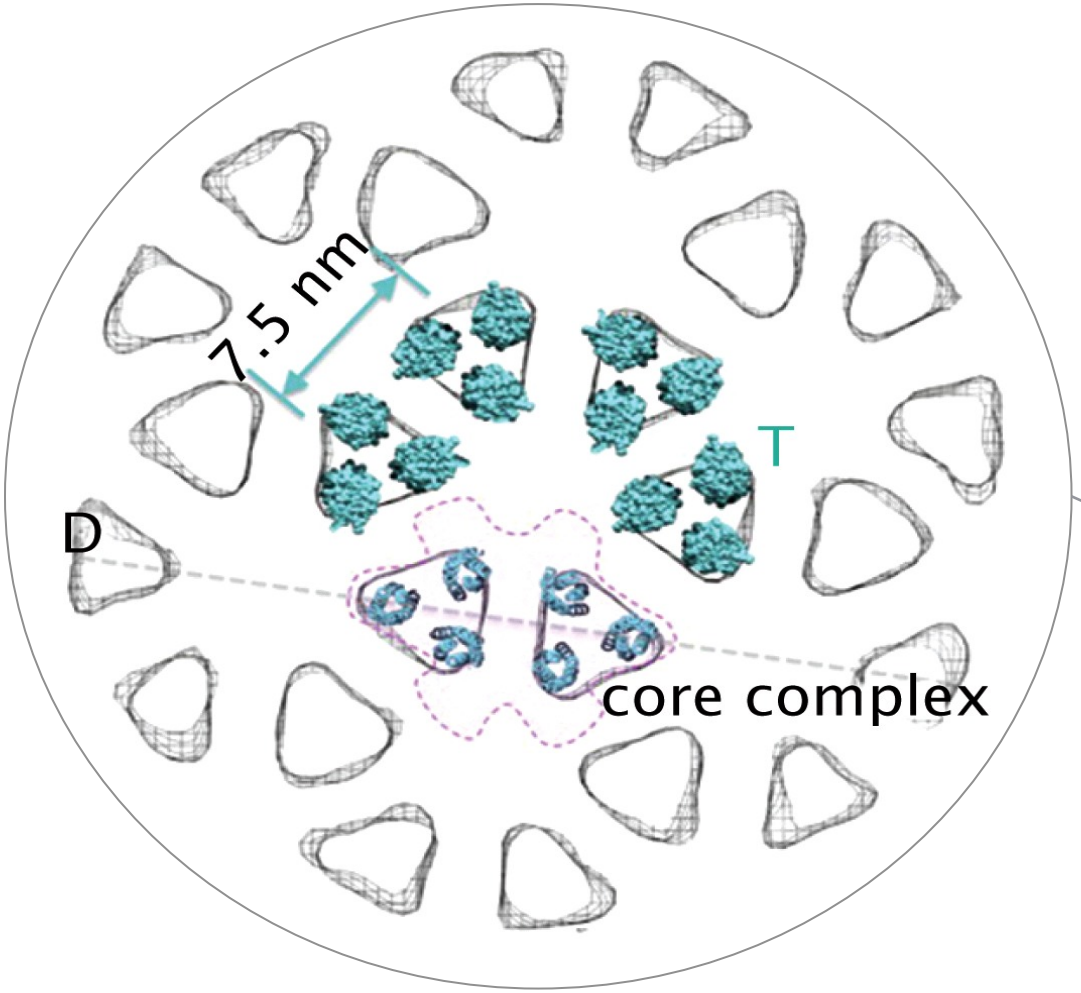


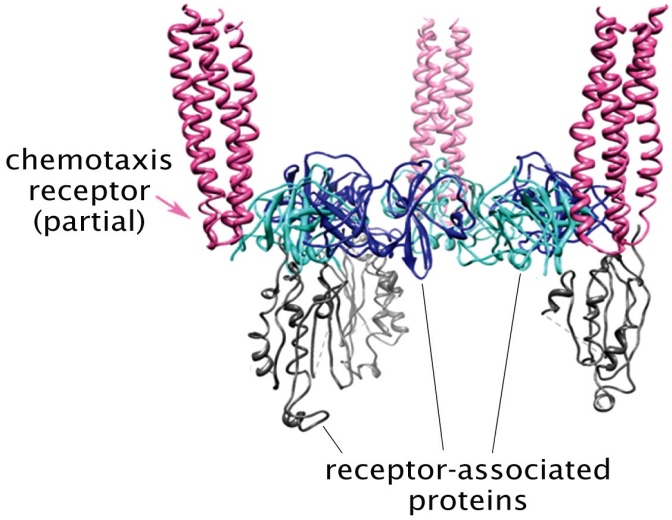
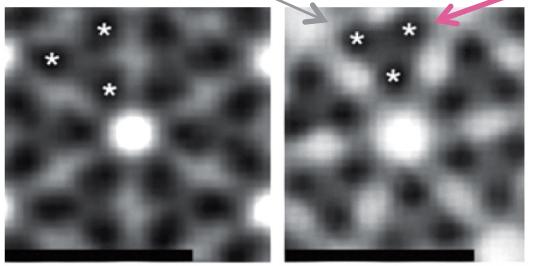
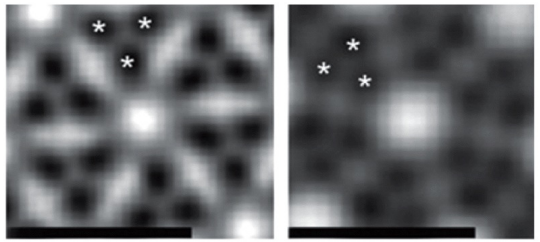


Figure 13.23f Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Single
receptor
dimer



E. coli *H. hepaticus*



S. enterica *B. subtilis*

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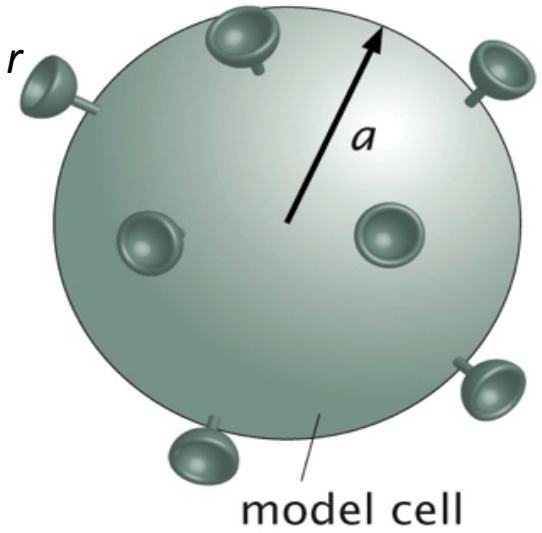
A very important biological lesson



M receptors on the surface, each of them *absorbing* with a rate *k**

If M is very large and the cell can be considered as absorbing everywhere, the rate is

$$k_S = 4\pi D a c_0$$ **Smoluchowski rate**

The question is what happens for a finite number of receptors?

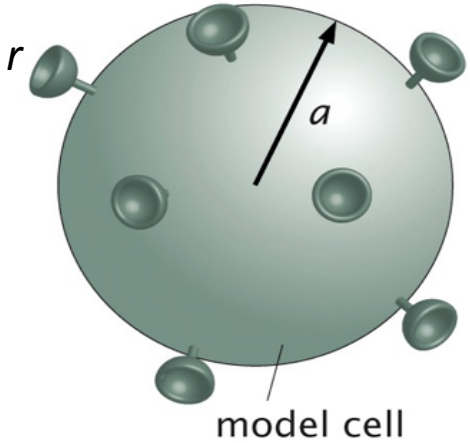
A classical result: the rate constant for an absorbing disc of radius *r* on an otherwise reflecting plane

$$k_d = 4Dr$$

The idea: consider the cell as a partially absorbing surface, with a reaction rate at the surface given by

$$k_* = M k_d = 4MDr$$

A very important biological lesson



$$k = \frac{k_S k_*}{k_* + 4\pi D a} = k_S \left(\frac{\beta}{1+\beta} \right) \qquad \beta = \frac{Mr}{\pi a}$$

Now we can calculate how many receptors are needed to reduce the rate to only one half that of the fully covered cell, i.e. k_S. This gives b = 1

Some numbers: $r \approx 1.5 \text{ nm}$

$a \approx 10 \ \mu\text{m}$

$$\beta = 1 \Longrightarrow M \approx 10^4$$

Is this a large number? To find out let us calculate the fraction of cell surface covered by receptors

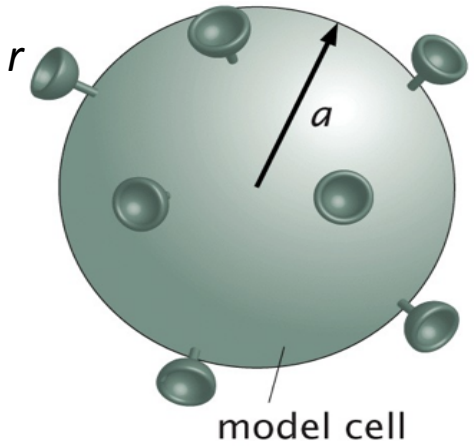
$$f = \frac{M\pi r^2}{4\pi a^2} \approx 10^{-4}$$

A very sparse uniform distribution of receptors is as good as a fully covered cell!

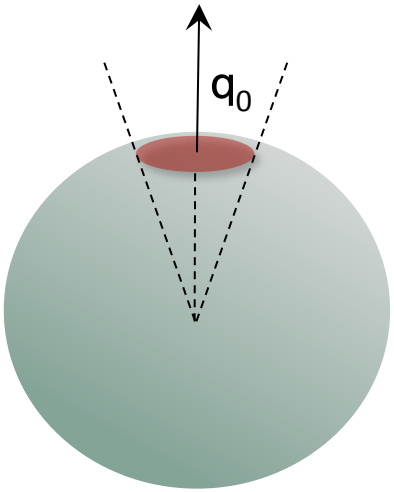
Another beautiful lesson on diffusion-limited reactions

We can ask another interesting question. We have seen that a tiny fraction of reactive surface on the cell is almost as good as a fully reactive cell. However, this is valid under the assumption that the M receptors were distributed uniformly on the cell surface.

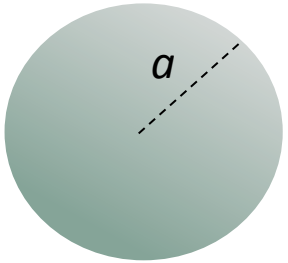
Is the cell going to be as good as an absorber if the M receptors are all clustered on one large reactive patch on the cell surface?



versus

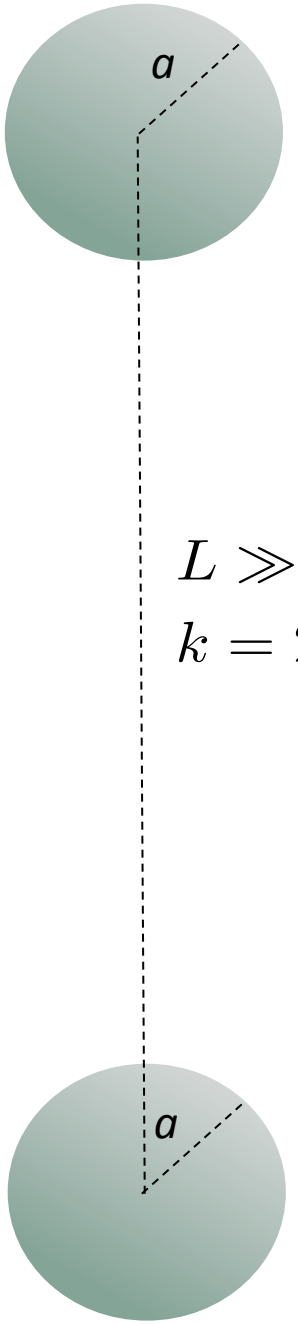


The concept of *diffusive interactions*

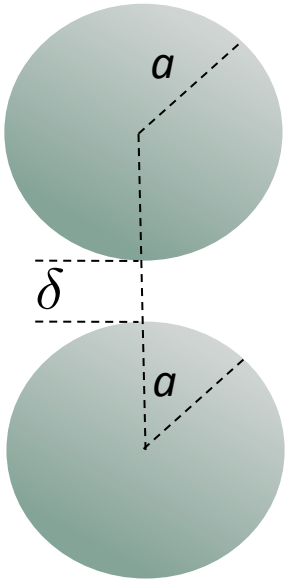


Fully absorbing sphere

$$k = k_S$$



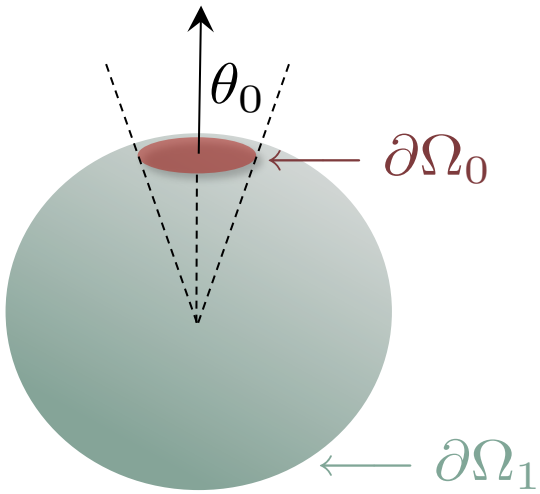
$$L \gg a$$
$$k = 2k_S$$



$$L \simeq 2a + \delta$$
$$k < 2k_S$$

This is because each sphere *shields* a part of flux from the other

Mixed boundary value problems



Absorbing BC for
$0 < \theta \leq \theta_0$

Reflecting BC for
$\theta_0 < \theta \leq \pi$

$$\begin{cases} \nabla^2 c = 0 \\ c|_{\partial\Omega_0} = 0 \\ \left.\dfrac{\partial c}{\partial r}\right|_{\partial\Omega_1} = 0 \\ \lim\limits_{|\mathbf{r}|\to\infty} c(\mathbf{r}) = c_0 \end{cases}$$

This complex boundary value problem can be solved analytically to any necessary accuracy using the theory of **Dual Series Relations (DSR)**!

I.N. Sneddon, Mixed boundary values in potential theory, North Holland, Amsterdam, 1966

Solving the mixed boundary value problems with DSRs

Let us define

$$n(\mathbf{r}) = 1 - \frac{c(\mathbf{r})}{c_0}$$

$$\xi = \frac{r}{a}$$

$$\mu = \cos\theta$$

$$\longrightarrow \quad \begin{cases} \nabla^2 n = 0 & (1) \\ n|_{\partial\Omega_0} = 1 & (2) \\ \left.\dfrac{\partial n}{\partial \xi}\right|_{\partial\Omega_1} = 0 & (3) \\ \lim\limits_{|\mathbf{r}|\to\infty} n(\mathbf{r}) = 0 & (4) \end{cases}$$

The general form for the solution of the Laplace equation with azimuthal symmetry and vanishing at infinity consists in an expansion over irregular *m* = 0 solid harmonics:

(5) $$n(r,\theta) = \sum_{l=0}^{\infty} A_l \xi^{-(1+l)} P_l(\mu)$$

Legendre polynomials

$$P_l(\mu) = \frac{1}{2^l l!}\frac{d^l}{d\mu^l}\left[(\mu^2-1)^l\right]$$

The problem then boils down to using the BCs to determine the coefficients A_l

Dual Series Relations: the solution

The following DSRs

$$\begin{cases} \sum_{l=0}^{\infty} X_l P_l(\mu) = g(\theta) & \text{for } \theta \in \partial\Omega_0 \\ \sum_{l=0}^{\infty} \left(l + \frac{1}{2}\right) X_l P_l(\mu) = 0 & \text{for } \theta \in \partial\Omega_1 \end{cases} \tag{6}$$

have an explicit analytic solution

$$X_l = \frac{\sqrt{2}}{\pi} \int_0^{\theta_0} \cos\left[\left(l + \frac{1}{2}\right) u\right] du \frac{d}{du} \int_0^u \frac{g(v) \sin v}{\sqrt{\cos v - cosu}} dv \tag{7}$$

[Sneddon 5.6.5]

If we substitute the general solution (5) in the boundary conditions (2) and (3), we get

$$\begin{cases} \sum_{l=0}^{\infty} A_l P_l(\mu) = 1 & \text{for } \theta \in \partial\Omega_0 \\ \sum_{l=0}^{\infty} (l+1) A_l P_l(\mu) = 0 & \text{for } \theta \in \partial\Omega_1 \end{cases} \tag{8}$$

These are not in canonical form, that is in the form given by eq. (6). We can put them in canonical form by defining new coefficients X_l

$$(l+1) A_l = \left(l + \frac{1}{2}\right) X_l \tag{9}$$

$$\begin{aligned} A_l &= X_l \left[1 - \frac{1}{2(l+1)}\right] \\ &\stackrel{\text{def}}{=} X_l (1 - q_l) \end{aligned} \tag{10}$$

definition of q_l

Therefore, our DRS (8) become

$$\begin{cases} \sum_{l=0}^{\infty} X_l P_l(\mu) = \overbrace{1 + \sum_{m=0}^{\infty} q_m X_m P_m(\mu)}^{g(\theta)} & \text{for } \theta \in \partial\Omega_0 \\ \sum_{l=0}^{\infty} \left(l + \frac{1}{2}\right) X_l P_l(\mu) = 0 & \text{for } \theta \in \partial\Omega_1 \end{cases} \quad (11)$$

