DIFFUSION AND THE PHYSICS
OF CHEMORECEPTION

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Abstract:

This review provides a manual which enables the reader to perform calculations on the rate with which a biological cell can capture certain chemical compounds (ligands) which are essential to its survival and which diffuse in its environment. After a discussion of spatial diffusion and the capture of ligands by a single receptor in the cell membrane, the theory of one-stage chemoreception is developed for the general case in which the cell is spherical and arbitrary forces act between the ligand and the cell. Our method can also be applied to cells with other shapes. Next we discuss membrane diffusion and develop a theory of two-stage chemoreception. Some hydrodynamic effects are also discussed.

*Dedicated to the memory of Dr. H.J. van Ouwerkerk.
1. Introduction

1.1. General considerations

The staggering complexity of the human body can be demonstrated to the physicist by some simple numbers. For example, the number of cells in an organism is of the order of $10^{12}$, which is comparable to the number of stars in a large galaxy. In contrast with the stars in a galaxy, the cells of a given organism are involved in a highly selective way in a process of information exchange which lasts as long as the organism is alive. Actually, most of the events in the life of a cell essentially involve processes by which the cell detects the presence of certain chemical compounds in its environment which are emitted by other cells of the same or another organism. These chemical compounds (usually called ligands) are present in the extracellular medium in small concentrations, and move from cell to cell by means of Brownian motion, electromagnetic fields, hydrodynamic convection and other physico-chemical processes. A cell can detect those ligands which are important to its proper functioning by means of receptor molecules. These are proteins or complexes consisting of proteins and other biopolymers which are specific for these ligands and which are embedded in the outer cell membrane. This means that there are as many receptor systems in the membrane of a cell as there are different types of ligands relevant to the cell’s existence. Each receptor molecule has a binding site which has the property that a ligand which is specific for this receptor is captured and transported through the membrane almost immediately, clearing the site for its next catch (non-specific ligands do not interact with the binding site). This process of a highly selective interaction of the cell with specific ligands is called chemoreception. In this review we discuss the role of diffusion in the physics of chemoreception. The main protagonists in chemoreception, which are schematically indicated in fig. 1, will now be discussed in some detail.

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Fig. 1. Basic steps in chemoreception. Ligands diffuse through the extracellular space till they hit specific receptor molecules (dashed) which are embedded in the lipid bilayer of the cell membrane. After a configurational change of the ligand-receptor complex the ligands are released into the cell’s interior and transported further by the cytoskeleton. In one-stage chemoreception the ligand immediately hits the binding site on the receptor molecule. In two-stage chemoreception the ligand is first adsorbed to the membrane and diffuses laterally in the membrane until it hits the binding site.
(a) The cell. For the purpose of modelling one often assumes that the typical biological cell is a sphere or a cylinder. In reality cells are of the most varied form and structure according to the function which they have to perform [1]. For order of magnitude estimations we shall use a cell radius $R = 5 \times 10^6 \text{Å}$. 

(b) The cell membrane. The basic component of the cell membrane is a lipid bilayer, which is usually in a dense, liquid-crystalline phase. The bilayer consists of two lipid monolayers which are apposed in such a way that the hydrophilic head groups of the lipids are in contact with the intra- and extracellular fluid, and the hydrophobic tails are shielded by the head groups from contact with water. The thickness $h$ of the lipid bilayer is typically of order 50 Å. It is remarkable that the bilayer itself shows phase transitions between several fluid- and solid phases. The extensive literature on phase transitions in lipid membranes has recently been reviewed by Wiegel and Kox [2], Nagle [3] and Wiegel [4]. These phase transitions will have considerable influence on the lateral diffusion of any object in the plane of the membrane, and thus on the efficiency of chemoreception.

(c) Membrane proteins. According to the fluid mosaic model of Singer and Nicolson [5] proteins are embedded in the lipid bilayer. They can cross-link to form complexes and protrude on either or both sides of the membrane (fig. 1). A receptor molecule consists of a complex of such membrane proteins cross-linked with other biopolymers. We shall usually model the receptor molecule as a cylindrical disk with a height equal to the thickness of the lipid bilayer and a radius of about 100 Å. The binding site of the receptor molecule is somewhat smaller than the molecule and might be represented by a circular region of radius $s \approx 50 \text{Å}$. Upon binding of a ligand to the binding site of a specific receptor molecule the whole ligand-receptor complex goes through a configurational change as a result of which the signal is transported through the membrane and released into the interior of the cell. The precise nature of this change is still unknown and the subject of vigorous biomedical research because of its enormous clinical significance. It seems likely that some of these configurational changes are accompanied by conformational phase transitions akin to those studied by statistical physicists during the past twenty years [4, 6].

(d) The cytoskeleton. Once the signal reaches the interior of the cell it will interact with the network of microtubules and other filaments which form the cytoskeleton. As a result of these interactions it will stimulate or inhibit the cell’s metabolism in a specific way, which was the goal of chemoreception to begin with.

1.2. Examples of chemoreception

The first theoretical description of ligand diffusion close to a cell membrane is due to Adam and Delbrück [7]. These authors were especially interested in the case in which the ligand is the sex attractant bombykol, exuded in the air by the female silkworm moth Bombyx mori. The cell is a sensory nerve cell in the antennae system of the male of this species. Because of the cylindrical shape of the nerve cell the work of Adam and Delbrück – and later work by Murray [8] – uses a cylindrical geometry rather than the spherical geometry which is relevant to chemoreception by many other cells. The case studied by Adam and Delbrück is typical for the chemoreception of a variety of pheromones. Pheromones are substances secreted to the environment by an organism and perceived by a second organism of the same species, thereby producing a change in its behavior.

Another important example is the phenomenon of chemotaxis in which a unicellular micro-organism is attracted to – or repelled by – certain chemicals. In order to accomplish this the cell has to monitor continually the concentration of these chemicals in the surrounding medium. Chemotaxis has been studied in detail for the bacteria Escherichia coli and Salmonella typhimurium [9–14]. These cells execute a three-dimensional random walk: they swim steadily along a smooth trajectory (run), move
briefly in a highly erratic manner, then run in a new direction [15]. They sense the concentration of
attractants or repellents as a function of time and bias their random walk by extending the duration of
runs which carry the bacterium to higher concentrations of attractants or to lower concentrations of
repellents. For the spherical geometry which approximately describes these bacteria Berg and Purcell
[16] developed a theory of the rate constant for ligands impinging upon a large number of receptors
which are distributed uniformly over the cell membrane.

A third example of chemoreception, and probably the most important one, is the binding of antigens
by the cells of the immune system. In this case the ligands are antigens, i.e. any micro-organism, protein,
cell or tissue which is foreign to the organism and which can induce a state of sensitivity of its immune
system. The receptors are antibody molecules (immunoglobulins) embedded in the outer membrane of
certain cells of the immune system. The theory of chemoreception by the immune system has been
developed in much detail, especially by groups at the Los Alamos National Laboratory and the National
Institutes of Health. The interested reader is referred to monographs by Bell, Perelson and Pimbley
[17], DeLisi [18] and Perelson, DeLisi and Wiegel [19] for reviews of part of this work.

A final example of chemoreception is the intermediate step in synaptic transmission of a signal
between two nerve cells. In this case the ligand is a transmitter substance excreted by the presynaptic
membrane, which diffuses across the narrow synaptic cleft and is absorbed by specific receptors on the
postsynaptic membrane (cf. Eccles [25]). There exist various transmitter substances, like acetylcholine,
glutamic acid, γ-aminobutyric acid and others. The nature of the receptor molecules is less well
understood in this case than in the case of an immune response. This form of chemoreception is
essential for the proper functioning of our nervous system, and while reading this text billions of such
events occur every second in your brain. We should also like to mention olfaction, the most important sense
for most animals.

1.3. Problems in the theory of chemoreception

This review provides a manual for performing calculations on the diffusion of ligands in the vicinity
of cells and on the rate of capture or emission of ligands by cells. We shall successively discuss the
following problems.

(a) The calculation of the translational diffusion coefficient of a ligand in the intercellular fluid. For a
protein the spatial diffusion coefficient is typically of order $10^{-6}$ cm$^2$ s$^{-1}$ under physiological conditions.
This is the subject of section 2.

(b) The calculation of the ligand current into a single receptor. In section 3 this problem will be
discussed for several models of the binding site.

(c) The calculation of the ligand current into a cell of arbitrary shape, which carries a large number
of receptor molecules in its outer membrane. In section 4 the theory will be developed especially for
spherical cells with spherically symmetric forces acting between the ligands and the cell.