Recall eq. (6), for which an explicit solution is known [Eq. (7)]:

$$\begin{cases} \sum_{l=0}^{\infty} X_l P_l(\mu) = g(\theta) & \text{for } \theta \in \partial\Omega_0 \\ \sum_{l=0}^{\infty} \left(l + \frac{1}{2}\right) X_l P_l(\mu) = 0 & \text{for } \theta \in \partial\Omega_1 \end{cases}$$

A formal solution can thus be written as follows

$$X_l = \frac{\sqrt{2}}{\pi} \int_0^{\theta_0} \cos\left[\left(l + \frac{1}{2}\right) u\right] du \frac{d}{du} \int_0^u \frac{\sin v}{\sqrt{\cos v - cosu}} \left(1 + \sum_{m=0}^{\infty} q_m X_m P_m(\cos v)\right) dv$$

(12)

You will need the following integral [Sneddon 2.6.7]

$$\int_0^u \frac{P_l(\cos v)\sin v}{\sqrt{2(cosv-\cos u)}}dv = \frac{\sin[(l+1/2)u]}{l+1/2} \qquad (13)$$

Performing the integrals in eq. (12) we obtain

$$X_l = \frac{2}{\pi}\int_0^{\theta_0} \cos\left[\left(l+\frac{1}{2}\right)u\right] du \frac{d}{du}\left(2\sin\left(\frac{u}{2}\right) + \sum_{m=0}^{\infty} q_m X_m \frac{\sin[(m+1/2)u]}{m+1/2}\right)$$

To proceed you will need the following integral: (14)

$$\begin{aligned} I_{lm} &= \int_0^{\theta_0} \cos[(l+1/2)u]\cos[(m+1/2)u]du \\ &= \begin{cases} \frac{1}{2}\left[\frac{\sin[(l-m)\theta_0]}{l-m} + \frac{\sin[(l+m+1)\theta_0]}{l+m+1}\right] & \text{for } l \neq m \\ \frac{\theta_0}{2} + \frac{1}{2}\frac{\sin[(2l+1)\theta_0]}{2l+1} & \text{for } l = m \end{cases} \qquad (15) \\ &= \frac{1}{2}\left[\frac{\sin[(l+m+1)\theta_0]}{l+m+1} + \frac{\sin[(l-m)\theta_0]}{l-m}(1-\delta_{lm}) + \frac{\theta_0}{2}\delta_{lm}\right] \end{aligned}$$

The final result is an infinite-dimensional linear system

$$X_l - \sum_{m=0}^{\infty} M_{lm} X_m = Q_{l0} \tag{16}$$

where

$$M_{lm} = q_m Q_{lm} \tag{17}$$

$$Q_{lm} = \frac{1}{\pi}\left[\frac{\sin[(l+m+1)\theta_0]}{l+m+1} + \frac{\sin[(l-m)\theta_0]}{l-m}(1-\delta_{lm}) + \frac{\theta_0}{2}\delta_{lm}\right]$$

The system (16) can be truncated and solved to any desired accuracy for the coefficients X_l.

The rate: only need to know the coefficient X_0

$$
\begin{aligned}
k &= 2\pi D a^2 \int_0^\pi \left.\frac{\partial c}{\partial r}\right|_{r=a} \sin\theta \, d\theta \\
&= -2\pi D a \int_0^\pi \left.\frac{\partial n}{\partial \xi}\right|_{\xi=1} \sin\theta \, d\theta \\
&= 2\pi D a c_0 \sum_{l=0}^{\infty} A_l (l+1) \int_0^\pi P_l(\cos\theta) \sin\theta \, d\theta \\
&= 4\pi D a c_0 A_0 \\
&= 2\pi D a c_0 X_0
\end{aligned}
$$

Since, in view of the orthogonality of Legendre polynomials, the only integral that gives a non-zero contribution is the one for *l* = 0.

$$
\int_0^\pi P_l(\cos\theta) P_m(\cos\theta) \sin\theta \, d\theta = \frac{2}{2l+1} \delta_{lm}
$$

The rate

$$
\frac{k}{k_S} = \frac{X_0}{2}
$$

The monopole approximation: obtaining an analytical estimate for the steric factor

$$X_0 - M_{00}X_0 = Q_{00}$$

$$\begin{cases} Q_{00} = \dfrac{1}{\pi}(\sin\theta_0 + \theta_0) \\ M_{00} = q_0 Q_{00} = \dfrac{1}{2\pi}(\sin\theta_0 + \theta_0) \end{cases}$$

The solution is

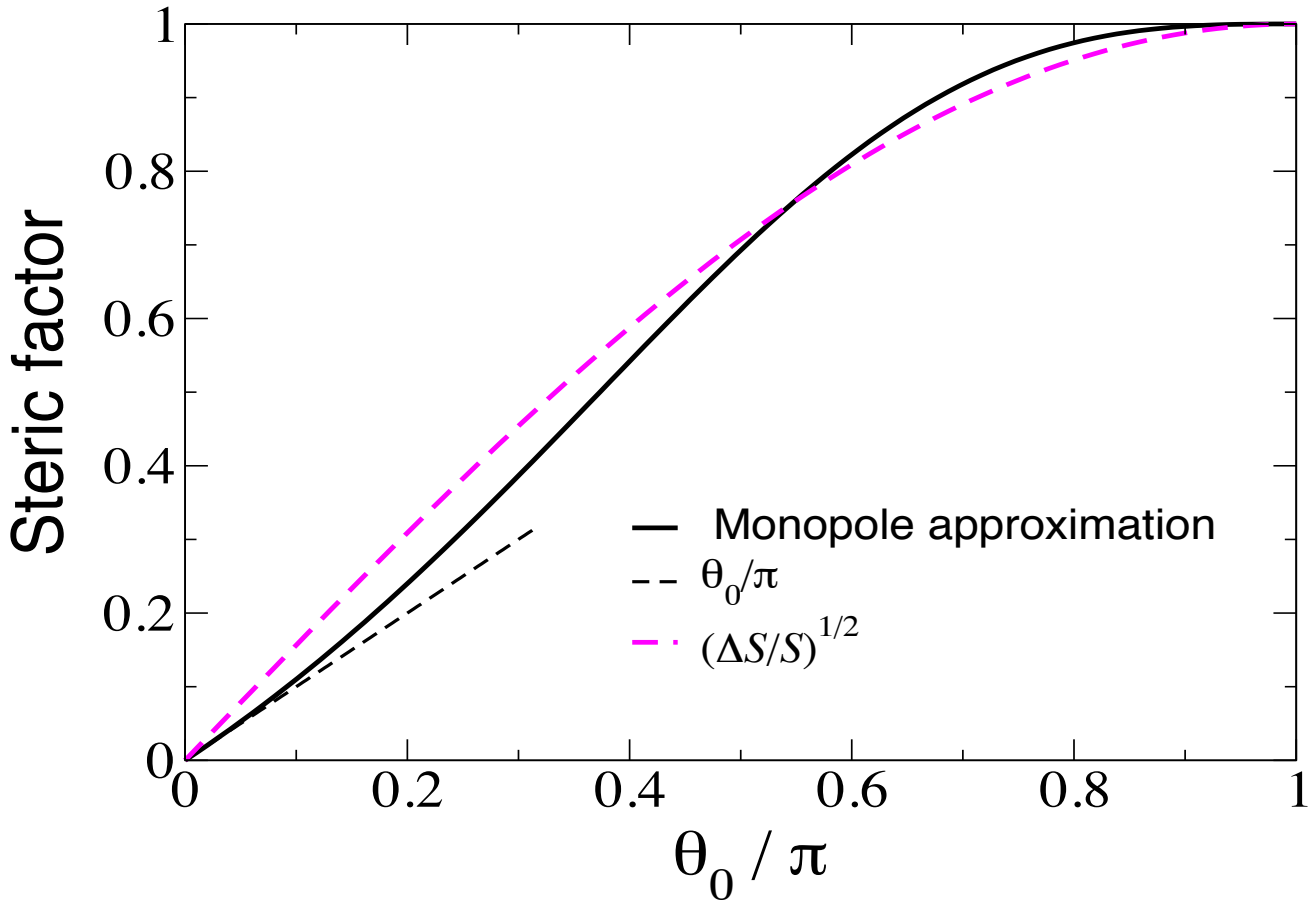
$$\frac{k}{k_S} \overset{\text{def}}{=} f_s(\theta_0) = \frac{\sin\theta_0 + \theta_0}{2\pi - (\sin\theta_0 + \theta_0)}$$

The *naïve* solution
One would imagine

$$f_s(\theta_0) = \frac{\Delta S}{S} = \frac{1}{4\pi}\int_{S_{\text{cap}}} d\Omega$$

$$= \frac{1}{2}\int_0^{\theta_0} \sin\theta\, d\theta = \sin^2\left(\frac{\theta_0}{2}\right)$$

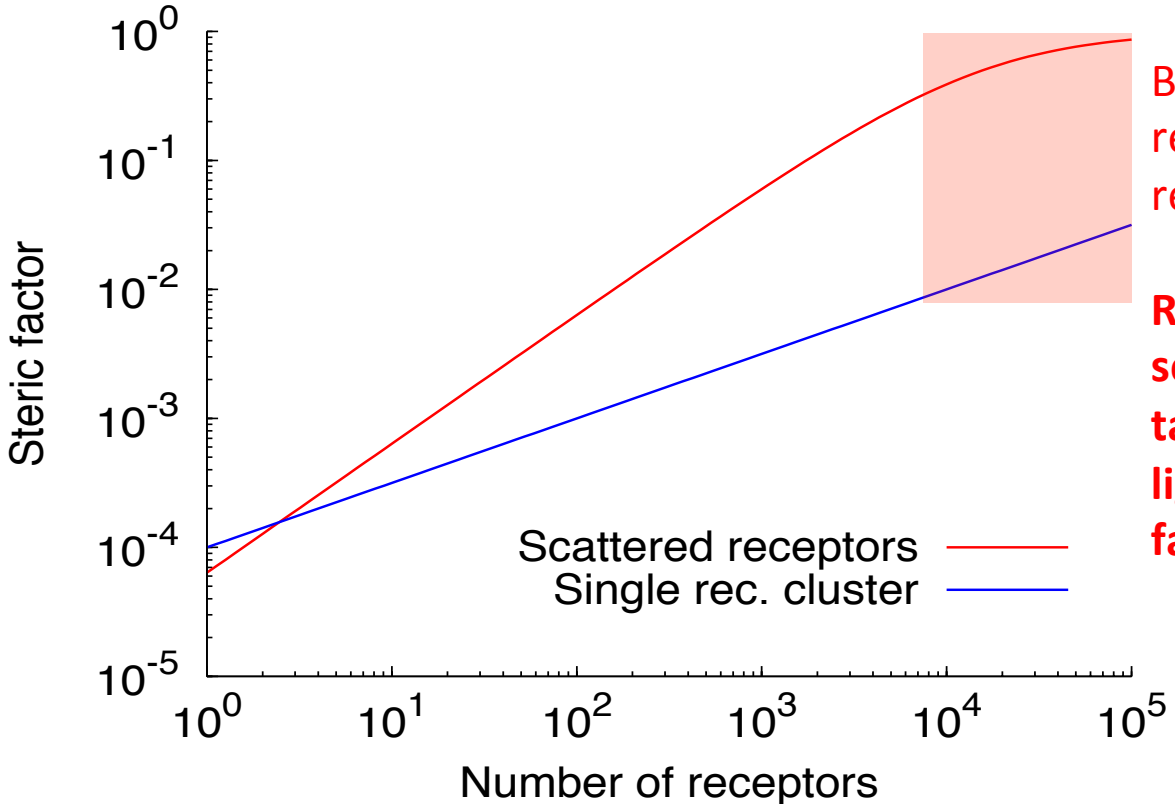
The reduction with respect to the cell completely covered in receptors goes as *the square root of the receptor-covered region*



Is a sparse uniform distribution of *M* receptors **better** or **worse** than a cluster containing all *M* receptors grouped together?

We have found that the **square root** of the covered area is a sensible approximation for the case of a uniform **patch** covered in receptors

$$\frac{\Delta S}{S} = \frac{N\pi r^2}{4\pi a^2} \Longrightarrow \begin{cases} f_{\text{many}} \simeq \dfrac{Nr}{Nr + \pi a} \\ f_{\text{clust}} \simeq \sqrt{N}\left(\dfrac{r}{2a}\right) \end{cases}$$

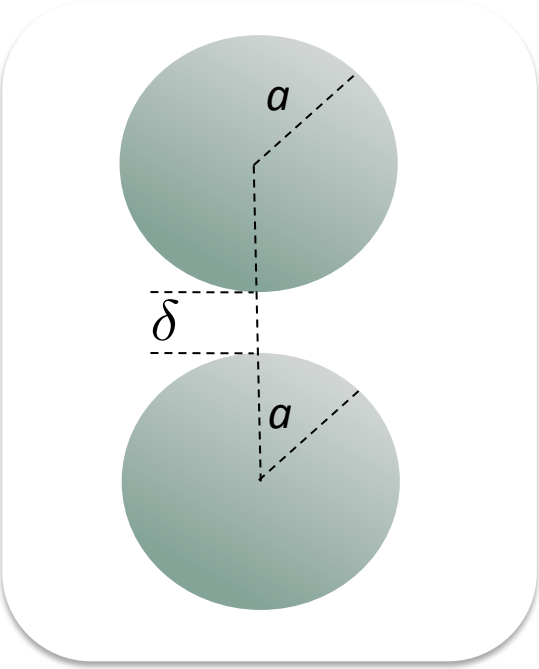


Biologically relevant region

Receptors uniformly scattered are a better target for diffusing ligand by a 100-fold factor!

Diffusive interactions II

Two neighboring cells uniformly covered in receptors



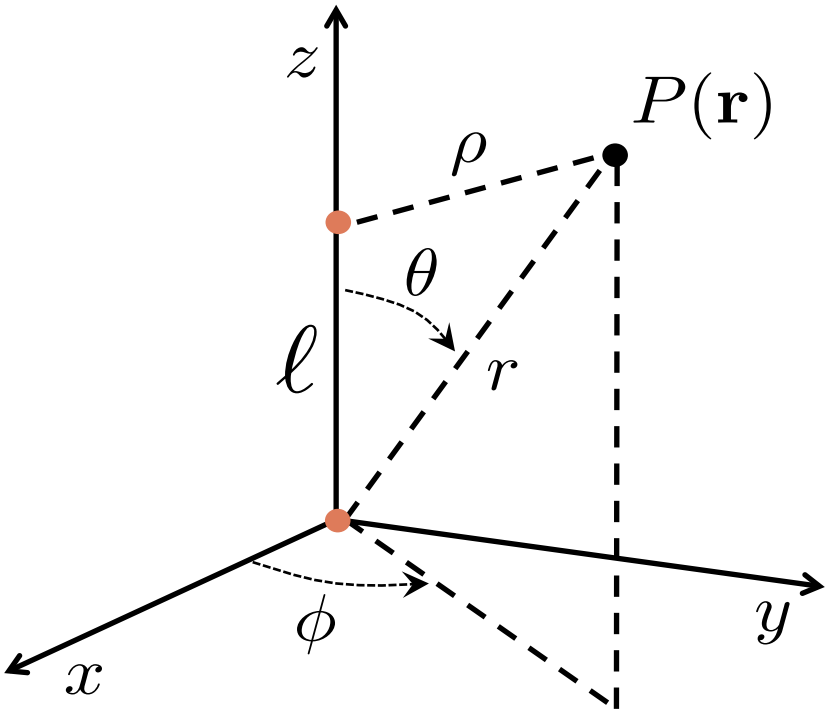
We can anticipate that

$$k < 2k_S$$

But how does this reduction depend on the distance between the cells?