(d) Once the absorbing properties of a single cell are known one can address the problem of the
diffusion of ligands through a tissue of absorbing cells. This problem has a quantum mechanical analogy,
which is the subject of section 5, together with some questions related to the mean time till ligand
capture and the probabilities of capture and escape.

(e) The calculation of the lateral diffusion coefficient of a ligand immersed in the cell membrane.
Experimentally this coefficient is typically of order $10^{-8}$ to $10^{-11}$ cm$^2$ s$^{-1}$. Various theoretical develop-
ments pertaining to this problem are reviewed in section 6.

(f) The calculation of the ligand current into a cell in the case in which both one-stage and two-stage
processes occur. In one-stage chemoreception the ligand can only be absorbed if it hits the binding site on the receptor molecule immediately. In two-stage chemoreception the ligand is first incorporated in the cell membrane, and diffuses laterally in the plane of the membrane till it hits the binding site. This is the subject of section 7.

(g) The effect of convection on the rate of ligand capture by a swimming cell is estimated in section 8.

2. Spatial diffusion

The calculation of the translational diffusion coefficient $D_T$ of proteins and other ligands in the intercellular fluid forms the subject of a vast literature; some of the classical papers are those by Chandrasekhar [20] and Einstein [21]. This transport coefficient is defined by the relation

$$j = -D_T \nabla c,$$

where $c(r, t)$ denotes the number density of ligands and $j(r, t)$ their current density. In the papers just quoted it is shown from the general principles of statistical physics that the diffusion coefficient is related to the translational friction coefficient $f_T$ by the Einstein relation

$$f_T D_T = k_B T,$$

where $k_B$ denotes Boltzmann's constant and $T$ the absolute temperature. This enables one to determine $D_T$ from a calculation of $f_T$, which is defined as the hydrodynamic drag force on the ligand per unit relative velocity.

For many models of the ligand the friction coefficient can be calculated a priori. Consider, for example the case in which the ligand is represented by a small hard sphere of radius $a$ and the extracellular fluid by a Newtonian fluid of viscosity $\eta$ and mass density $\rho_0$. Let the sphere be fixed at the origin of a Cartesian set of coordinates and let the asymptotic fluid velocity be directed along the negative $z$-axis with velocity $v_0$. One has to solve the pressure $P(r, t)$ and velocity $v(r, t)$ from the Navier–Stokes equation and the continuity equation for an incompressible fluid

$$\rho_0 \left( \frac{\partial}{\partial t} + v \cdot \nabla \right) v = -\nabla P + \eta \Delta v,$$

$$\text{div } v = 0,$$

subject to the boundary conditions that $v \to (0, 0, -v_0)$ at large distances from the sphere, and that $v = 0$ at the surface of the sphere. The latter "stick" boundary condition is sometimes replaced by the "slip" boundary condition that $v$ should be parallel to the surface of the sphere. For a time-independent flow problem the term $\partial v / \partial t$ in (2.3) can be omitted.

The ratio of the orders of magnitude of the non-linear term to the term $\eta \Delta v$ is given by the Reynolds number

$$\mathcal{R} = av_0 \rho_0 / \eta.$$
For a ligand with mass $m$ the average kinetic energy is $\frac{1}{2}k_B T$ so

$$v_0 = \left(\frac{k_B T}{m}\right)^{1/2}. \quad (2.5)$$

Hence the Reynolds number is given by

$$\mathcal{R} = \frac{a \rho_0}{\eta} \left(\frac{k_B T}{m}\right)^{1/2}, \quad (2.6)$$

and with the typical values $a \approx 2 \times 10^{-7}$ cm, $\eta \approx 10^{-2}$ g cm$^{-1}$ s$^{-1}$, $\rho_0 = 1$ g cm$^{-3}$, $k_B T \approx 4 \times 10^{-14}$ cm$^2$ g s$^{-2}$ and $m \approx 10^{-19}$ g one finds $\mathcal{R} \approx 10^{-3}$.

This enables one to approximate the Navier–Stokes equation by its linearized form

$$-\nabla P + \eta \Delta v = 0. \quad (2.7)$$

The solution of this equation with stick boundary conditions can be found, for example, in Landau and Lifshitz [22]. In spherical coordinates $(r, \phi, \theta)$ the velocity components in the direction of increasing values of $r$ and $\theta$ are given by

$$v_r = -v_0 \cos \theta \left(1 - \frac{3a}{2r} + \frac{a^3}{2r^3}\right), \quad (2.8)$$

$$v_\theta = +v_0 \sin \theta \left(1 - \frac{3a}{4r} - \frac{a^3}{4r^3}\right). \quad (2.9)$$

This flow field leads to the Stokes formula for the drag force $(F)$ on the sphere

$$F = 6\pi \eta a v_0. \quad (2.10)$$

Hence the friction coefficient is given by

$$f_T = F/v_0 = 6\pi \eta a, \quad (2.11)$$

and the diffusion coefficient by

$$D_T = \frac{k_B T}{6\pi \eta a}. \quad (2.12)$$

Using the orders of magnitude just quoted this gives values for the translational diffusion coefficient, at physiological temperatures, which are of the order $10^{-6}$ cm$^2$ s$^{-1}$, in agreement with the experiments.

Further corrections to the Stokes approximation, due to the non-linear term in the Navier–Stokes equation, have been discussed by several authors [23]. For example, the right-hand side of (2.10) turns out to be the first term of an asymptotic expansion

$$F = 6\pi \eta a v_0\left[1 + \frac{3}{8} \mathcal{R} + \frac{9}{10} \mathcal{R}^2 \ln \mathcal{R} + O(\mathcal{R}^2)\right]. \quad (2.13)$$
Hence for the small Reynolds numbers found in chemoreception the expression (2.12) should be an excellent approximation.

The a priori determination of the translational diffusion coefficient is also possible for other shapes of the ligand and for ligands that are permeable polymer coils or porous complexes of cross-linked macromolecules. These calculations are the subject of a recent monograph [24] to which the reader is referred for further study.

For the sake of completeness we also note the expression for the rotational diffusion coefficient \( D_R \) of a protein immersed in a Newtonian fluid. For the hard sphere model one has

\[
D_R = \frac{k_B T}{8\pi \eta a^2} \tag{2.14}
\]

and for other models expressions can be found in [24]. These rotational diffusion coefficients are less important to chemoreception than the translational ones.

The value \( D_T \approx 10^{-6} \text{ cm}^2 \text{ s}^{-1} \) for the translational diffusion coefficient of a typical ligand sets the scale for several physiological relaxation processes which are dominated by diffusion. For example, the average square of the distance over which a ligand travels in time \( t \) equals

\[
\langle r^2 \rangle = 6D_T t \tag{2.15}
\]

in three dimensions. As the diameter of a cell is typically of order \( 2R \approx 10^{-3} \text{ cm} \) the time which a ligand needs to diffuse over a distance comparable to the cell diameter is of the order 0.15 s. When two cell membranes are apposed their distance is of order \( 10^2 \text{ Å} = 10^{-6} \text{ cm} \). In this case—which applies to the synaptic transmission of a signal between two neurons—the transmitter substance needs as little as \( 1.5 \times 10^{-7} \text{ s} \) to diffuse across the synaptic cleft between the nerve cells.

### 3. Ligand current into a single receptor

If no ligands are created or annihilated in the intercellular medium and if there are no external forces or convective fluid motions, ligand conservation is expressed by the equation

\[
\frac{\partial c}{\partial t} = - \text{div } j. \tag{3.1}
\]

Combination with (2.1) gives the diffusion equation

\[
\frac{\partial c}{\partial t} = D_T \Delta c. \tag{3.2}
\]

In this section we calculate the ligand current into a single receptor, if the ligand concentration equals \( c(\infty) \) far from the receptor. This means that the time-independent equation

\[
\Delta c = 0 \tag{3.3}
\]

has to be solved under the following boundary conditions: (a) At large distances from the receptor \( c \to c(\infty) \). (b) The binding site is a perfect absorber, hence...
at the surface of the binding site. (c) The rest of the cell membrane is a reflector of ligands. As the size $a$ of the binding site is very small as compared to the size $R$ of the cell the shape of the cell surface in the vicinity of the binding site is often assumed to be flat. In a Cartesian set of coordinates with the $x, y$ plane coinciding with the surface of the cell membrane this implies

$$\frac{\partial c}{\partial z} = 0, \quad (z = 0),$$

outside of all binding sites.

Once this problem is solved the total ligand current into the receptor site is given by the surface integral

$$J = -\oint j \cdot d^2 S$$

where $d^2 S$ is directed into the extracellular medium. From (2.1) and boundary condition (a) it is clear that the ligand current density has the form $j = D_T c(\infty) j'$, where $j'$ depends on the binding site, but not on $D_T$ or $c(\infty)$. This implies that the ligand current has the form $J = D_T c(\infty) J'$, where $J'$ does not depend on $D_T$ or $c(\infty)$. Comparing dimensions on both sides shows that the dimension of $J'$ equals $[J'] = [\text{length}]$. Hence, if the linear dimensions of the binding site can be characterized by a single length $s$ the current $J'$ must be proportional to $s$ and

$$J = \alpha D_T c(\infty) s,$$

where the value of the numerical constant $\alpha$ depends on the geometrical shape of the binding site, but not on its size, nor on $D_T$ or $c(\infty)$. As the geometrical shape of the binding sites of most chemoreceptors is unknown we calculate the constant $\alpha$ for various models.

3.1. A hemispherical binding site

Suppose the binding site is a hemisphere of radius $s$ with the equatorial plane coinciding with the surface of the cell membrane. In this case one has to find the spherically symmetric solution of (3.3) which now reads in spherical coordinates $(r, \phi, \theta)$

$$\left( \frac{d^2}{dr^2} + \frac{2}{r} \frac{d}{dr} \right) c(r) = 0.$$

The boundary conditions are

$$c(s) = 0, \quad c \rightarrow c(\infty) \text{ for } r \rightarrow \infty.$$

The reflecting wall boundary condition (3.5) in the equatorial plane outside the site is satisfied automatically because of the spherical symmetry of the solution.
The magnitude of the ligand current density at the surface of the binding site is

\[ j = D_T (dc/dr)_{r=s} = D_T c(\infty)/s. \]  

(3.11)

As the area of the binding site is \( 2\pi s^2 \) the ligand current is

\[ J = 2\pi D_T c(\infty) s, \]  

(3.12)

which corresponds to (3.7) with \( \alpha = 2\pi \). Note that the perturbation of the concentration extends over a distance of order of magnitude \( s \).

### 3.2. A plane circular binding site

Another possible geometry of the binding site is a circular region of radius \( s \) in the plane of the membrane. In this case it seems natural to transform (3.3) to cylindrical coordinates \((r, \phi, z)\) where \( z = 0 \) corresponds to the cell membrane. As the stationary state can be expected to have cylindrical symmetry one finds

\[ \left( \frac{\partial^2}{\partial r^2} + \frac{1}{r} \frac{\partial}{\partial r} + \frac{\partial^2}{\partial z^2} \right) c(r, z) = 0 \quad (z \geq 0), \]  

(3.13)

with the boundary conditions

\begin{align*}
   c \to c(\infty) & \quad \text{for} \quad z \to \infty \quad \text{or} \quad r \to \infty, \quad (3.14a) \\
   c = 0 & \quad \text{for} \quad z = 0 \quad \text{and} \quad 0 < r < s, \quad (3.14b) \\
   \partial c/\partial z = 0 & \quad \text{for} \quad z = 0 \quad \text{and} \quad s < r < \infty. \quad (3.14c)
\end{align*}

The solution which obeys the first boundary condition is

\[ c(r, z) = c(\infty) + \int_0^\infty A(\lambda) J_0(\lambda r) \exp(-\lambda z) \, d\lambda, \]  

(3.15)

where the \( J_0 \) denote the Bessel functions of the first kind [26].

When the hitherto unknown function \( A(\lambda) \) is chosen in such a way that the two other boundary conditions are satisfied one finds the dual integral equations

\begin{align*}
   \int_0^\infty A(\lambda) J_0(\lambda r) \, d\lambda & = -c(\infty), \quad (0 < r < s), \quad (3.16) \\
   \int_0^\infty \lambda A(\lambda) J_0(\lambda r) \, d\lambda & = 0, \quad (s < r < \infty). \quad (3.17)
\end{align*}
This problem has been discussed in different contexts by various authors [27—29]. The solution is

$$A(\lambda) = \frac{2 \sin \lambda s}{m \lambda} c(\infty),$$  \hspace{1cm} (3.18)

which can be verified by substitution into (3.16, 17) and using eqs. 11.4.38 and 11.4.35 of ref. [26] to evaluate the resulting integrals. The ligand current into the binding site is given by the integral

$$J = 2\pi D_T \int_0^s r \left( \frac{\partial c}{\partial z} \right)_{z=0} dr$$

$$= 4D_T c(\infty) \int_0^s dr \int_0^\infty J_0(\lambda r) \sin \lambda s \, d\lambda = 4D_T c(\infty) s,$$  \hspace{1cm} (3.19)

where eq. 11.4.38 of [26] was used again. Hence in this case $\alpha = 4$. Combination of (3.15) and (3.18) shows that—just as in the previous model—the perturbation $c(r, z) - c(\infty)$ of the ligand concentration away from its asymptotic value at infinity is appreciable only in a region with a size of order $s$.

### 3.3. A dumbbell-shaped binding site

In some cases experimental evidence suggests that some receptors are preclustered on the cell surface. This seems to be the case with the receptors for low-density lipoproteins on human fibroblasts. Following recent work of Goldstein [30] we calculate the ligand current into a binding site which consists of two identical, perfectly absorbing half-spheres (radius $s$), the centers of which are in the plane of the membrane and fixed at a distance $d > 2s$.

The ligand concentration has the form

$$c(r) = c(\infty) - \phi(r), \quad \Delta \phi = 0,$$  \hspace{1cm} (3.20)

where $\phi \to 0$ far from the binding site and $\phi = c(\infty)$ at the surface of the half-spheres. Because of the rotational symmetry of the problem around an axis connecting the centers of the two spheres boundary condition (3.5) is satisfied automatically. As was remarked for the first time by Berg and Purcell [16] the function $\phi$ equals the electrostatic potential of a conductor which consists of two spheres at the surface of which the potential is $c(\infty)$; this problem was considered by Smythe [31] and solved by the method of the images. The essential steps are the following:

(a) The solution is written as the sum of two terms $\phi = \phi_1 + \phi_2$, both of which obey (3.20) and vanish at large distances from the binding site. Moreover $\phi_1 = c(\infty)$ on the surface of sphere 1 and $\phi_1 = 0$ on the surface of sphere 2; for $\phi_2$ the roles of the spheres are interchanged.

(b) In order to calculate $\phi_1$ we note that the function $c(\infty) s/r$, where $r$ is the distance to the center of sphere 1, is a solution of Laplace's equation with the proper boundary condition on the surface of sphere 1, but not on the surface of sphere 2. In order to correct the boundary condition on the surface of sphere 2 we add a term which corresponds to a ligand source of the appropriate strength on the line connecting the two centers, at a distance $s^2/d$ from the center of the second sphere. This turns out to
correct the boundary condition on sphere 2 but to spoil the boundary condition on sphere 1. This leads to another ligand sink to be placed on the line connecting the two centers, and so on.

(c) The contributions of the infinite series of alternating ligand sinks and sources of decreasing strengths can be summed and leads to the following expression for the flux into a dumbbell-shaped binding site

\[ J = 4\pi D_T c(\infty) s \sum_{n=1}^{\infty} (-1)^{n+1} \frac{\sinh \beta}{\sinh n\beta}, \]  
\[ \cosh \beta = d/2s. \]

In the limit \( d \to \infty \), in which the two half-spheres become independent, the flux approaches \( 4\pi D_T c(\infty) s \) which is twice the amount (3.12) for a single half-sphere. In the opposite limit, in which the spheres are made to touch, \( d = 2s \) and the flux approaches the value

\[ J = 4\pi D_T c(\infty) s \sum_{n=1}^{\infty} (-1)^{n+1} \frac{1}{n} = 4\pi D_T c(\infty) s \ln 2. \]

Hence in this case \( \alpha \) has the value \( 4\pi \ln 2 \).

As \( J \) is an increasing function of the separation \( d \) of the two half-spheres the calculation in this subsection shows that clustering of the receptors in the cell membrane will decrease their ability to catch ligands.