We will prove that there exists **a long-range interaction** between the two cells with respect to the rate of a ligand that can bind either of them

A mathematical interlude: re-expansion formulas for axially symmetric systems



We will prove the following identity

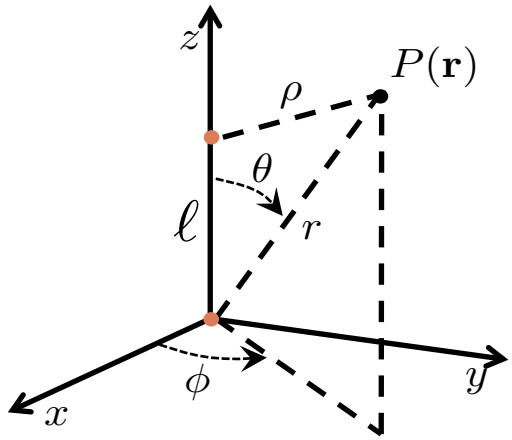
$$\frac{1}{r^{n+1}} P_n(\mu) = \frac{(-1)^n}{n!} \frac{\partial^n}{\partial z^n} \left(\frac{1}{r}\right)$$

Start by expanding 1/r

(1)
$$\frac{1}{\rho} = \frac{1}{\sqrt{x^2 + y^2 + (z-\ell)^2}}$$
$$= \frac{1}{r} + \left[\frac{\partial}{\partial \ell}\left(\frac{1}{\rho}\right)\right]_{\ell=0} \ell + \frac{1}{2}\left[\frac{\partial^2}{\partial \ell^2}\left(\frac{1}{\rho}\right)\right]_{\ell=0} \ell^2 + \dots$$

$$\frac{1}{\rho} = \frac{1}{\sqrt{x^2+y^2+(z-\ell)^2}}$$

$$= \frac{1}{r} + \left[\frac{\partial}{\partial \ell}\left(\frac{1}{\rho}\right)\right]_{\ell=0} \ell + \frac{1}{2}\left[\frac{\partial^2}{\partial \ell^2}\left(\frac{1}{\rho}\right)\right]_{\ell=0} \ell^2 + \dots \quad (1)$$



$$\left.\frac{\partial}{\partial \ell}\left(\frac{1}{\rho}\right)\right|_{\ell=0} = -\left.\frac{\partial}{\partial (z-\ell)}\left(\frac{1}{\rho}\right)\right|_{\ell=0} = -\frac{\partial}{\partial z}\left(\frac{1}{r}\right) \Bigg\} \Longrightarrow \boxed{\left.\frac{\partial^n}{\partial \ell^n}\left(\frac{1}{\rho}\right)\right|_{\ell=0} = (-1)^n \frac{\partial^n}{\partial z^n}\left(\frac{1}{r}\right)}$$

(2)

Inserting the identity (2) into the expansion (1), we get

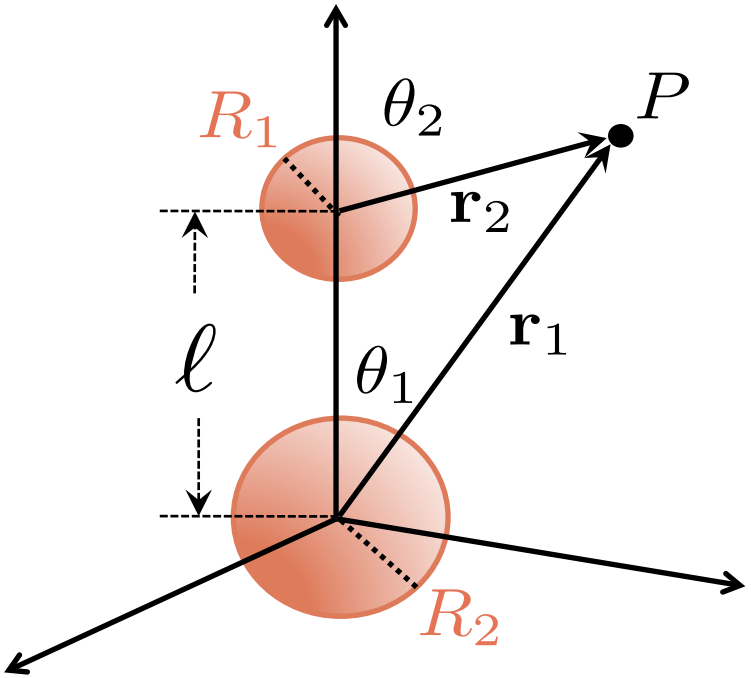
(3) $$\frac{1}{\rho} = \sum_{n=0}^{\infty} \frac{(-1)^n}{n!} \frac{\partial^n}{\partial z^n}\left(\frac{1}{r}\right) \ell^n$$

On the other side, it is well known that

(4) $$\frac{1}{\rho} = \frac{1}{r} \sum_{n=0}^{\infty} P_n(\cos\theta) \left(\frac{\ell}{r}\right)^n \qquad \text{for } l < r$$

Comparing (3) and (4) we have

$$\frac{P_n(\mu)}{r^{n+1}} = \frac{(-1)^n}{n!} \frac{\partial^n}{\partial z^n}\left(\frac{1}{r}\right)$$



The basic idea

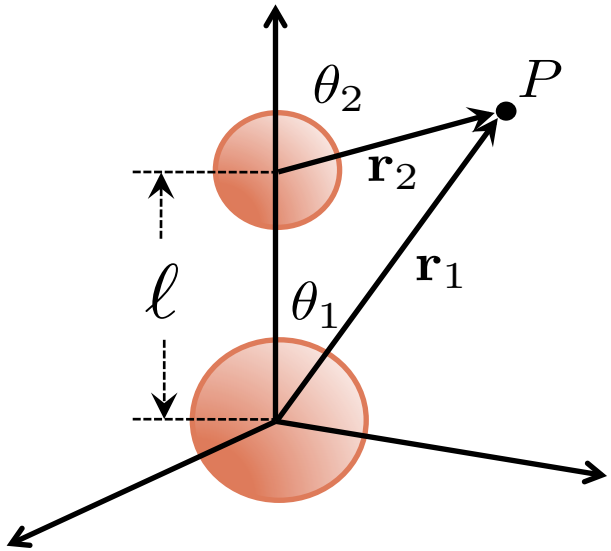
Two local coordinate systems (centered on either sphere) in the manifold where I have to solve Laplace equation.

The general solution of Laplace equation

$$u = u_1(\mathbf{r}_1) + u_2(\mathbf{r}_2)$$
$$= \sum_{n=0}^{\infty} A_n^1 \left(\frac{R_1}{r}\right)^{n+1} P_n(\cos\theta_1) + \sum_{n=0}^{\infty} A_n^2 \left(\frac{R_2}{r}\right)^{n+1} P_n(\cos\theta_2)$$

In order to impose the boundary conditions on sphere 1 we have to express $u_2(r_2)$ in the local frame of reference of sphere 1, and *viceversa*.

The first identity



$$\frac{1}{r_2^{k+1}} P_k(\mu_2) = \frac{(-1)^k}{k!} \frac{\partial^k}{\partial z_2^k} \frac{1}{r_2}$$

$$= \frac{(-1)^k}{k!} \frac{\partial^k}{\partial z_2^k} \frac{1}{\sqrt{x_2^2 + y_2^2 + (z_1 - \ell)^2}}$$

$$= \frac{1}{k!} \frac{\partial^k}{\partial \ell^k} \frac{1}{\sqrt{x_2^2 + y_2^2 + (z_1 - \ell)^2}}$$

Carnot theorem

$$= \frac{1}{k!} \frac{\partial^k}{\partial \ell^k} \frac{1}{\sqrt{r_1^2 + \ell^2 - 2 r_1 \ell \mu_1}}$$

I am expressing u_2 in the vicinity of S1, hence $r_1 < l$

$$= \frac{1}{k!} \frac{\partial^k}{\partial \ell^k} \frac{1}{\ell \sqrt{1 + \left(\frac{r_1}{\ell}\right)^2 - 2\mu_1 \left(\frac{r_1}{\ell}\right)}}$$

using eq. (4)

$$= \frac{1}{k!} \frac{\partial^k}{\partial \ell^k} \sum_{n=0}^{\infty} P_n(\mu_1) \frac{r_1^n}{\ell^{n+1}} = \sum_{n=0}^{\infty} (-1)^k \binom{n+k}{n} P_n(\mu_1) \frac{r_1^n}{\ell^{n+k+1}}$$

The second identity

$$\frac{1}{r_1^{k+1}} P_k(\mu_1) = \frac{(-1)^k}{k!} \frac{\partial^k}{\partial z_1^k} \frac{1}{r_1}$$

$$= \frac{(-1)^k}{k!} \frac{\partial^k}{\partial z_1^k} \frac{1}{\sqrt{x_1^2 + y_1^2 + (z_2 + \ell)^2}}$$

$$= \frac{(-1)^k}{k!} \frac{\partial^k}{\partial \ell^k} \frac{1}{\sqrt{x_1^2 + y_1^2 + (z_2 + \ell)^2}}$$

Carnot theorem

$$= \frac{(-1)^k}{k!} \frac{\partial^k}{\partial \ell^k} \frac{1}{\sqrt{r_2^2 + \ell^2 + 2 r_2 \ell \mu_2}}$$

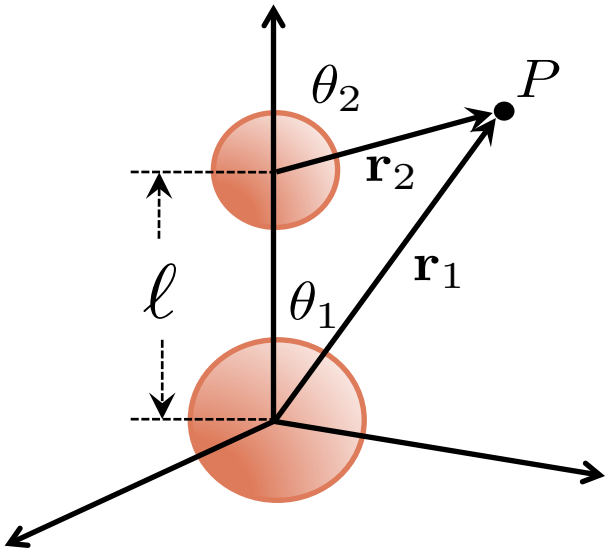
I am expressing u_1 in the vicinity of S2, hence $r_2 < l$

$$= \frac{(-1)^k}{k!} \frac{\partial^k}{\partial \ell^k} \frac{1}{\ell \sqrt{1 + \left(\frac{r_2}{\ell}\right)^2 + 2\mu_2 \left(\frac{r_2}{\ell}\right)}}$$

using eq. (4)

$$= \frac{(-1)^k}{k!} \frac{\partial^k}{\partial \ell^k} \sum_{n=0}^{\infty} (-1)^n P_n(\mu_2) \frac{r_2^n}{\ell^{n+1}}$$

$$= \sum_{n=0}^{\infty} (-1)^n \binom{n+k}{n} P_n(\mu_2) \frac{r_2^n}{\ell^{n+k+1}}$$



Pay attention: there is an additional (-1)^n in eq.(4) if the angle is $\pi - \theta_2$!

The two important identities that will allow to solve the problem

$$\frac{1}{r_1^{k+1}} P_k(\mu_1) = \sum_{n=0}^{\infty} (-1)^n \binom{n+k}{n} P_n(\mu_2) \frac{r_2^n}{\ell^{n+k+1}} \tag{5}$$

$$\frac{1}{r_2^{k+1}} P_k(\mu_2) = \sum_{n=0}^{\infty} (-1)^k \binom{n+k}{n} P_n(\mu_1) \frac{r_1^n}{\ell^{n+k+1}} \tag{6}$$

Useful non-dimensional variables

$$u(\mathbf{r}_i) = 1 - \frac{c(\mathbf{r}_i)}{c_0} \qquad \xi_i = \frac{r_i}{R_i} \qquad \epsilon_i = \frac{R_i}{\ell}$$

We have to solve this boundary value problem

$$\nabla^2 u = 0$$

$$u|_{\xi_1=1} = u|_{\xi_2=1} = 0 \tag{7}$$

$$\lim_{\xi_1 \to \infty} u = \lim_{\xi_2 \to \infty} u = 0 \tag{8}$$

The solution

We look for solutions in the form:

$$\begin{aligned} u &= u_1(\mathbf{r}_1) + u_2(\mathbf{r}_2) \\ &= \sum_{n=0}^{\infty} A_n^1 \xi_1^{-(n+1)} P_n(\mu_1) + \sum_{n=0}^{\infty} A_n^2 \xi_2^{-(n+1)} P_n(\mu_2) \end{aligned} \tag{9}$$

Now we insert the general solution (9) in the boundary conditions (7) to determine the unknown expansion coefficients A^1_n and A^2_n. When I write the first eq. of (7), BC on S1, I will use eq. (6) to express u_2 in the local frame of reference of S1. I will use (5) to do the opposite. When I do this, I can write the solution u in either frames of references, that can conveniently be used to write the BCs in the vicinity of either sphere.

$$\begin{cases} u = \displaystyle\sum_{n=0}^{\infty} \left[A_n^1 \, \xi_1^{-(n+1)} + \sum_{k=0}^{\infty} (-1)^k \epsilon_2^{k+1} \epsilon_1^n \, \xi_1^n \binom{n+k}{n} A_k^2 \right] P_n(\mu_1) & (10) \\ u = \displaystyle\sum_{n=0}^{\infty} \left[\sum_{k=0}^{\infty} (-1)^n \epsilon_1^{k+1} \epsilon_2^n \, \xi_2^n \binom{n+k}{n} A_k^1 + A_n^2 \, \xi_2^{-(n+1)} \right] P_n(\mu_2) & (11) \end{cases}$$

Let us simplify the notation. We introduce the matrices U^{12} and U^{21}

$$\begin{cases} U_{nk}^{12} = (-1)^k \epsilon_2^{k+1} \epsilon_1^n \binom{n+k}{n} & (12) \\ U_{nk}^{21} = (-1)^n \epsilon_1^{k+1} \epsilon_2^n \binom{n+k}{n} & (13) \end{cases}$$

Using the expressions (10) and (11) in the two BC (7), we obtain the following system of linear equations

$$\begin{cases} A_n^1 + \sum_{k=0}^{\infty} U_{nk}^{12} A_k^2 = \delta_{n0} \\ \sum_{k=0}^{\infty} U_{nk}^{21} A_k^1 + A_n^2 = \delta_{n0} \end{cases} \quad (14)$$

Again, the problem can be solved to any desired accuracy by truncating the system (14) to any number of multipoles.

The rate

As we now know, the diffusive encounter rate of a ligand of diffusivity D with the two-cell system is the total flux into the two spheres

$$
\begin{aligned}
k &= 2\pi D R_1^2 \int_0^\pi \left.\frac{\partial \rho}{\partial r_1}\right|_{r_1=R_1} \sin\theta_1 \, d\theta_1 + 2\pi D R_2^2 \int_0^\pi \left.\frac{\partial \rho}{\partial r_2}\right|_{r_2=R_2} \sin\theta_2 \, d\theta_2 \\
&= -2\pi D R_1 \int_0^\pi \left.\frac{\partial u}{\partial \xi_1}\right|_{\xi_1=1} \sin\theta_1 \, d\theta_1 - 2\pi D R_2 \int_0^\pi \left.\frac{\partial u}{\partial \xi_2}\right|_{\xi_2=1} \sin\theta_2 \, d\theta_2 \\
&= k_{S_1} A_0^1 + k_{S_2} A_0^2 \qquad (15)
\end{aligned}
$$

where we have used

$$
\int_0^\pi P_n(\cos\theta_i) \sin\theta_i \, d\theta_i = 2\delta_{n0}
$$

and introduced the **Smoluchowski** rates for each sphere $k_{S_i} = 4\pi D R_i c_0$

A simple yet accurate analytical approximation: the *monopole* solution

We only retain $n,k = 0$ in the system of equations (14). Therefore,

$$\begin{cases} A_0^1 + U_{00}^{12} A_0^2 = 1 \\ U_{00}^{21} A_0^1 + A_0^2 = 1 \end{cases} \qquad U_{00}^{12} = \epsilon_2, U_{00}^{21} = \epsilon_1 \tag{16}$$

The system (16) can be solved easily and eq. (15) can then be used to evaluate the rate

$$\begin{aligned} k &= k_{S_1} \left(\frac{1-\epsilon_2}{1-\epsilon_1\epsilon_2} \right) + k_{S_2} \left(\frac{1-\epsilon_1}{1-\epsilon_1\epsilon_2} \right) \\ &= k_{S_1} \left(\frac{\ell^2 - \ell R_2}{\ell^2 - R_1 R_2} \right) + k_{S_2} \left(\frac{\ell^2 - \ell R_1}{\ell^2 - R_1 R_2} \right) \end{aligned} \tag{17}$$

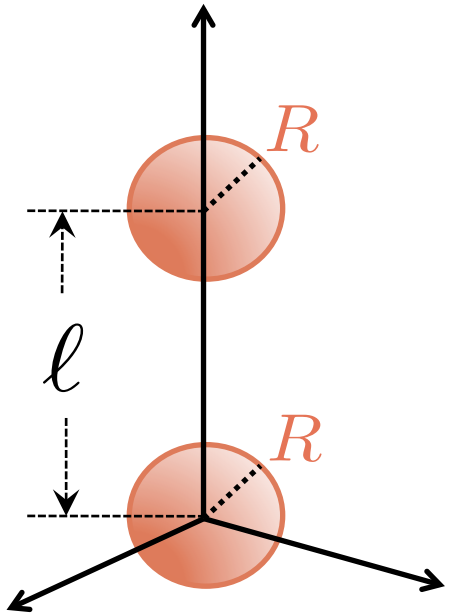
Diffusive interactions are *long-range*!

Let us consider for simplicity the case $R_1 = R_2 = R$

$$\frac{k}{2k_S} = \frac{\ell}{R+\ell} \approx 1 - \frac{R}{\ell} < 1$$

When the two cells are enough far apart

This is long-range, like Coulomb forces



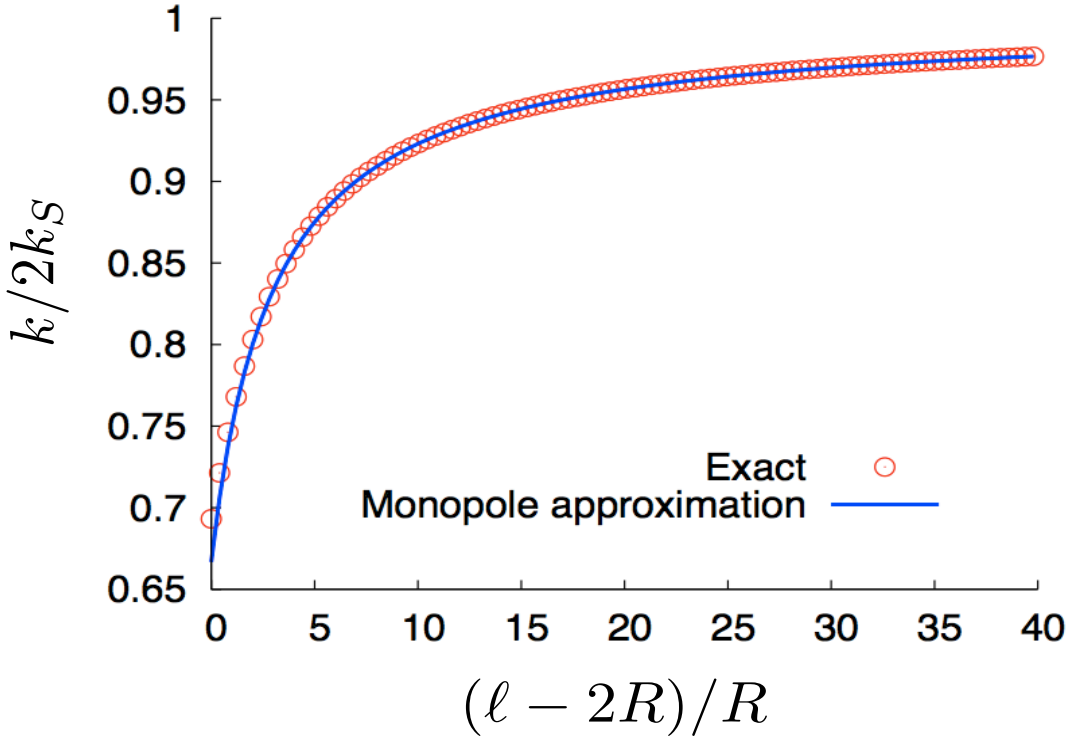
The maximum reduction in the monopole approximation is

$$\ell = 2R \Longrightarrow \frac{k}{2k_S} = \frac{2}{3}$$

The exact value is

$$\log 2 \approx 0.693$$

How good is the simple monopole approximation?