4. Theory of one-stage chemoreception

Once the ligand current into a single receptor site is known the next task is to develop a general theory for the rate of absorption of ligands by a cell which carries a large number of receptor molecules in its cell membrane. In this section we consider this problem and work out the details of the solution for the case in which the cell is a sphere with spherically symmetric forces acting between the ligand and the center of the cell. We follow the method of DeLisi and Wiegel [32] which can in principle be applied to cells of any shape, with any distribution of receptor molecules on their surface and with an arbitrary form of the ligand-cell interaction potential.

Consider a spherical cell of radius \( R \) immersed in an unbounded medium in which ligands diffuse with translational diffusion coefficient \( D_T \). The ligands are also subject to an external force \( F \) which is directed towards the center of the cell and whose magnitude depends only on the radial distance \( r \). The cell carries \( N \) receptors in its outer membrane, each with a binding site of linear dimension \( s \). Typical values for these parameters are

\[ R \approx 5 \times 10^{-4} \text{ cm} = 50000 \text{ Å}, \quad D_T \approx 10^{-6} \text{ cm}^2 \text{ s}^{-1}, \]
\[ s \approx 5 \times 10^{-7} \text{ cm} = 50 \text{ Å}, \quad N \approx 10^4. \] 

The model calculation of section 3.3 shows that the rate of ligand capture is as large as possible if the receptors are distributed in such a way that the nearest neighbor distances are as large as possible. For
simplicity we study a uniform distribution in which the number of binding sites per unit area on the membrane equals

\[ \nu = \frac{N}{4\pi R^2}. \]  

(4.2)

Another argument which underlines the biological significance of a uniform receptor distribution has been stressed by Purcell [33]: at the scale of a swimming micro-organism the effect of rotational Brownian motion is so large that the cell cannot tell the difference between "up" and "down". In order to further specify the model we assume that the binding sites are perfect absorbers of ligands and that the cell membrane is a perfect reflector. These boundary conditions, which are identical to those used in section 3, define what is called one-stage chemoreception. We calculate the total number \( J_N \) of ligands assimilated by the cell, per unit of time, in a medium in which the ligand concentration approaches a constant value at large distances from the cell.

For this model with external forces the ligand current density \( j \) has a term in addition to the diffusion term (2.1)

\[ j = -D_r \nabla c + \frac{c}{f} F \]  

(4.3)

where \( f \) is the ligand friction coefficient (cf. 2.2). In the stationary state the concentration should be solved from the time-independent Smoluchowski equation

\[ \frac{\partial c}{\partial t} = D_T \Delta c - \frac{1}{f} F \cdot \nabla c - \frac{c}{f} \text{div} F = 0. \]  

(4.4)

Writing the force as minus the gradient of a potential

\[ F = -\nabla V, \]  

(4.5)

where we normalize \( V \) in such a way that \( V(\infty) = 0 \). Using the Einstein relation (2.2), and introducing spherical coordinates the Smoluchowski equation becomes

\[ \frac{d^2 c}{dr^2} + \frac{2}{r} \frac{dc}{dr} + \frac{1}{k_B T} \frac{dV}{dr} \frac{dc}{dr} + \frac{c}{k_B T} \left( \frac{d^2 V}{dr^2} + \frac{2}{r} \frac{dV}{dr} \right) = 0. \]  

(4.6)

This equation can be generally solved [cf. 32] by writing it in the form

\[ \frac{1}{r^2} \frac{d}{dr} \left( r^2 \frac{dc}{dr} + \frac{r^2 c}{k_B T} \frac{dV}{dr} \right) = 0. \]  

(4.7)

One integration gives

\[ \frac{dc}{dr} + \frac{c}{k_B T} \frac{dV}{dr} = \frac{A}{r^2} \]  

(4.8)
where $A$ is a constant. This equation simply expresses the fact that the ligand current should be the same through any spherical surface around the cell. The general solution is found to have the form

$$c(r) = c(\infty) \lambda(r) - A \lambda(r) \int_{r}^{\infty} \rho^{-2} \lambda^{-1}(\rho) \, d\rho,$$

(4.9)

$$\lambda(r) = \exp(-V/k_B T).$$

(4.10)

In order to determine the value of $A$ one notes that the flux $J_1$ into a single receptor will be given by the expression (3.7)

$$J_1 = \alpha D_T s c(R),$$

(4.11)

where $c(R)$ denotes the concentration just outside the cell membrane and where $\alpha$ is a numerical constant of order unity. In using this formula we rely on two approximations: (a) The distance over which the concentration profile (4.9) changes appreciably—which is comparable to the cell’s radius $R$—is very large as compared to the size of the binding site: this leads to the requirement

$$s \ll R.$$

(4.12)

(b) The flux $J_1$ into a single receptor can be calculated neglecting the external force. As the diffusion term in the ligand current density (4.3) is of order $D_T c(R)/s$ and the drift term of order $F(R) c(R)/f$ this will be true provided

$$F(R) s \ll fD_T = k_BT.$$  

(4.13)

This means that the work performed by the external force in moving a ligand over a distance equal to the radius of a binding site should be small as compared to the thermal energy.

The ligand current density into the cell membrane can now be written either as $j_N = \alpha v D_T s c(R)$, where $v$ is the density of binding sites (4.2), or as $j_N = D_T (dc/dr)_{r=R} - (1/f) F(R) c(R)$. Hence the constant $A$ can be determined from the boundary condition

$$\frac{dc}{dr} + \frac{1}{k_B T} \frac{dV}{dr} c = \alpha v sc, \quad (r = R),$$

(4.14)

which is similar to the condition for matching two asymptotic expansions in hydrodynamics [cf. 23]. Substitution of (4.8, 9) into the last equation gives the value

$$A = c(\infty) R^2 \alpha v s \lambda(R) \left\{1 + \alpha v s \lambda(R) \int_{R}^{\infty} \rho^{-2} \lambda^{-1}(\rho) \, d\rho\right\}^{-1},$$

(4.15)

which implies a general expression for the total ligand current into the cell.
\[ J_N = \alpha N D_T s c(R) \]
\[ = \alpha N D_T s c(\infty) \lambda(R) \left\{ 1 + \alpha \nu \lambda(R) R^2 \int_{\rho}^{\infty} \rho^{-2} \lambda^{-1}(\rho) \, d\rho \right\}^{-1}. \]  
(4.16)

This solves the problem set out at the beginning of this section. The method followed here can be generalized to cells of arbitrary shape and with non-uniform receptor distributions. In the remaining part of this section we consider special cases of (4.16) and some of their biophysical implications.

### 4.1. Free diffusion

For the case originally considered by Berg and Purcell [16] the receptors have plane circular binding sites and no external forces act on the ligands. Substituting \( V = 0 \), \( \alpha = 4 \) into the last equation the ligand current is found to equal

\[ J_N = 4 \pi R D_T c(\infty) \frac{sN}{\pi R + sN}. \]  
(4.17)

The first factor \( 4 \pi R D_T c(\infty) \) is the ligand current into a perfectly absorbing sphere, considered in subsection 3.1. It is striking how fast this saturation value is reached when \( N \) increases. For example, \( J_N \) will equal 50% of the maximum current if \( N = \pi R/s \approx 3100 \) using the estimates (4.1). For this value of \( N \) only a fraction \( 0.8 \times 10^{-3} \) of the area of the cell is occupied by receptor binding sites. This implies that the cell can house receptor systems for up to a hundred different types of ligands in less than 10% of its surface, each receptor system catching ligands at 50% of the largest possible rate.

This remarkable efficiency of chemoreception is due to the erratic shape of the trajectories of a Brownian particle: when a ligand hits the cell outside a binding site it will bounce back, but because of the extremely erratic shape of its path it is likely to hit the membrane many times before it can escape from the vicinity of the membrane, and one of those hits might hit a binding site. This is nowadays often called the fractal nature of the Brownian paths [34].

### 4.2. Electrostatic attraction

In the case of electrostatic attraction, first considered by DeLisi and Wiegel [32, 35], the cell has charge \( Q \), the ligand has a charge \( q \) of the opposite sign and

\[ V(r) = qQ/\varepsilon_0 r, \]  
(4.18)

where \( \varepsilon_0 \) is the dielectric constant of the extracellular medium. For plane circular binding sites (4.16) gives a rate of ligand capture

\[ J_N = 4 \pi D_T c(\infty) \frac{sN\delta \exp(\delta/R)}{\pi \delta + sN(\exp(\delta/R) - 1)}. \]  
(4.19)

\[ \delta = -qQ/k_B T \varepsilon_0 > 0. \]  
(4.20)
The dimensionless ratio $\delta/R$ is of the order of magnitude of the ratio of the potential energy of a ligand at the cell surface to the thermal energy. For $\delta/R \ll 1$ the ligand current approaches the free diffusion value (4.17). If, in the case $N_s = \pi R$ considered in subsection 4.1, the cell picks up a small amount of charge $\delta/R = 1$, the ligand current doubles from the value $2\pi R D_T c(\infty)$ to $4\pi R D_T c(\infty)$. Of course, this new value is smaller than the saturation value of the current in the presence of electrostatic attraction, which is

$$
\lim_{N \to \infty} J_N = 4\pi D_T c(\infty) R \left( \frac{\delta/R \exp(\delta/R)}{\exp(\delta/R)} \right)
$$

and hence in this case still larger by a factor $e/(e - 1) \approx 1.6$.

5. Miscellaneous comments on one-stage chemoreception

5.1. A tissue of absorbing cells

In the tissues of any organism absorbing cells will often not occur in isolation but in great numbers. This leads us to consider chemoreception by identical cells which are distributed in space with some number density $n(r, t)$ which can be a function of space and time. The treatment of this problem is particularly simple if the distance between cells is large as compared to the size of the cells

$$
n R^3 \ll 1.
$$

In this case it is advantageous to define a coarse-grained ligand concentration

$$
C(r, t) = \frac{1}{V} \int_V c(r', t) \, d^3 r'
$$

where the integration extends over a volume $V$ which includes the point $r$, is large enough to contain many cells, but small enough that $C(r, t)$ is approximately constant inside $V$. The balance equation for the number of ligands gives

$$
\frac{\partial C}{\partial t} = D_T \Delta C - 4\pi R D_T \beta n C.
$$

The value of the constant $\beta$ depends on the model used: $\beta = 1$ for a perfectly absorbing cell, $\beta = sN(\pi R + sN)^{-1}$ for the model of subsection 4.1, $\beta = sN (\delta/R) \exp(\delta/R) \left[ \pi \delta + sN \{ \exp(\delta/R) - 1 \} \right]^{-1}$ for the case of electrostatic attraction studied in subsection 4.2, and so on. The distribution of ligands throughout the tissue can be calculated by solving (5.3) under the appropriate initial- and boundary conditions.

An important application is the stationary state of the ligand concentration throughout a tissue if ligands are replenished at the interface between the tissue and the rest of the organism. Putting the $x$-axis perpendicular to a plane interface and assuming $n = n_0 = \text{constant}$ throughout the tissue the last equation simplifies to
\[ \frac{d^2 C}{dx^2} = 4\pi R\beta n_0 C. \] (5.4)

The solution

\[ C(x) = C(0) \exp(-x\sqrt{4\pi R\beta n_0}), \] (5.5)

which is independent of the value of the diffusion coefficient, shows that ligands penetrate the tissue over a distance of the order of magnitude

\[ \text{penetration depth} \approx \left( \frac{\text{distance between cells}}{\text{radius of a cell}} \right)^{1/2}. \] (5.6)

5.2. The mean time till ligand capture

Consider an arbitrary cell geometry, with or without attractive forces and a ligand which originally \((t = 0)\) is located at position \(r_0\) in intercellular space. Let \(T(r_0)\) denote the mean time that lapses till this ligand is captured by one of the cells. In this subsection we develop a general formalism to calculate this mean time till ligand capture.

First, one writes (4.4) in the form

\[ \frac{\partial c}{\partial t} = \mathcal{L} c; \quad \mathcal{L} = D_T \Delta - \frac{1}{f} F \cdot \nabla - \frac{1}{f} (\text{div } F). \] (5.7)

The probability density \(P(r, t| r_0)\) to find the ligand near \(r\) at time \(t\) can be expanded in the orthonormalized eigenfunctions of the linear operator \(\mathcal{L}\)

\[ P(r, t| r_0) = \sum_n \phi_n(r) \phi_n^*(r_0) \exp(-\lambda_n t), \] (5.8)

\[ \mathcal{L} \phi_n = -\lambda_n \phi_n. \] (5.9)

The boundary conditions are that \(\phi_n = 0\) on any binding site, and that \(-D_T \nabla \phi_n + (1/f) F \phi_n\) will be parallel to the membranes outside the binding sites.

Second, one notes that the probability \(W(t)\) that the ligand is not yet captured at time \(t\) is given by the integral

\[ W(t) = \int_E P(r, t| r_0) \, d^3 r \] (5.10)

which extends over all extracellular space \(E\). As the probability that the ligand will be captured during the time interval \((t, t + dt)\) is obviously given by \(-\partial W/\partial t\) \(dt\) the mean time till capture equals

\[ T(r_0) = -\int_0^\infty t \frac{\partial W}{\partial t} \, dt = \int_0^\infty W(t) \, dt. \] (5.11)
Substitution of (5.8) and (5.10) gives the eigenfunction expansion

$$ T(r_0) = \int_0^\infty dt \int E d^3r \sum_n \phi_n(r) \phi_n^*(r_0) \exp(-\lambda_n t) $$

$$ = \sum_n \lambda_n^{-1} \phi_n^*(r_0) \int_E \phi_n(r) d^3r. $$

(5.12)

In most cases of practical interest the external force on the ligands can be written as the derivative of a scalar potential

$$ F(r) = -\nabla V(r). $$

(4.5)

It will shortly be shown that in this case all eigenvalues are real. Hence the previous equation gives

$$ \mathcal{L} T(r) = -\int E \sum_n \phi_n^*(r) \phi_n(r') d^3r' = -1. $$

(5.13)

This partial differential equation generalizes a result of ref. [16] to the case of external forces. The boundary conditions for $T$ are the same as those for the eigenfunctions $\phi_n$, as can be seen from (5.12).

As an example of this formalism consider the mean time till capture for a perfectly absorbing cell with freely diffusing ligands. In polar coordinates one should solve

$$ \left( \frac{d}{dr^2} + \frac{2}{r} \frac{d}{dr} \right) T(r) = -\frac{1}{D_T}; $$

(5.14)

under the boundary condition

$$ T(R) = 0. $$

(5.15)

In order to get a finite mean time till absorption one has to impose a reflecting spherical boundary condition at some $R_1 > R$, so

$$ \frac{dT}{dr} = 0, \quad (r = R_1). $$

(5.16)

The solution is

$$ T(r) = \frac{1}{6D_T} \left( R^2 + \frac{2R_1^3}{R} - \frac{2R_1^3}{r} - r^2 \right). $$

(5.17)

We end this subsection by pointing out a quantum mechanical eigenvalue problem which is related to the probability density (5.8). Write
\[ P(r, t|r_0) = Q(r, t|r_0) \exp \left\{ \frac{1}{2D_T f} \int_0^r F \cdot dl \right\}; \quad (5.18) \]

If the external force is conservative the line integral in the exponential will be independent of the choice of contour between \( r_0 \) and \( r \). Substitution into (5.7) shows that \( Q \) is the solution of the equation

\[ \frac{\partial Q}{\partial t} = D_T \Delta Q - WQ, \quad (5.19) \]

\[ W = \frac{F^2}{4Df} + \frac{\text{div} \, F}{2f}. \quad (5.20) \]

Hence the eigenfunction expansion (5.8) can also be written in the form

\[ P(r, t|r_0) = \exp \left[ \sum_n \psi_n(r) \psi_n^*(r_0) \exp(-\lambda_n t) \right], \quad (5.21) \]

\[ -D_T \Delta \psi_n + W\psi_n = \lambda_n \psi_n. \quad (5.22) \]

This shows that all eigenvalues are real and that for large times the probability distribution will decay like

\[ P \approx \exp \left\{ -\frac{V(r)}{2k_B T} \right\} \psi_0(r) \exp(-\lambda_0 t), \quad (5.23) \]

where \( \psi_0 \) is the ground state of the quantum mechanical eigenvalue problem (5.22). It should of course be kept in mind that the boundary conditions on the \( \psi_n \) are not necessarily those pertinent to a quantum mechanical particle. However, for perfectly absorbing cells of arbitrary shape the boundary condition \( \psi_n = 0 \) is the one for a quantum mechanical particle at a hard wall. In any case the last equation shows that the mean time till ligand capture will be of the order of magnitude \( \lambda_0^{-1} \).

5.3. The probabilities of capture and escape

Consider the model of a spherical cell with \( N \) receptors and ligands subject to an external force, as studied in section 4. If a ligand is located at \( t = 0 \) a distance \( r_0 > R \) from the center of the cell one can ask for the probability \( P_c(r_0) \) that this ligand will eventually be captured by the cell, or for the probability \( P_e(r_0) = 1 - P_c(r_0) \) that it will escape capture by the cell forever. The calculation of these probabilities will be demonstrated for the important case \( r_0 = R \).