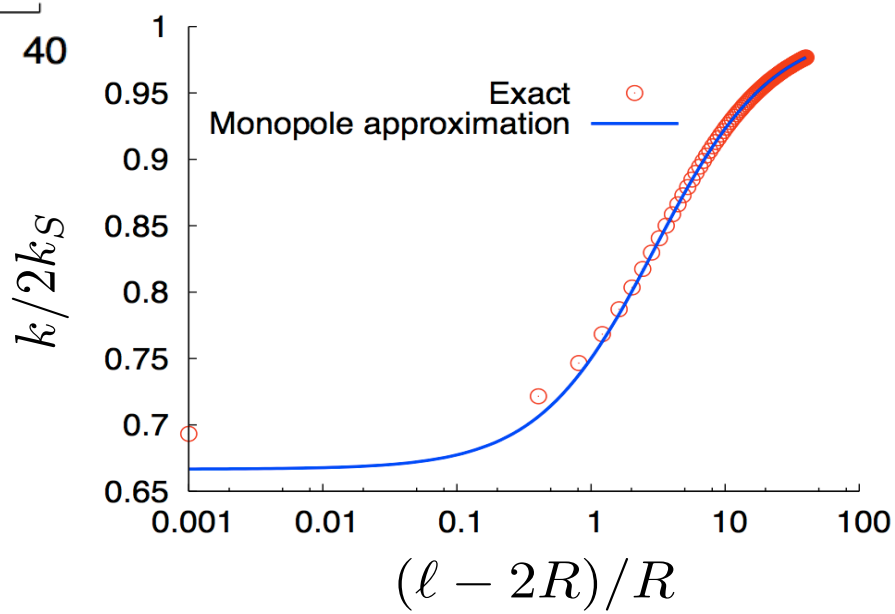


It is **extraordinarily** good!

Some deviations appear only in the region

$$\ell < 3R$$

For greater separations the MP is extremely good



Exercise: diffusive interaction between two partially covered cells

We want to investigate how the diffusion interaction is modified when the two cells are covered in receptors only on a fraction of their surfaces. We now know how to model this situation (we have seen this for one isolated cell). We have to introduce a finite *surface* reaction rate k* which is not infinite with respect to k_s. Therefore, you have to solve the following boundary value problem

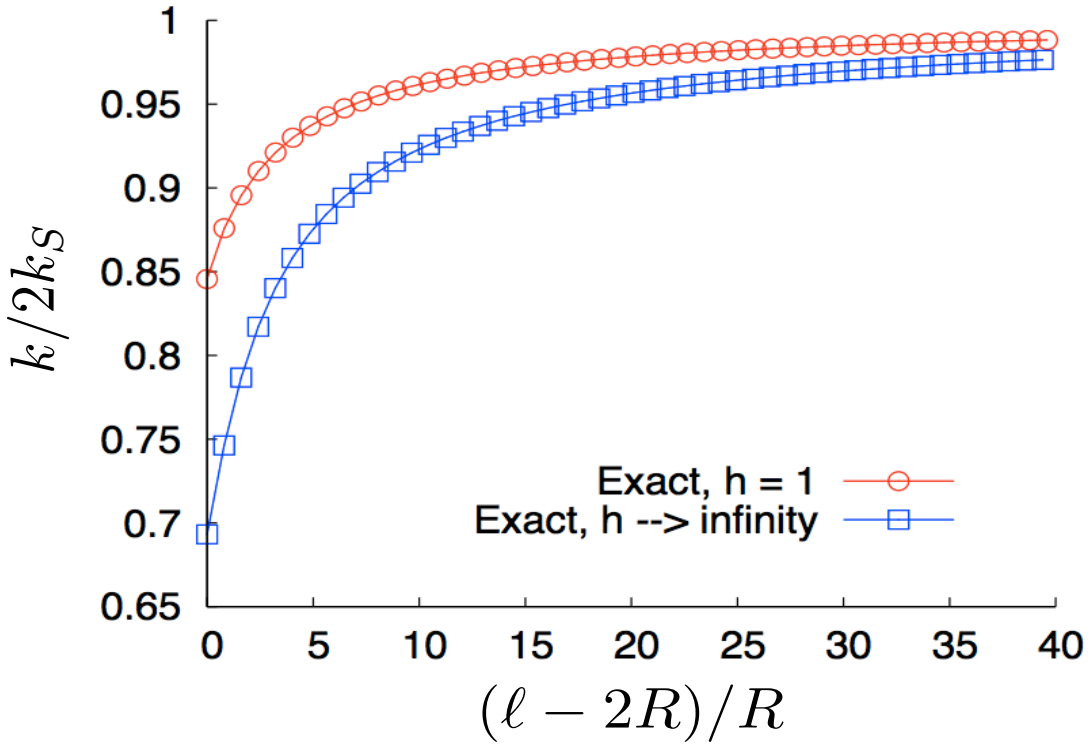
$$\begin{cases} \nabla^2 u = 0 \\ \left[\dfrac{\partial u}{\partial \xi_1} - h_1(u-1)\right]_{\xi_1=1} = 0 \\ \left[\dfrac{\partial u}{\partial \xi_2} - h_2(u-1)\right]_{\xi_2=1} = 0 \\ \lim\limits_{\xi_1\to\infty} u = \lim\limits_{\xi_2\to\infty} u = 0 \end{cases} \qquad h_i = \frac{k_i^*}{4\pi D R_i}$$

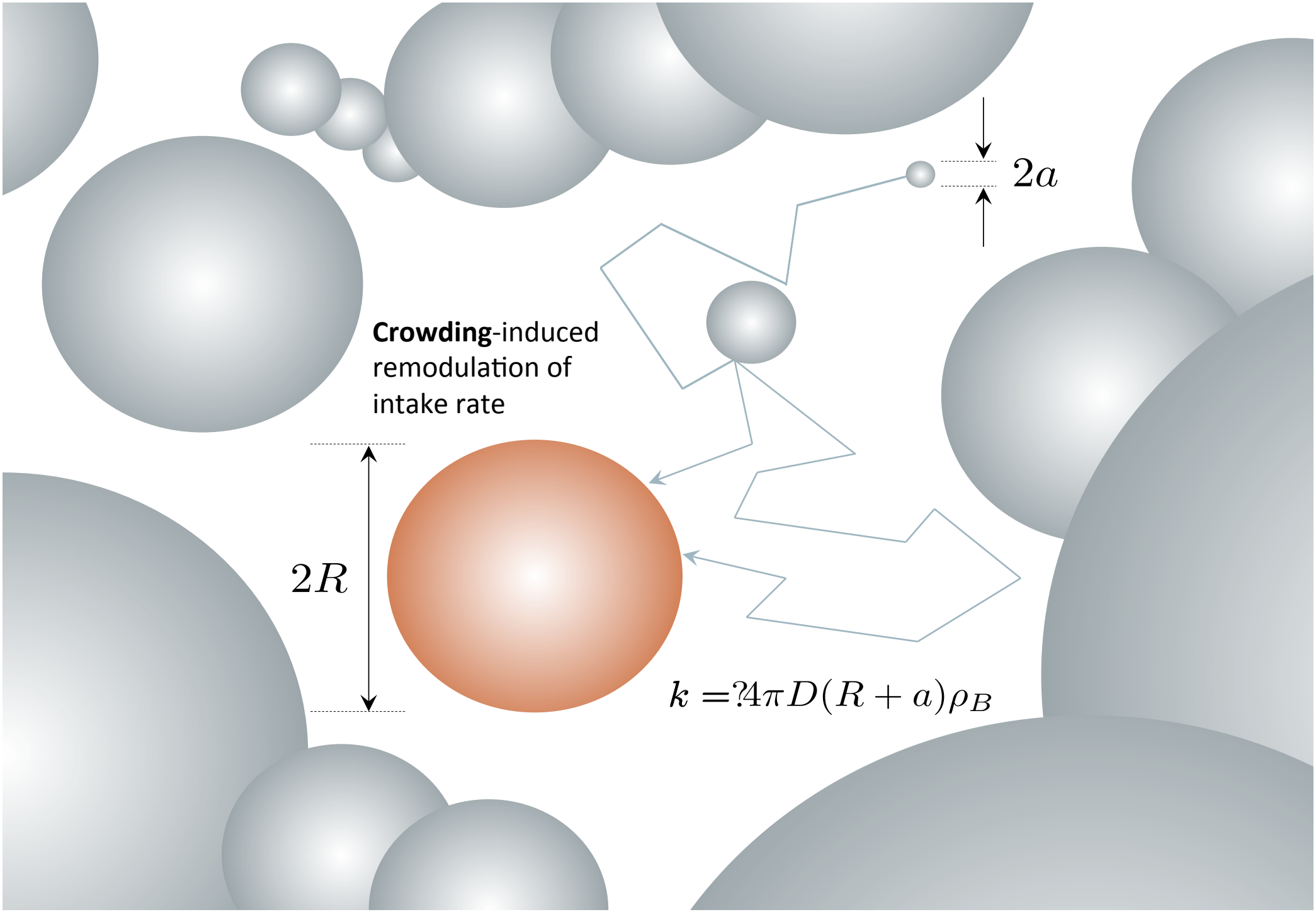
1. Show that in the monopole approximation, the rate is

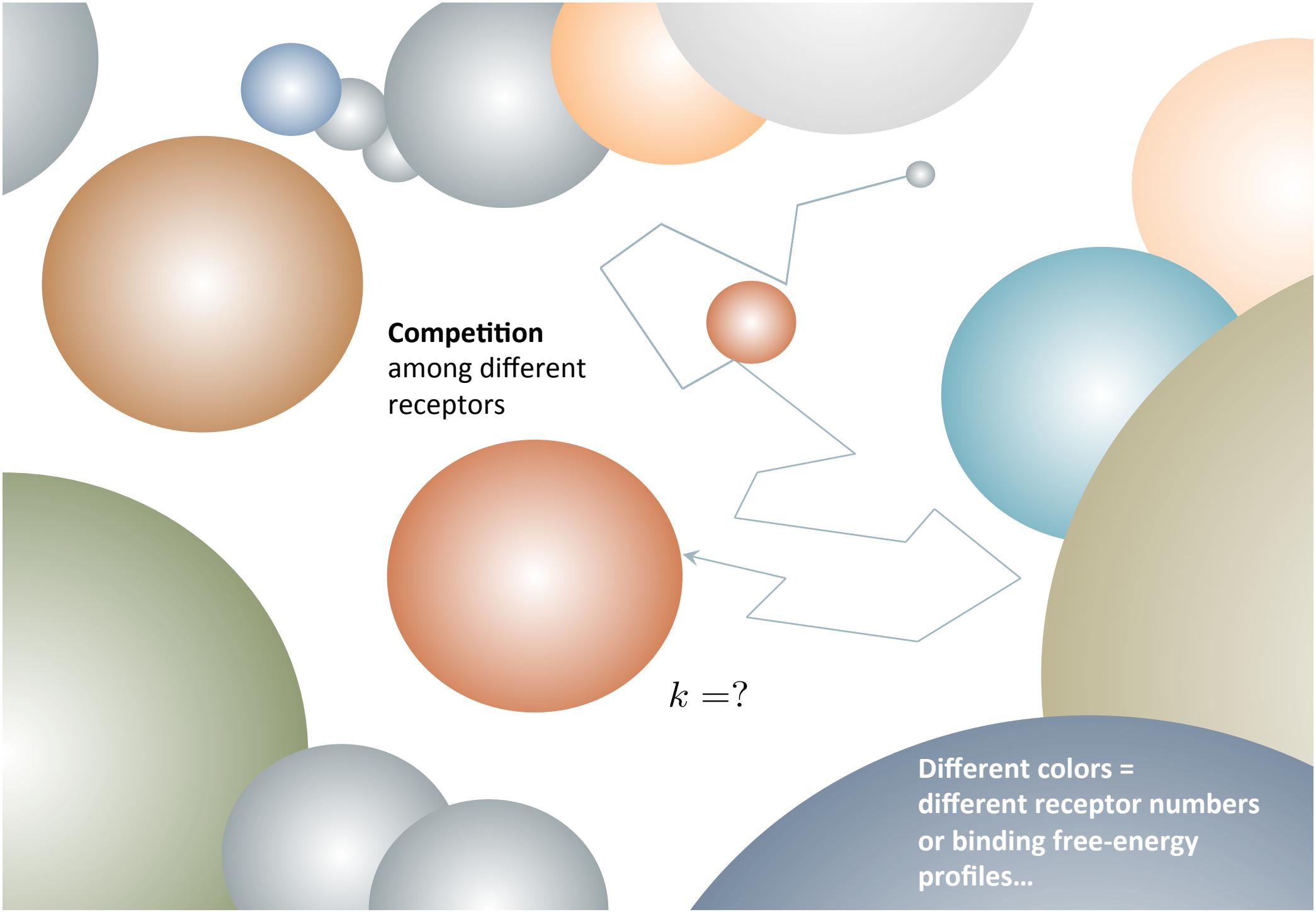
$$k = k_{S_1}\left[\frac{q_1(1-q_2\epsilon_2)}{1-q_1q_2\epsilon_1\epsilon_2}\right] + k_{S_2}\left[\frac{q_2(1-q_1\epsilon_1)}{1-q_1q_2\epsilon_1\epsilon_2}\right] \qquad q_i = \frac{h_i}{1+h_i}$$

2. Use this expression to show that the diffusive interaction is reduced for finite values of the parameters h_i, *i.e.* cells not completely covered in receptors. This case, which corresponds to h_i going to infinity, is the *worst* case for diffusive interactions.

Here it is a plot of the exact solution (identical spheres, relative accuracy of 1e-06) that shows to what extent the diffusive interactions are reduced for h = 1, *i.e.* an intrinsic rate at the surface of the same order as the rate for diffusive encounters.