A fictitious experiment would consist of creating a stationary state in which the ligand concentration at \( r = r_0 \) is kept fixed at the value \( c(r_0) = c_0 \). Solving (4.4) with the additional boundary condition \( c(\infty) = 0 \) gives

\[ c(r) = c_0 \lambda(r) \int_0^r \rho^{-2} \lambda^{-1}(\rho) \, d\rho / \lambda(r_0) \int_0^\infty \rho^{-2} \lambda^{-1}(\rho) \, d\rho. \quad (5.24) \]
The total outward ligand flux is given by (4.3, 8)

\[ J_{\text{out}}(r_0) = 4\pi r^2 \left( -D_T \frac{dc}{dr} - \frac{c dV}{dr} \right) = \frac{4\pi D_T c_0}{\lambda(r_0)} \int_{r_0}^{\infty} \rho^{-2} \lambda^{-1}(\rho) \, d\rho \]  

(5.25)

In the limit \( r_0 \downarrow R \) this becomes

\[ J_{\text{out}}(R) = \frac{4\pi D_T c(R)}{\lambda(R)} \int_{R}^{\infty} \rho^{-2} \lambda^{-1}(\rho) \, d\rho \]  

(5.26)

In this same limit the total inward flux of ligands captured by the receptors on the cell membrane is found with the argument leading to (4.14)

\[ J_{\text{in}}(R) = N\alpha D_T s c(R) \]  

(5.27)

Hence the probabilities of capture and escape are given by

\[ P_c(R) = \frac{J_{\text{in}}}{J_{\text{out}} + J_{\text{in}}} = \frac{N\alpha s \lambda(R) \int_{R}^{\infty} \rho^{-2} \lambda^{-1}(\rho) \, d\rho}{4\pi + N\alpha s \lambda(R) \int_{R}^{\infty} \rho^{-2} \lambda^{-1}(\rho) \, d\rho} \]  

(5.28)

\[ P_e(R) = \frac{J_{\text{out}}}{J_{\text{out}} + J_{\text{in}}} = \frac{4\pi}{4\pi + N\alpha s \lambda(R) \int_{R}^{\infty} \rho^{-2} \lambda^{-1}(\rho) \, d\rho} \]  

(5.29)

These expressions were first derived in [32]. Their relevance to the \textit{a priori} calculation of ligand–receptor rate constants has been discussed by DeLisi [36]. For free ligands they simplify to

\[ P_e(R) = \frac{4\pi R}{4\pi R + N\alpha s} = 1 - P_c(R) \]  

(5.30)

For ligands which diffuse subject to the electrostatic attraction (4.18) they give

\[ P_e(R) = \frac{4\pi R}{4\pi R + N\alpha s (R/\delta) (e^{\delta R} - 1)} = 1 - P_c(R) \]  

(5.31)
Membrane diffusion

In the four preceding sections we developed the theory of one-stage chemoreception, in which a ligand can only be absorbed by a cell by a direct hit of the binding site on the receptor molecule. In the next section the theory will be extended to incorporate two-stage capture processes in which the ligand is first incorporated in the cell membrane, and then diffuses laterally in the plane of the membrane till it hits a binding site. Actually, two-stage chemoreception is only one of a variety of processes which occur at the surface of the living cell and in which the lateral translational- or rotational diffusion of proteins play an essential role. It is for this reason that the experimental determination of the relevant diffusion coefficients has been pursued vigorously during the last decade [37–44]. Experimental values of the lateral translational diffusion coefficient \( D_T \) range from \( 10^{-8} \) to \( 10^{-11} \text{ cm}^2\text{s}^{-1} \). For the rotational diffusion coefficient \( D_R \) of proteins embedded in the cell membrane one measures values in the range from \( 10^5 \) to \( 10^3 \text{ s}^{-1} \). The physiological time scale set by membrane diffusion can be illustrated by the following numerical examples. The square of the circumference of a spherical cell is typically of order \( (2\pi R)^2 \approx 10^{11} \text{ Å}^2 \). Substituting this number into the left hand side of

\[
\langle r^2 \rangle = 4D_T t
\]  

(6.1)

one finds that a protein with a diffusion coefficient \( D_T \approx 10^{-8} \text{ cm}^2\text{s}^{-1} \) will diffuse once around the cell in about four minutes.

In this section the lateral diffusion coefficients \( (D_T, D_R) \) of a ligand immersed in the cell membrane are calculated from “first principles”, which in this case means hydrodynamics. This problem will be studied in the geometry of fig. 2. The protein is represented by a cylindrical disk of thickness \( h \) and radius \( a \) which is constrained to move in the plane of the membrane. The lipid bilayer fraction of the membrane is represented by a layer of continuous fluid of thickness \( h \) and viscosity \( \eta \). The membrane is embedded in a fluid of viscosity \( \eta' \). For a hard disk this problem was studied by Saffman and Delbrück [45, 46]. For permeable polymer coils or porous complexes of cross-linked proteins it was studied in a series of papers by Wiegel and Mijnlieff [24, 35, 47–53]. The asymptotic analysis by Saffman of the translational lateral diffusion coefficient of a hard disk is outlined in the next section. For the record only we note that the rotational lateral diffusion coefficient of a hard disk is much easier to calculate; in the lowest order of approximation one finds

\[
D_R = \frac{k_B T}{4\pi \eta a^2}.
\]  

(6.2)

Fig. 2. Geometry for the calculation of the lateral diffusion coefficients of a protein or a complex of cross-linked proteins.
With the typical values $h \approx 4 \times 10^{-7}$ cm, $a \approx 2 \times 10^{-7}$ cm, $\eta \approx 2$ g cm$^{-1}$ s$^{-1}$, $k_B T \approx 4 \times 10^{-14}$ cm$^2$ g s$^{-2}$ one finds $D_R = 10^5$ s$^{-1}$, in fair agreement with the experiments.

6.1. Asymptotic analysis

As in section 2 one uses Cartesian coordinates $(x, y, z)$ with the $z$-axis along the axis of the cylinder and the $x, y$ plane parallel to the membrane surface. The membrane is located at $-h < z < 0$ and the intra- and extracellular fluid at $z < -h$ and $z > 0$.

First, the pressure $p$ and velocity $v = (v_1, v_2, v_3)$ of the fluid at $z > 0$ and $z < -h$ have to be solved from

$$-\nabla p + \eta' \Delta v = 0,$$  \hspace{1cm} (6.3a)

$$\text{div } v = 0,$$  \hspace{1cm} (6.3b)

under the boundary conditions that at large distances from the $z$-axis $v_1 \to -v_0$, $v_2 \to 0$, $v_3 \to 0$.

Second the pressure $P$ and velocity $V$ of the membrane ($-h < z < 0$) are functions of $x$ and $y$ only, as the membrane flow will be strictly two-dimensional to a very good approximation. They have to be solved from

$$-\nabla P + \eta \Delta V + \frac{2\eta'}{h} \left( \frac{\partial v}{\partial z} \right)_{z=0} = 0,$$  \hspace{1cm} (6.4a)

$$\text{div } V = 0.$$  \hspace{1cm} (6.4b)

The third term represents the force of viscous friction exerted by the intra- and extracellular fluid on the membrane. The boundary conditions are that for large values of $x$ or $y$ the velocity approaches $V_1 = -v_0$, $V_2 = 0$. The continuity of the flow fields inside and outside the membrane are expressed by the condition

$$V(x, y) = v(x, y, 0).$$  \hspace{1cm} (6.5)

For a hard disk one also needs a boundary condition at the surface of the disk, which takes the form

$$V(x, y) = 0 \quad \text{if} \quad x^2 + y^2 = a^2.$$  \hspace{1cm} (6.6)

The asymptotic analysis makes use of a singular perturbation technique [cf. 23] which works only provided the parameter

$$\theta = h\eta/a\eta'$$  \hspace{1cm} (6.7)

is very large as compared to unity. As full details can be found in refs. [46, 52 or 24] we only outline the basic idea. For $r \gg a$ the hard wall boundary condition (6.6) can be replaced by adding a sharply peaked force density $F$ to the left hand side of (6.4a), with the $x$- and $y$-components,
Here $F$ denotes the magnitude of the total force which the protein exerts on the membrane fluid. The resulting set of equations, with the appropriate boundary conditions at infinity, can be solved analytically. The solution is called the outer asymptotic expansion of the flow field.

For $r \ll h\eta/\eta'$ the third term in the left hand side of (6.4a) can be neglected with respect to the second term. The solution of the resulting equations, with the appropriate boundary conditions along the $z$-axis, is called the inner asymptotic expansion.

For $\theta \gg 1$ both asymptotic expansions hold for $a \ll r \ll h\eta/\eta'$. This enabled Saffman to determine the value of the unknown constant $F$. In this way one finds for the translational lateral diffusion coefficient

$$D_\tau \equiv \frac{k_B T}{4\pi \eta h} (-\gamma + \ln \theta), \quad (\theta \gg 1),$$

(6.9)

where $\gamma = 0.5772$ denotes Euler's constant.

Saffman’s work has been generalized by various authors. In a remarkable paper Hughes, Pailthorpe and White [54] calculate further terms in the asymptotic expansion (also cf. Hughes [55] and Hughes, Pailthorpe, Sawyer and White [56]). They find

$$D_\tau = \frac{k_B T}{4\pi \eta h} \left[ -\gamma + \ln \theta + \frac{8}{\pi \theta} - 2 \ln \theta + O(\theta^{-2}) \right].$$

(6.10)

Actually, these authors can in principle calculate the full result through the following steps: (a) The boundary value problem defined by (6.3–6) is reduced to a set of dual integral equations. (b) These are transformed into a single integral equation using Erdélyi–Kober operators (cf. Sneddon [28]). (c) The integral equation is transformed into an equation for an infinite matrix. (d) This matrix equation is solved numerically.

In many cases of biological interest proteins in the cell membrane form aggregates as a result of some cross-linking process. For example, IgG immunoglobulins in the lymphocyte membrane can be cross-linked by multivalent antigens outside the membrane. In this way a patch consisting of hundreds or thousands of IgG molecules can form. Such an aggregate can diffuse laterally as a single entity in the membrane, and one should calculate the appropriate diffusion coefficient.

In order to do so one can describe the aggregate as a cylindrical disk of radius $a$, as in fig. 2. When the disk moves laterally in the membrane the lipids can flow through the space in between the “stems” of the IgG molecules (see fig. 3). Hence one should give the disk a certain constant hydrodynamic

Fig. 3. Four IgG proteins (Y shapes) immersed in the lipid bilayer phase of the cell membrane (dashed) and cross-linked by multivalent antigens outside the membrane.
permeability \( k_0 \). Writing
\[
\sigma = \frac{a}{\sqrt{k_0}}
\] (6.11)

one finds for the lateral diffusion coefficients
\[
D_r = \frac{k_B T}{4\pi \eta h} \left\{ -\gamma + \ln \theta + \frac{2}{\sigma^2} + \frac{I_0(\sigma)}{\sigma I_1(\sigma)} \right\}, \quad (\theta \gg 1),
\] (6.12)

\[
D'_r = \frac{k_B T}{4\pi \eta h \alpha^2} \frac{I_0(\sigma)}{I_2(\sigma)}, \quad (\theta \gg 1),
\] (6.13)

where the \( I_n \) denote the modified Bessel functions, which are tabulated in [26]. The derivations of these asymptotic formulae have been given elsewhere [24, 51, 52].

A problem with all the asymptotic results quoted in this subsection is that it is not clear how fast the asymptotic behavior is reached, i.e. how good are they for the typical values \( \theta = 100, \sigma = 1 \)? In order to answer this question unambiguously Heringa, Wiegel and van Beckum [57] solved the linearized hydrodynamic equations numerically for a wide range of the relevant parameters \( \theta \) and \( \sigma \). For the special case \( \sigma = \infty \), which corresponds to Saffman’s model with an impermeable disk, the numerical results for the dimensionless quantity \( k_B T (2\pi \eta h D'_r)^{-1} \) are listed in table 1. A glance at the table shows that Saffman’s formula is already fairly accurate for \( \theta \) as small as 15. Note that for the special case \( \sigma = \infty \) the numerical results of refs. [54] and [57] should be identical; at the time of writing no such comparison has been completed yet.

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6.2. Theory versus experiments in membrane diffusion

If one substitutes into the asymptotic formulae of the last subsection the same typical values for the parameters as were used in (6.2), one finds the order of magnitude estimate \( D'_r \approx 2 \times 10^{-8} \text{ cm}^2 \text{ s}^{-1} \). However, experimental values [37–44] for \( D'_r \) range from \( 10^{-8} \) to \( 10^{-11} \text{ cm}^2 \text{ s}^{-1} \). What is wrong? Possible
deficiencies of Saffman’s model have been discussed by a variety of authors [35, 56, 58–60]; the main ones are the following.

(a) The simplest approximation of membrane diffusion is to describe it as a strictly two-dimensional diffusion process. However, as was pointed out in this context by Buas [58], macroscopic hydrodynamic calculations on the surface of a sphere are plagued by theoretical difficulties, which lead to ambiguities in the definition of the transport coefficients. Of course, in Saffman’s model the two-dimensional membrane is coupled to the three-dimensional intra- and extracellular fluid, but because of the smallness of the coupling constant $\theta^{-1} = 10^{-2}$ this coupling is weak. This weak coupling in turn causes the disturbance of the flow field around a protein to extend beyond the positions of other nearby proteins. As a result, for actual experiments, the movements of different proteins in the same cell membrane are not independent. To the author’s knowledge this effect has not been analysed theoretically.

(b) Bloom [61] has suggested that certain proteins in membranes have a “fluid-like” outer region which provides an approximate match with the lipid membrane. This effect could be taken into account by altering the boundary condition in Saffman’s model. Zero tangential stress leads to a term $+\frac{1}{2}$ added inside the bracket of (6.9) [46], and leads to a larger diffusion coefficient than predicted by (6.9). As the experimental values of $D_T'$ are smaller than the values predicted by (6.9) it is unlikely that Bloom’s suggestion would improve the situation in this respect.

(c) If the protein binds to and dissociates from the cytoskeleton or other submembraneous binding sites the ensuing diffusing process will be slowed down considerably. If we can describe this binding by a single dissociation constant $K$, the effective lateral translational diffusion coefficient was estimated by Elson and Reidler [62] to be given by

$$D_T = D'_T \frac{KS}{N + KS} + D'_S \frac{N}{N + KS},$$

(6.14)

where $S$ is the surface area of the cell, $N$ the average number of free binding sites, $D'_T$ the translational lateral diffusion coefficient of free proteins and $D'_S$ the translational lateral diffusion coefficient of proteins bound to submembraneous structures. At the time of writing there is increasing evidence that tethering does play a substantial role in membrane diffusion [cf. 60].

(d) Another possibility is suggested by Owicki and McConnell [63]. The membrane may not be in the pure fluid phase, but in a mixed state in which regions characterized by a high density and a very small diffusivity $D'_F$ are immersed in a fluid phase with much higher diffusion coefficient $D'_F$. The observed Brownian motion of a protein actually consists of an alternation of rapid and slow diffusion in the two types of environment. The effective diffusion coefficient is shifted down towards $D'_S$ and even anisotropy can arise [64].

The effective lateral diffusion coefficients given in [63] for a model where the membrane consists of layers with alternating slow and fast diffusion are

$$D_F = fD'_F + (1 - f)D'_S,$$

$$\frac{1}{D_s} = \frac{f}{D'_F} + \frac{1-f}{D'_S},$$

(6.15)

(6.16)

respectively for the effective diffusion parallel and perpendicular to the layers, where $f$ is the surface fraction of fluid membrane.
7. Theory of two-stage chemoreception

An important property of the cell is its ability to bind certain ligands nonspecifically, i.e. many ligands can bind weakly to the nonreceptor portion of the cell surface as well as specifically to appropriate receptors. Consequently, ligands may bind nonspecifically and then diffuse in the plane of the membrane until they encounter a receptor molecule. Such binding paths will be referred to as non-specific. These paths will be in competition with specific paths that involve binding directly from solution; in general both types of paths will contribute to the rate with which the cell captures ligands. In this section we develop the theory of two-stage chemoreception for the standard model of section 4, following recent work by Wiegel and DeLisi [67].

The first attempt to model two-stage chemoreception is due to Adam and Delbrück ([7], also cf. [8] and [16]). They used a cylindrical geometry and did not reach a definite conclusion. Yet the basic idea is clearly expressed: the ligand is led to the binding site on the cell by a process of random search in which the dimensionality of the space in which the random walk proceeds is decreased in steps. First the ligand performs a three-dimensional random walk until it hits a cell membrane, next it performs a two-dimensional random walk till it hits the binding site.