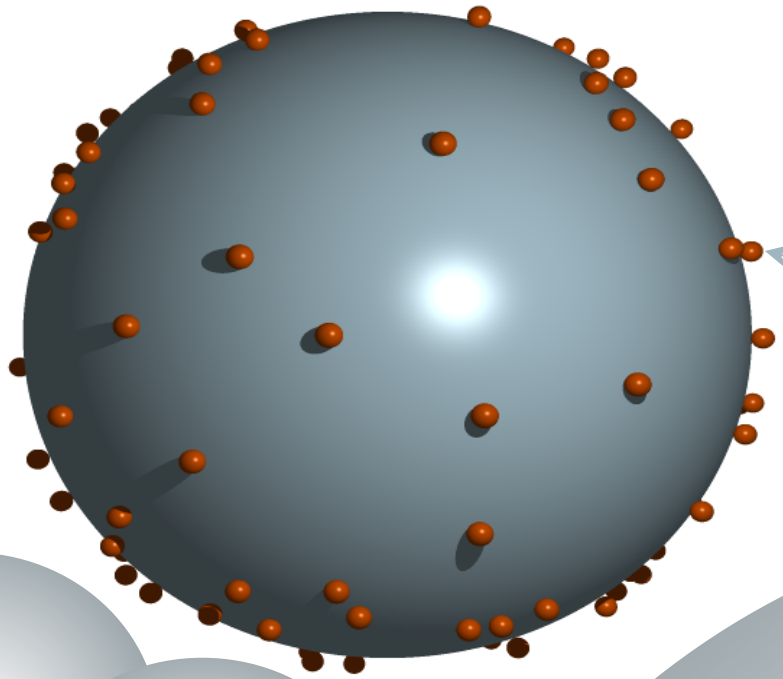



2a
Crowding-induced
remodulation of
intake rate
2R
k =?4πD(R + a)ρB

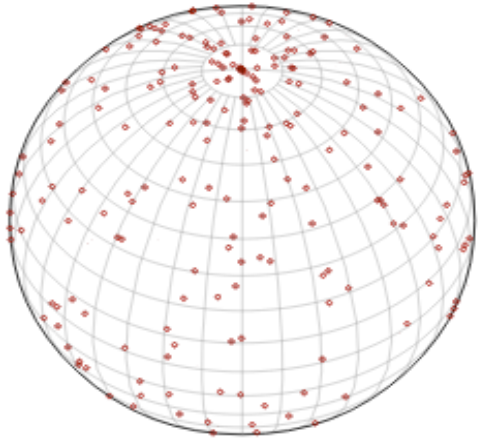

Competition
among different
receptors
$k = ?$
Different colors =
different receptor numbers
or binding free-energy
profiles…

ming

The rate of binding of a tiny ligand to a system
of spherical receptors of the same kind
on the surface of an otherwise inert cell



Rate to capture to a receptor-covered cell – Berg & Purcell (1977)



N absorbing circular patches of radius a on a sphere of radius R

Shoup & Szabo (1982): The idea is to use Radiative BCs

A sphere with random absorbing circular patches and otherwise reflecting can be thought as **uniformly *partially* absorbing**, in the sense of radiative boundary conditions:

$$k^* = N \times 4Da$$

Rate constant for an absorbing disk on an infinite reflecting plane

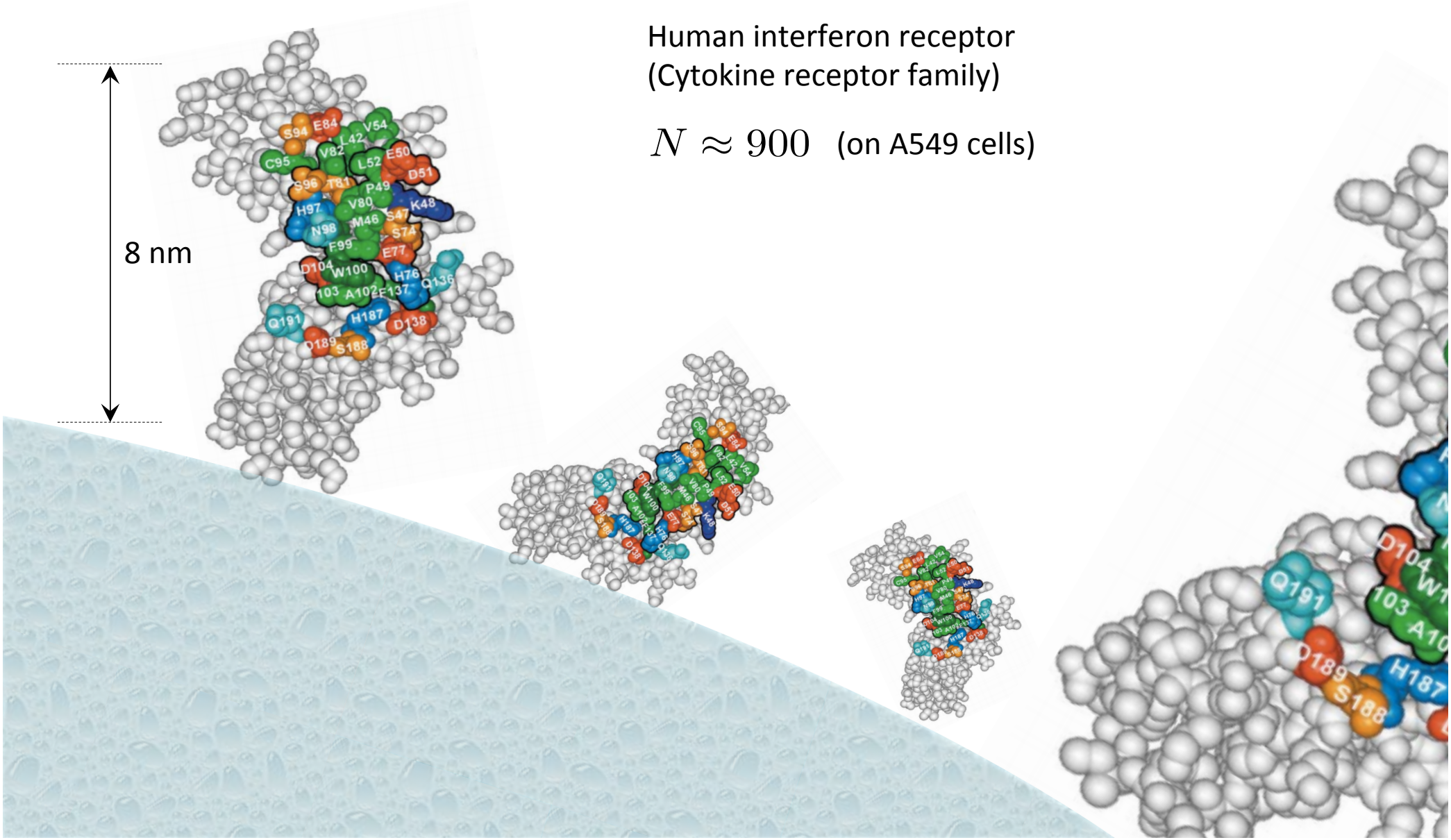
$$\begin{cases} \nabla^2 \rho = 0 \\ \left(4\pi D R^2 \dfrac{\partial \rho}{\partial r} - k^* \rho \right) \Big|_R = 0 \\ \lim\limits_{r \to \infty} \rho(r) = \rho_B \end{cases}$$

$$\frac{k}{k_S} = \frac{Na}{Na + \pi R}$$

$$k_S = 4\pi D R \rho_B$$

Rate to capture of a uniformly absorbing sphere

Real receptors are not flat disks on the cell surface



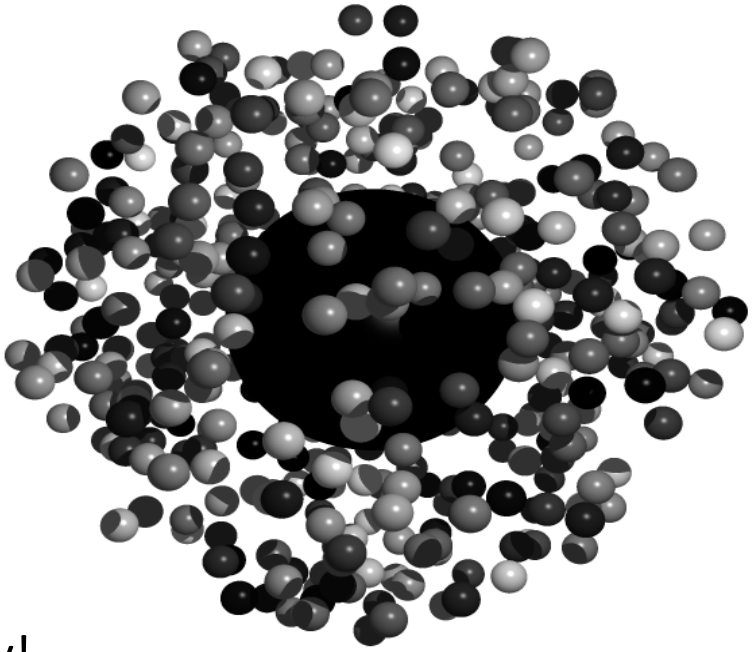
Human interferon receptor
(Cytokine receptor family)

$N \approx 900$ (on A549 cells)

There is a more serious and general issue…

The problem is a many-body one: that is, many receptors **interfere with each other** on the surface of the same cell…

Also, neighbouring receptor-covered cells compete for the same ligands…



Many-body means we have to solve Laplace equation with many disconnected reactive boundaries

DIFFUSIVE INTERACTIONS

The good news is: this problem can be solved exactly!

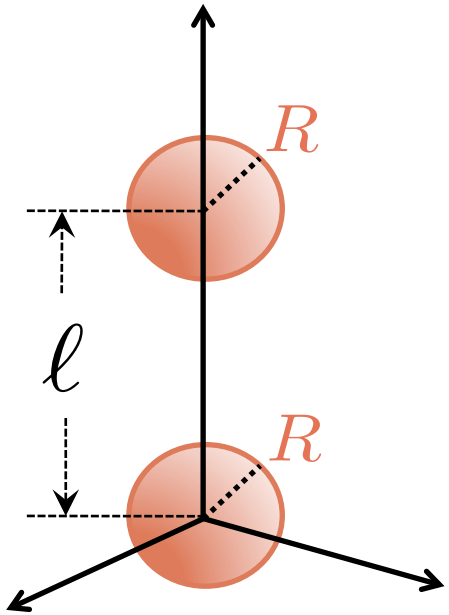
The first discovery: diffusive interactions are *long-range*

Let us consider for simplicity the case $R_1 = R_2 = R$. The **monopole approximation (MOA)** consists in keeping only the $n = 0$ terms in the multipole expansion.

$$\frac{k}{2k_S} = \frac{\ell}{R+\ell} \approx 1 - \frac{R}{\ell} < 1$$

When the two cells are enough far apart

This is long-range, like Coulomb energy



The maximum reduction in the monopole approximation is

$$\ell = 2R \Longrightarrow \frac{k}{2k_S} = \frac{2}{3}$$

The exact value is

$$\log 2 \approx 0.693$$

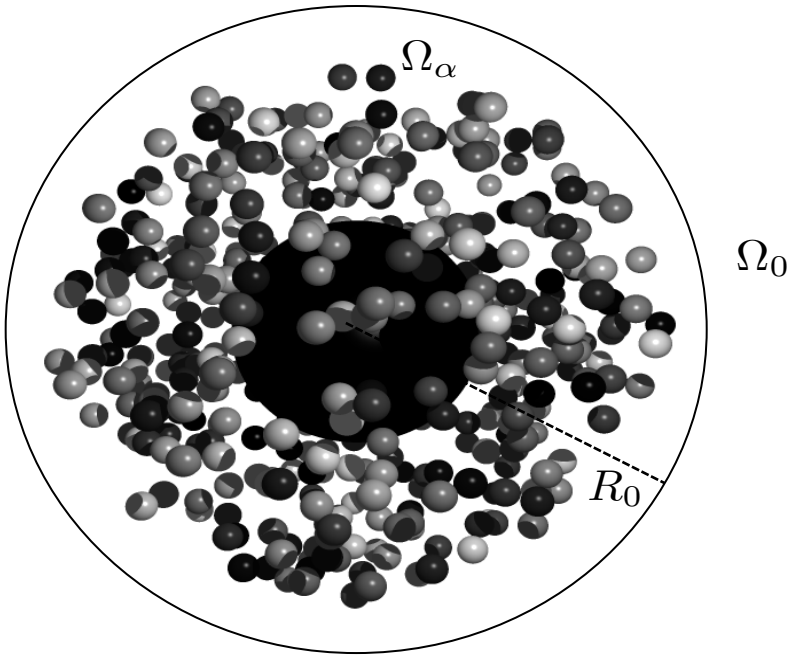
… if we can solve the problem of two spheres…

we can solve the problem of *N* spheres (use addition theorems for solid harmonics)

… sized and arranged as we wish…

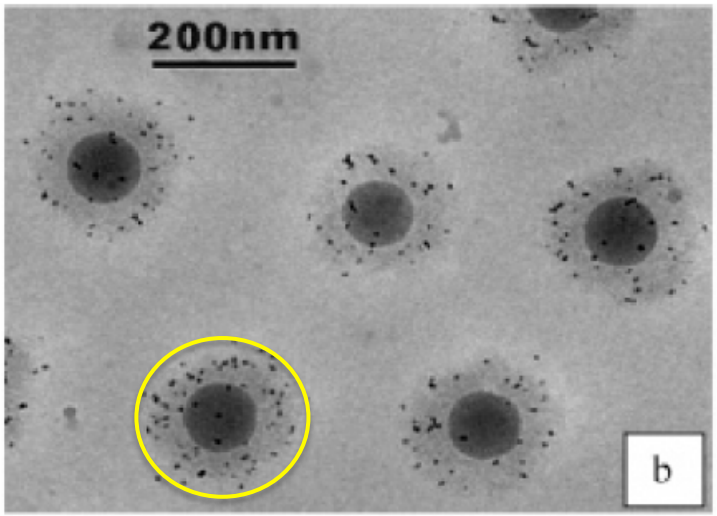
… and endowed with arbitrary intrinsic reactivities…

… some of them may be just obstacles (reflecting)…

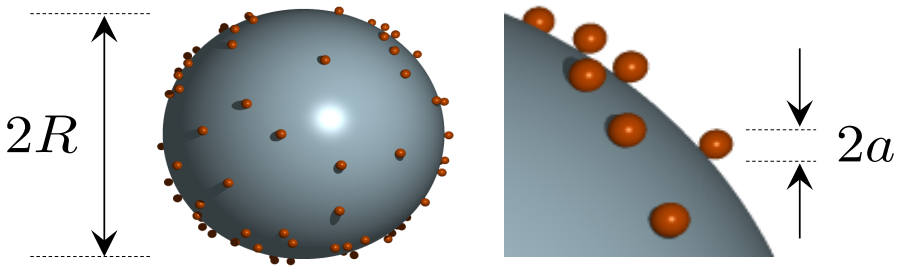


Countless applications! For example …

We can compute exactly the rate constant for a composite core-shell nanoreactor



We can consider cells covered in *spherical* receptors



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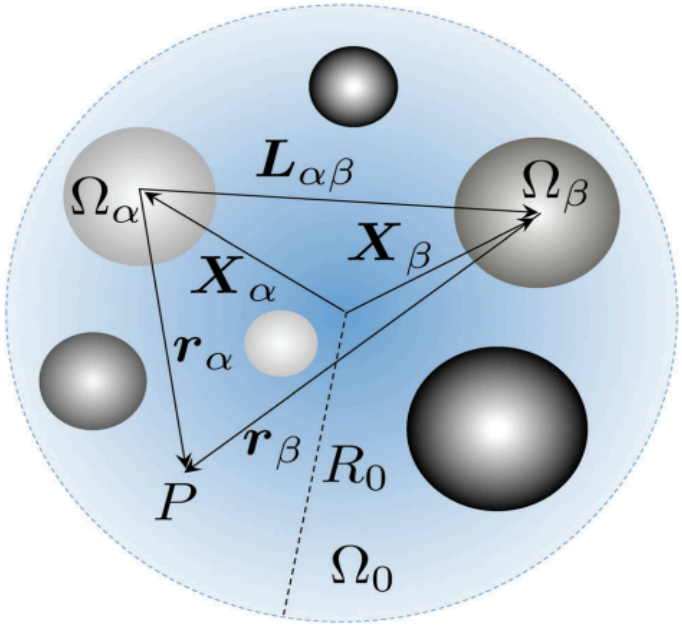
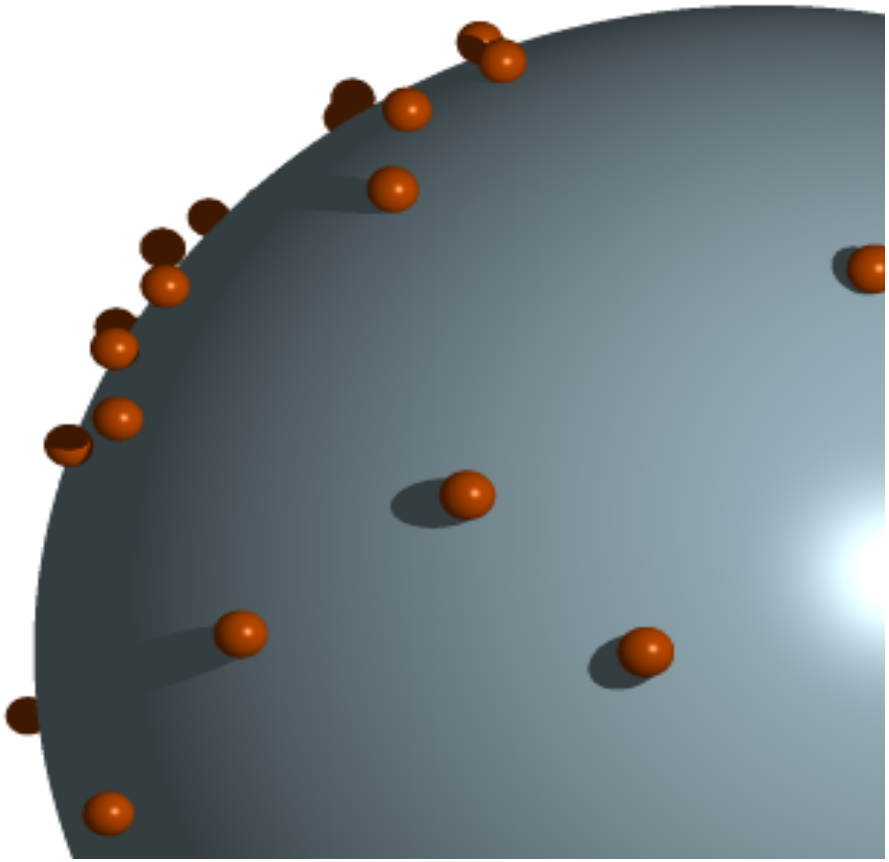
Theory of diffusion-influenced reactions in complex geometries†

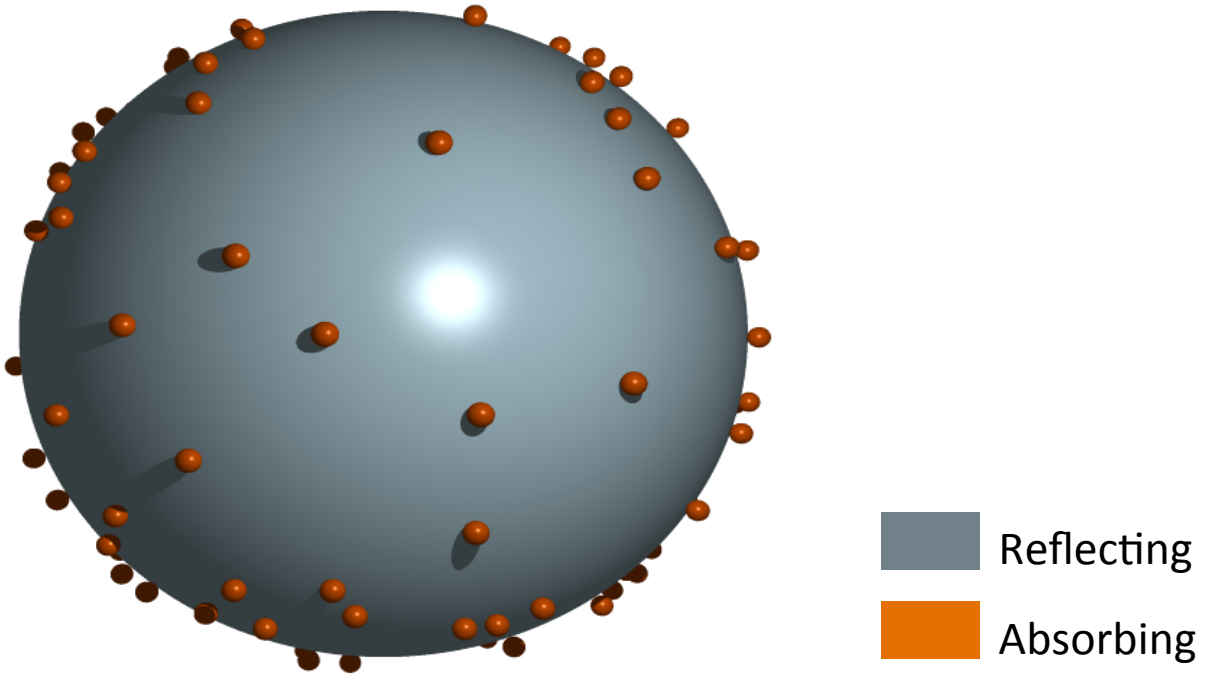
Marta Galanti,[abcde] Duccio Fanelli,[ac] Sergey D. Traytak[f] and Francesco Piazza*[a]



1 A tale of many receptors



We are now in a position to consider the rate to capture of a more realistic model of receptor-covered cell



The technique is the same. Solve the stationary diffusion equation with the appropriate boundary conditions on all spheres and compute the total ligand flux into this complex, multi-reactive sink

This calculation can be done analytically, thanks to re-expansion formulas for solid harmonics [see PCCP paper]

A matter of π

According to Shoup and Szabo's argument, one may expect that a cell covered with spherical receptors might be assimilated again to a **uniformly *partially* absorbing** sphere with

$$k^* = N \times 4\pi Da$$

Rate constant for an absorbing **sphere** of radius a

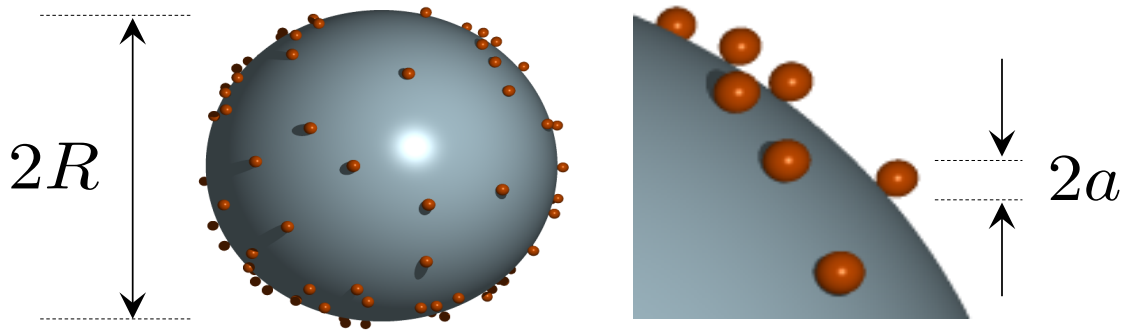
This would amount to the substitution $a \longrightarrow \pi a$ in the Berg & Purcell formula

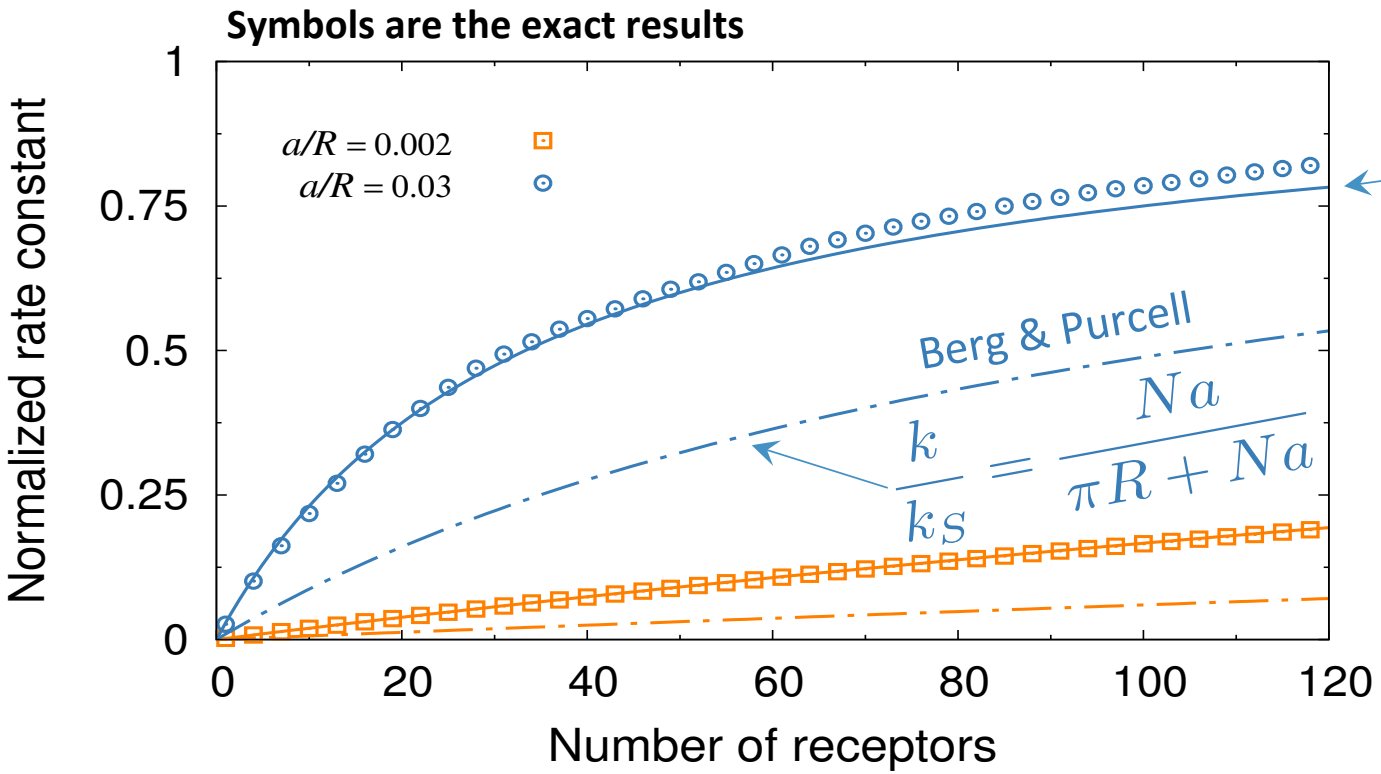
$$\frac{k}{k_S} = \frac{Na}{R + Na}$$

versus

$$\frac{k}{k_S} = \frac{Na}{\pi R + Na}$$

Even for very small receptor sizes, the flat-receptor approximation fails



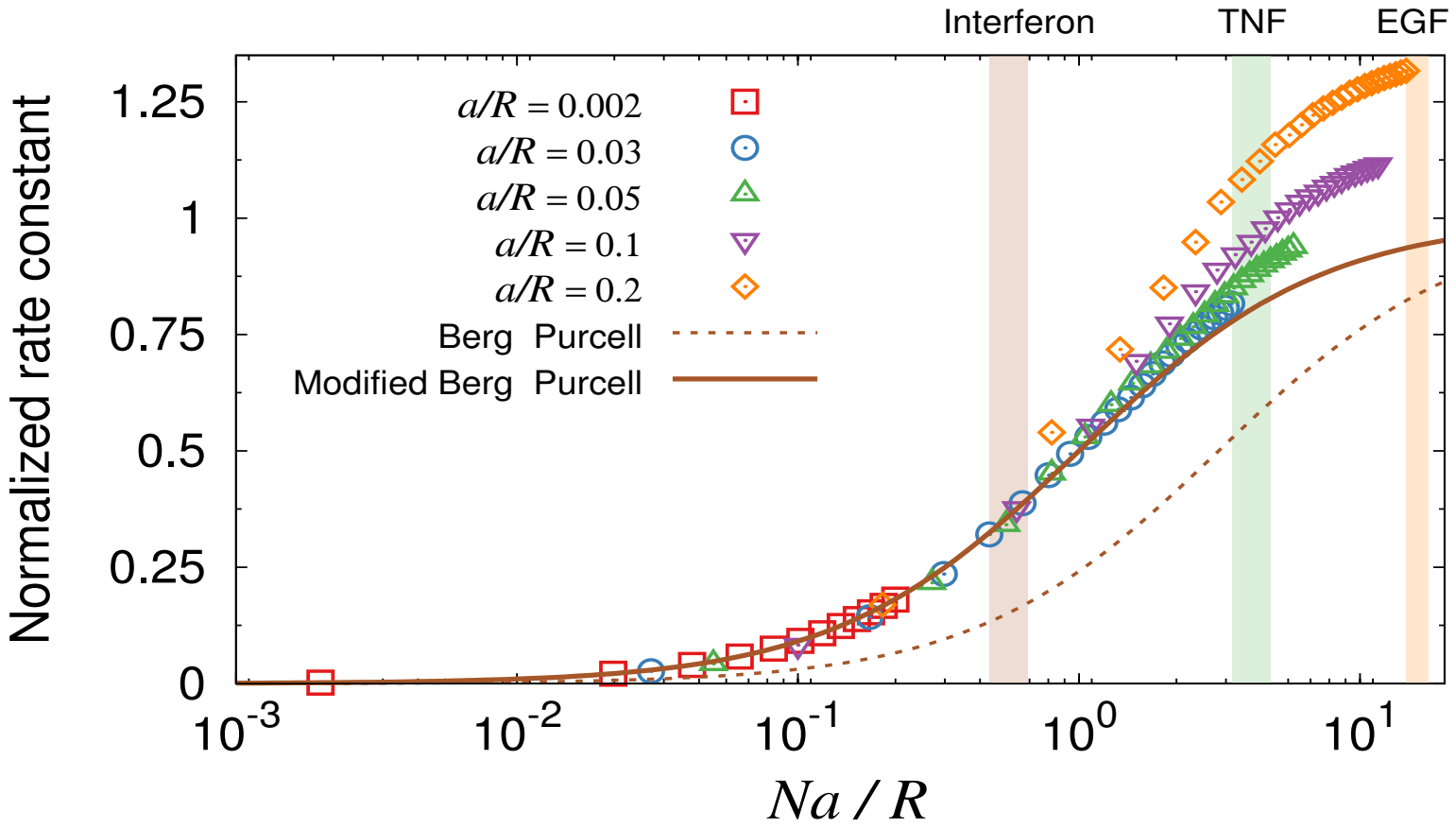


$$\frac{k}{k_S} = \frac{Na}{R + Na}$$

Modified BP

$$a \longrightarrow \pi a$$

Receptor	Ligand	Cell type	N	a [nm]	R [μm]
Interferon	Human interferon- α_2	A549	900	4	5.5 – 7.5
Tumor necrosis factor (TNF)	TNF	A549	6600	4	5.5 – 7.5
Epidermal growth factor (EGF)	EGF	Fetal rat lung	25000	4	5 – 6



Since

$$\frac{a}{R} \simeq 10^{-3}$$

the modified BP formula is a good approximation for a wide range of receptor numbers

Doing better by neglecting more: the monopole approximation (MOA)

The simplest closed-form solution of the many-body problem, which neglects:

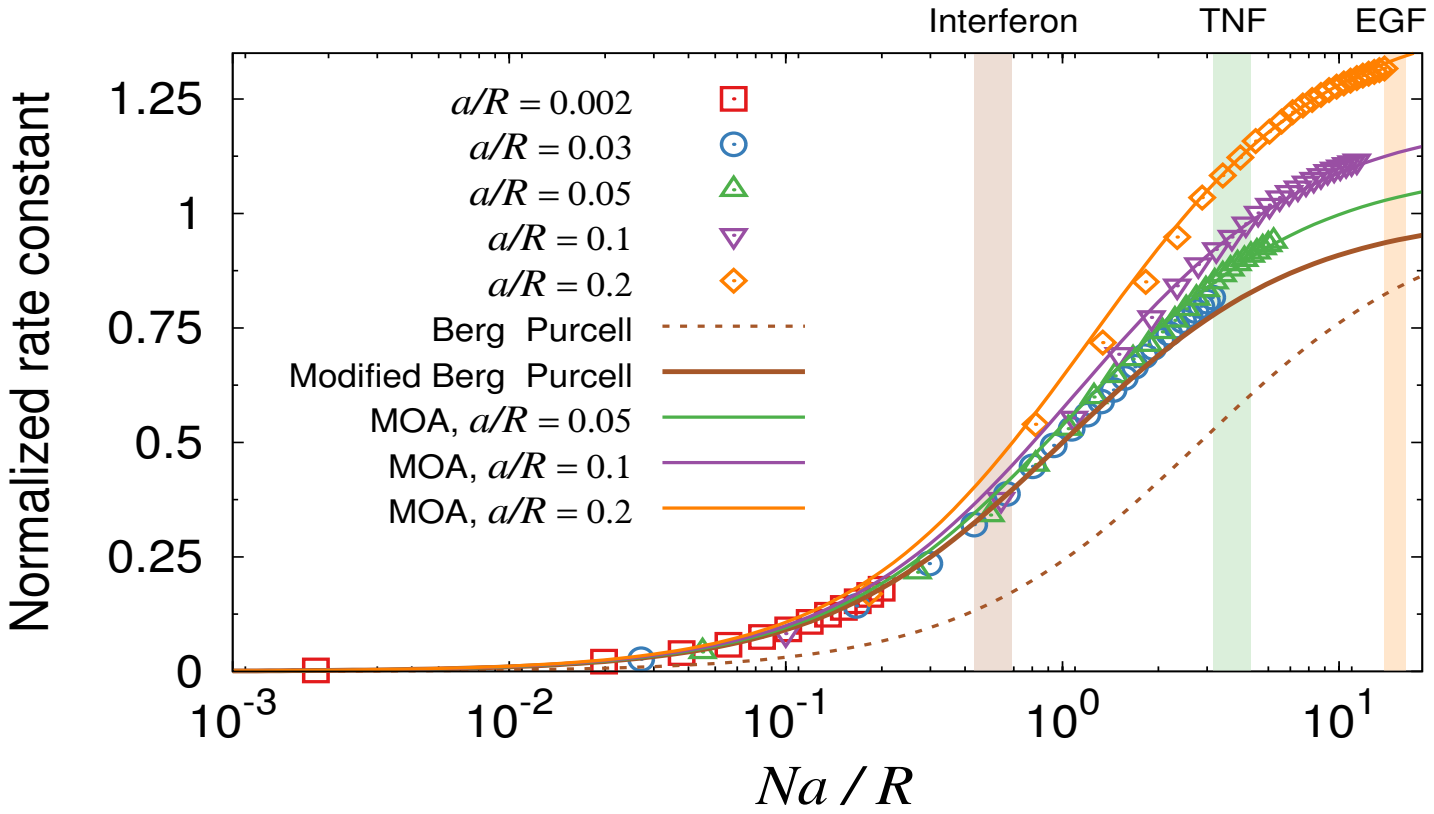
1. The presence of the reflecting sphere (cell surface)
2. The diffusive interaction among receptors (mutual screening of ligand flux)

$$\frac{k}{k_S} = \frac{N\lambda(1+\lambda)^2}{(1+\lambda)^2 - \lambda + N\lambda}$$

with

$$k_S = 4\pi D R \rho_B$$

$$\lambda = a/R$$



The MOA should be used for values of a/R greater than about 0.01

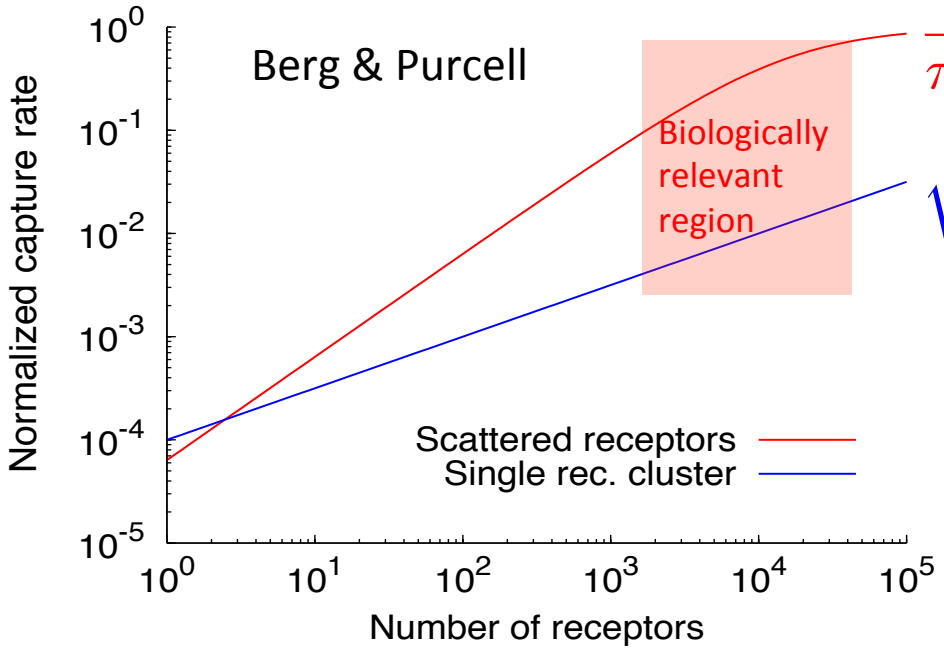
So much for intake/capture rates averaged over many configurations of the receptors …

To what extent does a given configuration of the receptors impact on the overall rate of capture?

Berg & Purcell (1977)

"[…] It is important that the receptor patches be well dispersed. If they were combined into a single absorbent patch of the same total area, the current would be severely reduced […]."

"[…] A numerical calculation comparing uniformly distributed with randomly distributed receptors showed that the difference in current, for the same number of receptors *N*, does not exceed a few percent if *N* is larger than 50. […]."



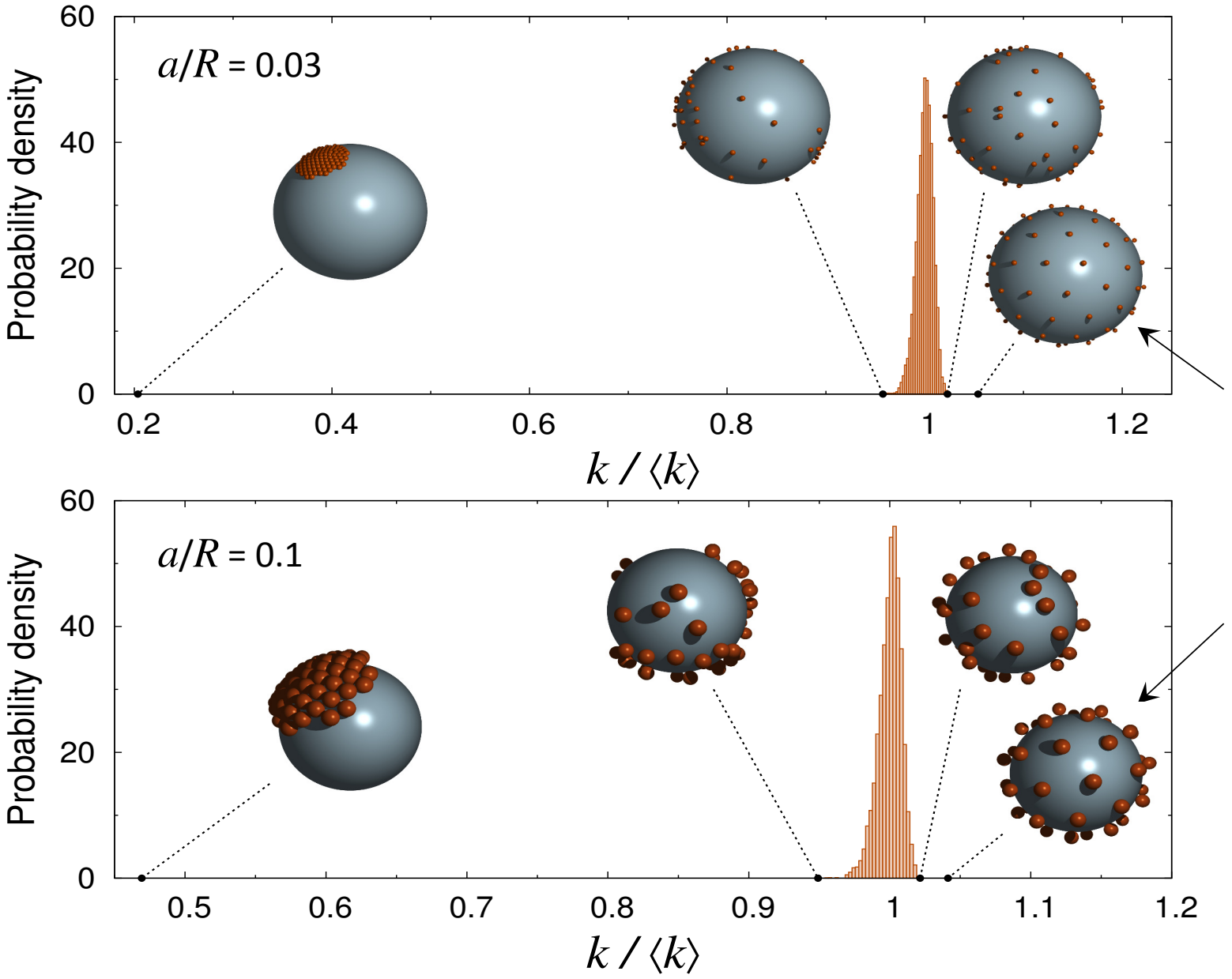
$$\frac{Na}{\pi R + Na}$$

$$\sqrt{\frac{\Delta S}{S}} = \frac{a}{2R}\sqrt{N}$$

$$a = 1.5 \text{ nm}$$
$$R = 10\ \mu\text{m}$$

Berg & Purcell
Receptors uniformly scattered are a better target for diffusing ligand by a factor up to 100-fold.

The advantage offered by uniformly distributed receptors over randomly distributed receptors is more prominent the smaller their size



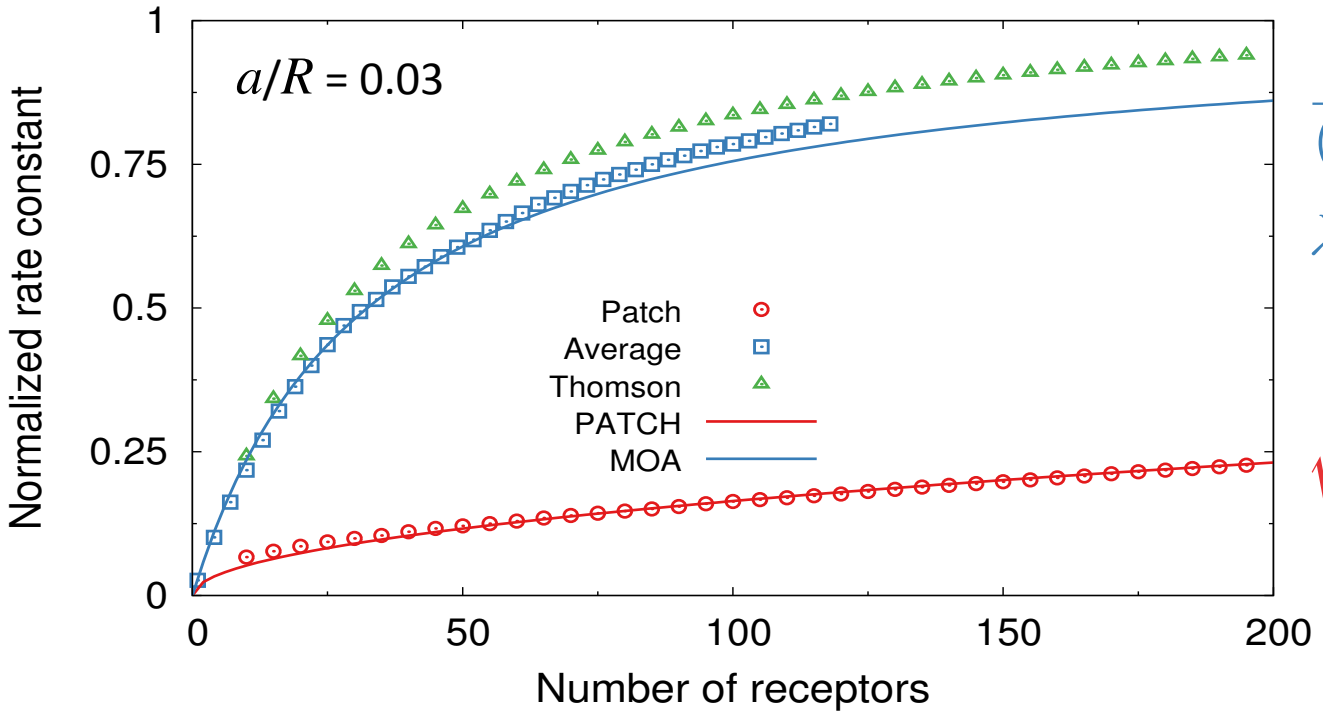
The configurations that maximize the intake rate are the so-called **Thomson configurations**, that equally minimize the electrostatic energy of *N* equal charges on a sphere.

Recall: diffusive interactions are long-range …

The effect of the specific configuration

Patch versus average versus Thomson configurations of receptors

In agreement with Berg & Purcell's intuition, **random** and **optimally dispersed** configurations differ by a few percent at most



$$\frac{N\lambda(1+\lambda)^2}{(1+\lambda)^2-\lambda+N\lambda}$$

$$\lambda = a/R$$

$$\sqrt{\frac{1-\cos(\gamma a\sqrt{N}/R)}{2}}$$

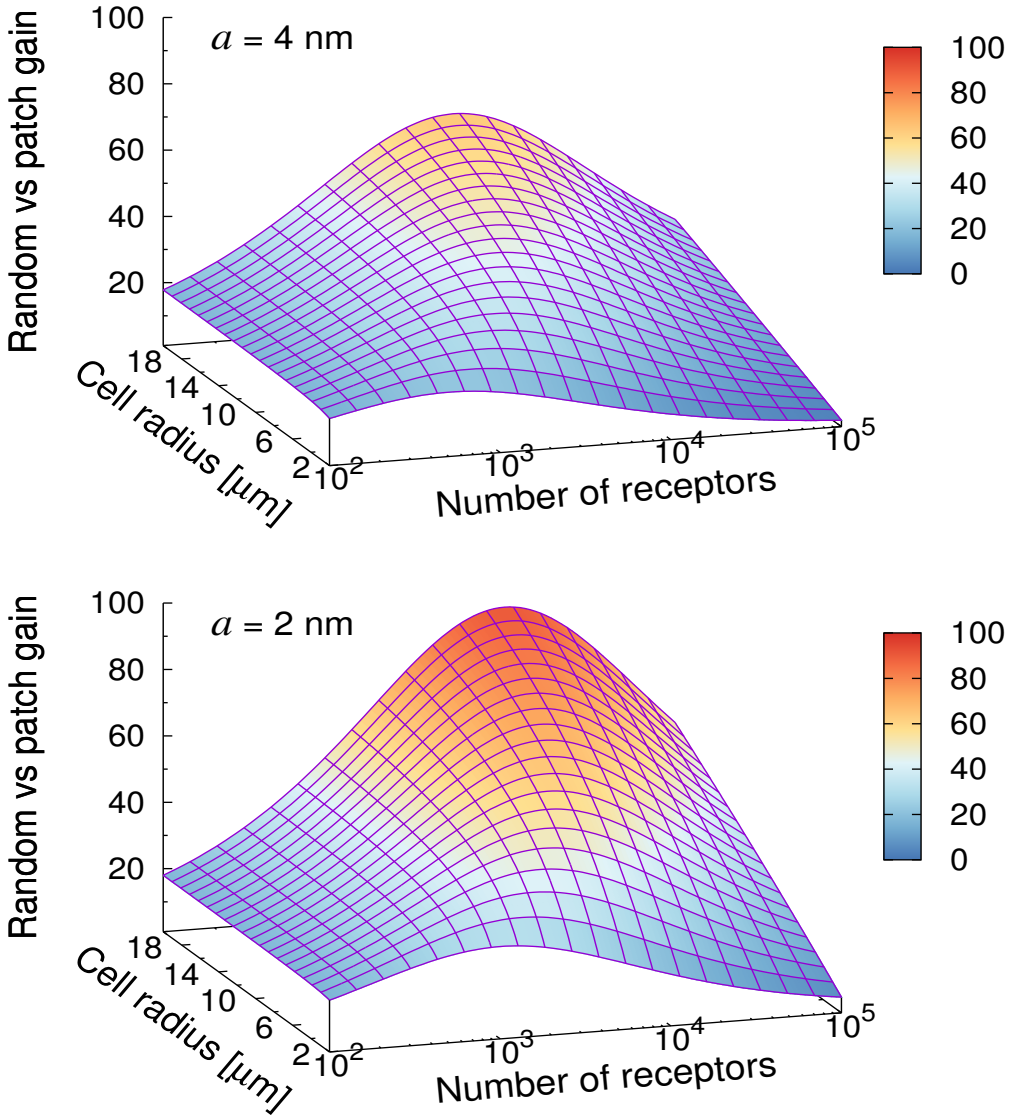
We can compute a working analytic estimate of the advantage of uniform vs concentrated configurations of receptors

$$\text{Gain} = \frac{\text{MOA}}{\text{PATCH}}$$

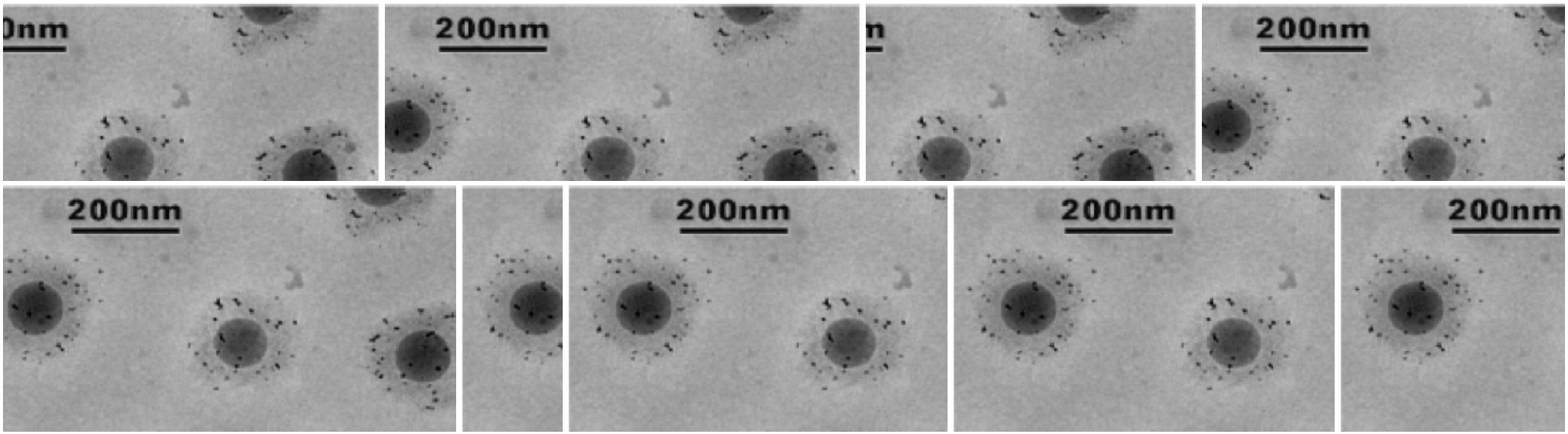
$$= \frac{\dfrac{N\lambda(1+\lambda)^2}{(1+\lambda)^2 - \lambda + N\lambda}}{\sqrt{\dfrac{1-\cos(\gamma a\sqrt{N}/R)}{2}}}$$

$$\lambda = a/R$$

The impact of receptor configurations is huge (higher for small receptors)

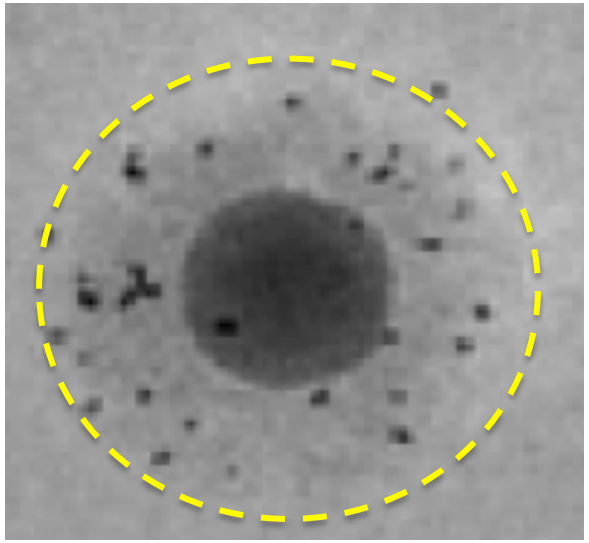


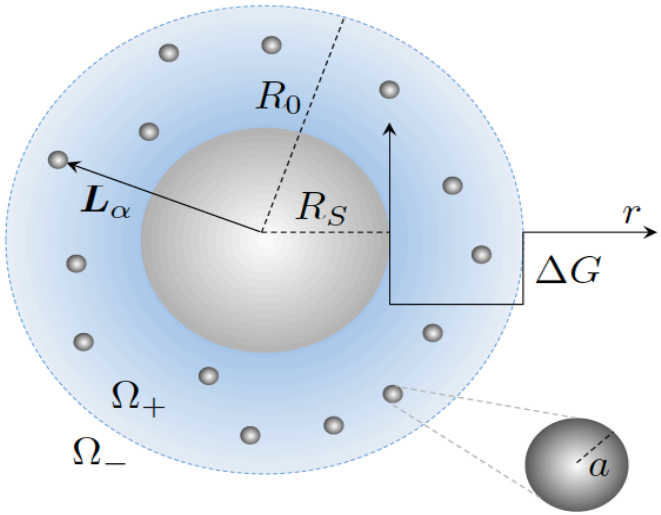
2 Core-shell nanoreactors



$$C + B \underset{k_{-D}}{\overset{k_D}{\rightleftharpoons}} C \cdot B \xrightarrow{k^*} C + P$$

B = substrates
C = nanoreactor
CB = encounter complex
P = product





$$\nabla^2 u^{\pm} = 0 \quad \text{in } \Omega^{\pm}$$

$\left(\frac{\partial u^+}{\partial \xi_\alpha} - h u^+\right)\Big\|_{\partial\Omega_\alpha} = 0 \quad \alpha = 2,3,\ldots,N+1$	Radiative BCs at the nanocatalysts' surface
$\lim_{\xi_0 \to \infty} u^-(\xi_0) = 1$	Constant bulk concentration of substrate
$\left.\frac{\partial u^+}{\partial \xi_1}\right\|_{\xi_1=1} = 0$	Inert (reflecting) PS core
$(u^+ - \lambda u^-)\big\|_{\partial\Omega_0} = 0$	Solvation free-energy jump
$\left(\zeta \frac{\partial u^+}{\partial \xi_0} - \frac{\partial u^-}{\partial \xi_0}\right)\Big\|_{\partial\Omega_0} = 0$	Continuity of substrate current at the bulk-shell interface

$$h = \frac{k^*}{4\pi D_i a}$$

$$\lambda = \exp(-\beta \Delta G)$$

$$\zeta = D_{\text{in}} / D_{\text{out}}$$

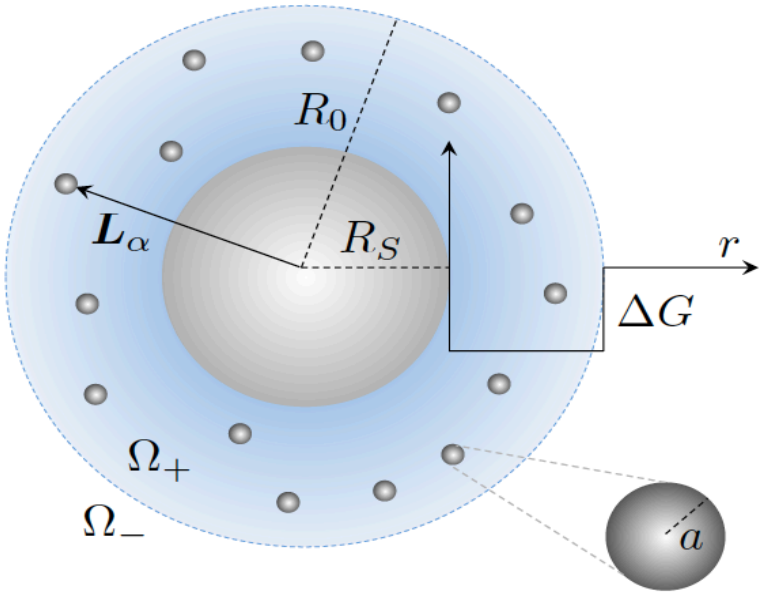
Exact solution versus monopole approximation

In the monopole approximation simple analytical expressions can be derived

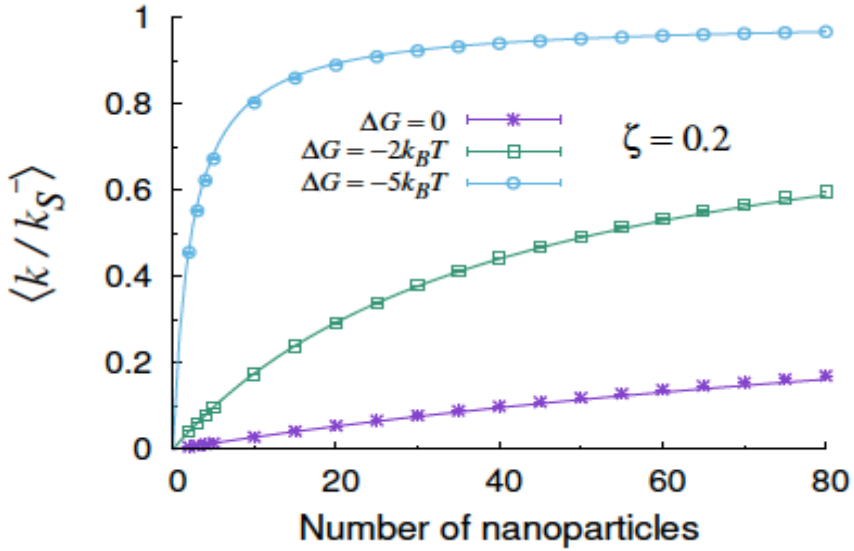
$$\frac{k}{k_S^-} = \frac{N\varepsilon\zeta e^{-\beta\Delta G}}{1 + N\varepsilon\zeta e^{-\beta\Delta G}}$$

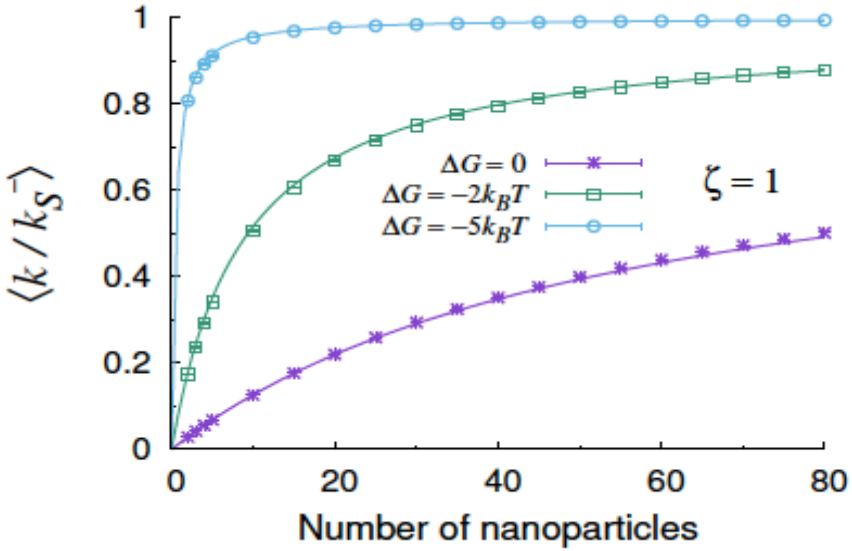
$$\varepsilon = a/R_0$$

$$\zeta = D_{\text{in}}/D_{\text{out}}$$



Symbols are the exact results, solid lines are MOA





The diffusion-limited regime: optimizing the performance of a core-shell nanoreactor

It is instructive to define an **efficiency factor *f* between 0 and 1**, that quantifies the efficiency of the nanoreactor (NR). Unit efficiency is when the NR behaves as a uniformly absorbing sphere of radius equal to the overall N radius.

This allows one to compute the **optimal numbers of nanocatalysts** per nanoreactor as a function of the relevant physico-chemical parameters

$$N_f = \left(\frac{e^{\beta \Delta G}}{\varepsilon \zeta} \right) \frac{f}{1-f}$$

$$\varepsilon = a/R_0$$
$$\zeta = D_{\rm in}/D_{\rm out}$$

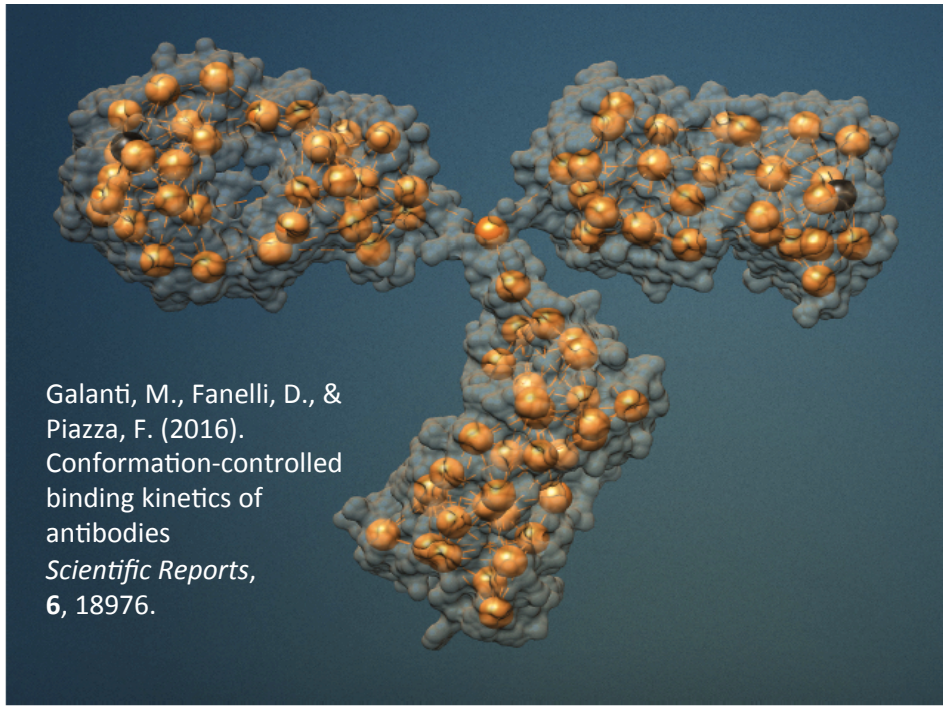
For example, $\zeta = 0.2,\ \varepsilon = 0.01,\ \text{and}\ \beta\Delta G = -1 \Longrightarrow N_f = 184$ to achieve $f = 50\%$

If $\beta\Delta G = -2$ the number N_f would drop by a factor of 1/e

Take-home message:

Build your own confining & reactive landscape

We have developed a comprehensive theory that allows one to describe diffusion-influenced reactions in the presence of an **arbitrary number of spherical reactive boundaries** of given size and reactivity arranged at will in 3D



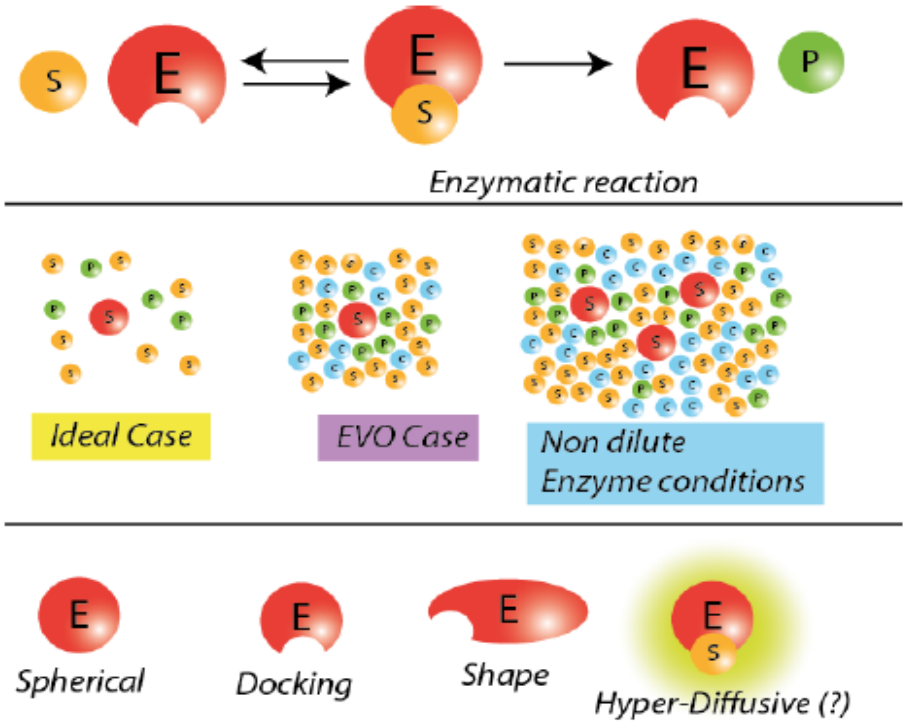
Another example: the binding rate of a small antigen to an antibody composed of refecting spheres (the body) and two absorbing spheres (the active sites)

The theory can accommodate for:

1. Reactions occurring in unbounded and bounded domains
2. **Free-energy jumps** at interfaces between different media
3. Differences in **diffusion coefficients** in different media
4. Arbitrary **confining landscapes** (built trough collections of reflecting spheres).

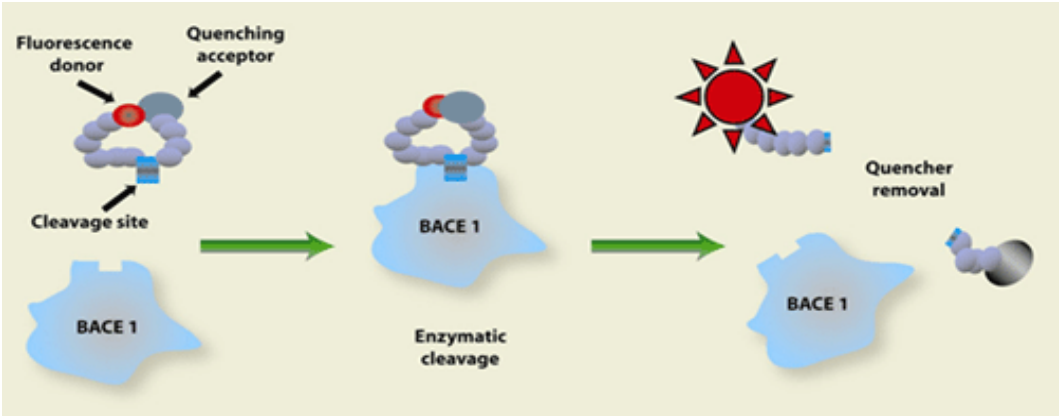
Study of enzyme kinetics in realistic conditions

1. Effect of macromolecular crowding, excluded-volume (EVO)
2. In cells enzyme catalysis takes place in small compartments, low copy numbers!
   Fluctuations are important: fluctuating hydrodynamics approach



Brownian Dynamics simulation scheme of a Michaelis-Menten kinetics in the presence of crowding agents

Experiments with beta-secretase activity in the presence of artificial crowding agents, Ficoll 70 and 400
(in collaboration with the group of J. Hamacek, also at CBM)



Behind all that:

Sergey Traytak, Semenov Institute (RAS) , Moscow

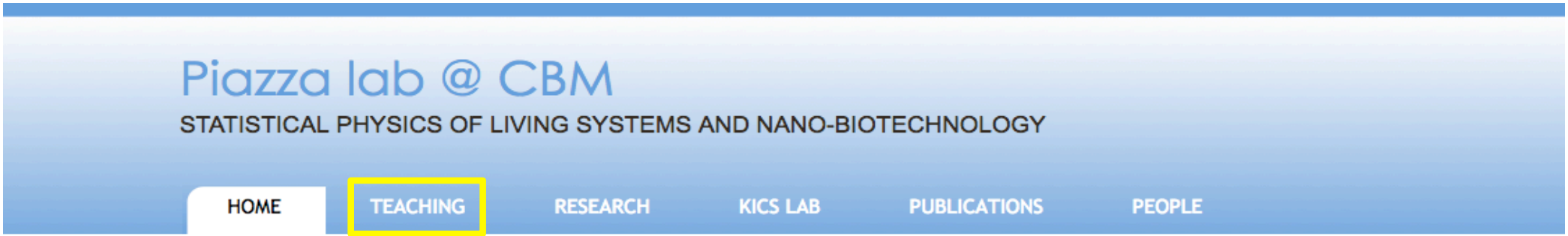
Marta Galanti * CBM, Orléans and Univ. of Florence
Duccio Fanelli, Univ. of Florence

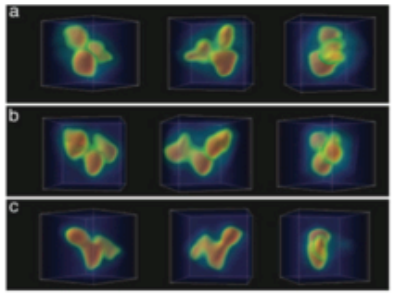
Funding from :

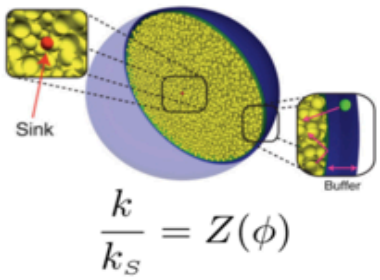
PICS scheme

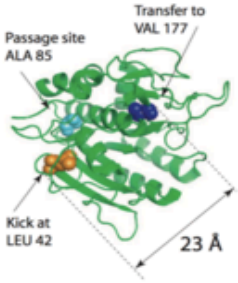
(*) Just finished her Ph.D. … looking for a post-doc

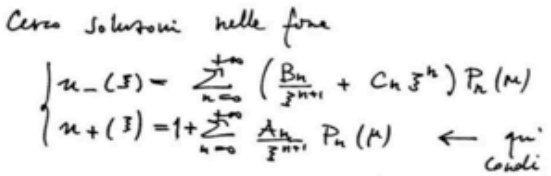
All this material is available on my group's webpage: http://dirac.cnrs-orleans.fr/~piazza/PB/











Candidates interested in doing a Ph.D. or a postdoc in my group, please contact me to discuss possible subjects.

I have the possibility to post projects on the CampusFrance/CONACYT web site and you can postulate for a scholarship associated with these projects