Many cells carry glycoproteins in their outer membranes. These polymers have long, flexible tails which extend into the extracellular medium and which might also be involved in facilitating chemoreception. In this case we should speak of three-stage chemoreception: (a) the ligand diffuses through space until it hits the tail of a glycoprotein; (b) it diffuses along this polymer until it hits the cell membrane; (c) it diffuses laterally in the membrane until it hits the receptor. At the time of writing no theory exists for chemoreception in which three-stage capture plays a role. Three-stage capture has certain features in common with the association of a repressor to the corresponding operator on the
DNA molecule, which process has been studied in considerable detail by Berg and Blomberg [68, 69]. It should, therefore, be expected that the relevant theory will be worked out in the near future.

In order to derive an expression for the rate of ligand capture in two-stage chemoreception we remind the reader of the expression (4.9)

\[ c(r) = c(\infty) \lambda (r) - B \lambda (r) \int_0^\infty \rho^{-2} \lambda^{-1}(\rho) d\rho \]  

(7.1)

for the ligand concentration in the space around the cell. The ligand current density at the cell surface

\[ j_N = D_T \left( \frac{dc}{dr} \right)_{r=R} - \frac{1}{f} F(R) c(R) \]

is now the sum of two terms

\[ j_N = j^{(Q)}_N + j^{(Q)}_R, \]  

(7.2)

where \( j^{(Q)}_N \) is the direct current density into the binding sites of the receptor molecules

\[ j^{(Q)}_N = \alpha \nu D_T s c(R), \]

(7.3)

and \( j^{(Q)}_R \) is the indirect current density due to adsorbed ligands. The calculation of the latter quantity forces us to adopt a model for the adsorbing properties of the cell membrane, which we choose as follows. Represent the membrane by a square potential well of depth \(-E < 0\) and a thickness \(d\) which is approximately equal to the width of the shell to which a bound ligand is constrained. If the volume concentration of ligand just outside the membrane equals \(c(R)\) the surface concentration (number of ligands per unit area) will be given by

\[ n = d c(R) \exp(E/k_B T) \]  

(7.4)

because close to the membrane bound- and free ligands will be in thermal equilibrium with each other. One can now write

\[ j^{(Q)}_R = \zeta d c(R) \exp(E/k_B T), \]  

(7.5)

where the value of the proportionality constant \(\zeta\) will be calculated shortly.

Combination of (7.2–5) with the analog of (4.8) gives

\[ B = c(\infty) \left\{ \frac{\alpha}{4\pi} Ns + \zeta R^2 \frac{d}{D_T} \exp(E/k_B T) \right\} \lambda (R) \]

\times \left[ 1 + \left\{ \frac{\alpha}{4\pi} Ns + \zeta R^2 \frac{d}{D_T} \exp(E/k_B T) \right\} \lambda (R) \int_R^\infty \rho^{-2} \lambda^{-1}(\rho) d\rho \right]^{-1}. \]  

(7.6)
Using once more the analog of (4.8), the total flux of ligands into the cell is found to equal

\[ J_N = 4\pi D_T B. \]  

(7.7)

In order to complete the calculation we need an expression for the parameter \( \zeta \).

Consider a spherical cell of radius \( R \), which carries \( N \) circular receptors uniformly distributed over the surface. Ligands diffuse laterally in the membrane with a diffusion coefficient \( D'_T \). Moreover, there is a constant flux of ligands \( q_0 \) into the membrane; this flux equals the number of ligands that hit a unit area of the membrane minus the number of ligands that "evaporate" from that area, per unit of time. There are essentially two ways to describe the surface concentration \( n \) of ligands in the stationary state.

The first method, followed by all previous authors, amounts to trying to solve the two-dimensional diffusion equation

\[ \frac{\partial n}{\partial t} = D'_T \Delta n + q_0 = 0 \]  

(7.8)

subject to the boundary condition

\[ n = 0 \]  

on all binding sites. \( (7.9) \)

Here \( \Delta \) denotes the Laplacian in two dimensions. Actually, the complicated nature of the boundary conditions \( (7.9) \) makes an analytic solution of \( (7.8) \) prohibitive. (The results of a numerical solution are discussed in appendix B of ref. [16]. Also note that this model is related to the quantized version of Sinai’s billiard, which was recently studied by Berry [70].) Because of this, most authors replace the complicated boundary condition by the much simpler, but somewhat arbitrary, condition that the normal derivative of \( n \) vanishes everywhere on a circle around each receptor with a radius equal to one half the average distance between sites.

The second method, which we shall follow in this paper, uses a coarse-grained description of the type common in the theory of fluid flow in porous media [24], electromagnetic fields in matter, etc. One defines the coarse-grained surface concentration \( C \) as the average of the surface concentration \( c \) over an area \( s \) such that many receptors are located inside \( s \) and the coarse-grained density \( C \) is practically constant within \( s \). The local time variation \( \frac{\partial C}{\partial t} \) of this coarse-grained concentration will be caused by:

(a) Diffusion, which leads to a term \( D'_T \Delta C \);
(b) The constant source density \( q_0 \);
(c) Absorption of ligand by receptors. If the concentration of receptors is denoted by \( \nu \) this absorption leads to a term \(-\zeta C\). Hence, the stationary state has to be solved from

\[ \frac{\partial C}{\partial t} = D'_T \Delta C - \zeta C + q_0 = 0. \]  

(7.10)

The solution is

\[ C = C_0 = \frac{q_0}{\zeta}. \]  

(7.11)

The unknown constant \( \zeta \) can be calculated if one notes that \( \zeta C_0/\nu \) by definition equals the number of ligands which are absorbed by a single receptor if the concentration approaches \( C_0 \) at a large distance \( (r) \) from this receptor. The solution of \( (7.10) \) which vanishes for \( r \downarrow s \) and which approaches \( C_0 \) for \( r \to \infty \) is found to equal
where the $K_n$ denote the modified Bessel functions. The total lateral flux $J_1$ into this receptor site is found to be

$$J_1 = 2\pi s D' \left| \frac{dC}{dr} \right|_{r=s} = 2\pi s \sqrt{\xi D_T} \frac{K_1(s\sqrt{\xi/D_T})}{K_0(s\sqrt{\xi/D_T})} C_0.$$  (7.13)

As this should equal $(\zeta/\nu)C_0$ we find the self-consistency condition

$$\phi(\xi) = \xi K_0(\xi)/K_1(\xi) = 2\pi s^2$$  (7.14)

where

$$\xi = s\sqrt{\zeta/D_T}.  \quad (7.15)$$

This condition implies that $\xi^2$ is a function $\xi^2(2\pi s^2)$ of the variable $2\pi s^2$ only, and hence

$$\xi = \frac{D'_T}{s^2} \xi^2(2\pi s^2). \quad (7.16)$$

The dimensionless parameter $2\pi s^2$ is of order of the fraction of the cell surface which is occupied by binding sites; this number is typically of order $10^{-3}$ and hence $\ll 1$. For $\xi \ll 1$ one has $\phi(\xi) \approx \xi^2 |\ln \xi|$. Therefore, in realistic cases $\xi$ will be small compared to unity and approximately given by

$$\xi \approx \left\{ \frac{4\pi \rho s^2}{|\ln(2\pi s^2)|} \right\}^{1/2}, \quad (2\pi s^2 \ll 1). \quad (7.17)$$

Combination of (7.14) with (7.16) gives an implicit expression for the parameter $\xi$ in terms of $D'_T$, $s^2$ and $2\pi s^2$, which was needed to complete the calculation of the total ligand flux into the cell.

In the absence of attractive forces between ligands and the cell, the rate of ligand capture by circular receptors equals

$$J_N = 4\pi R D_T c(\infty) \frac{Ns + \pi R^2 \xi (d/D_T) \exp(E/k_B T)}{Ns + \pi R + \pi R^2 \xi (d/D_T) \exp(E/k_B T)}.$$  (7.18)

Two-stage capture is switched off by taking the limit $D'_T/D_T \to 0$, in which case the expression reduces to eq. (4.17) for one-stage chemoreception in the absence of attractive forces.

In the case of an electrostatic attraction, defined by eqs. (4.18, 20) the rate of ligand capture by receptors with circular binding sites is found to be given by

$$J_N = 4\pi R D_T c(\infty) \frac{\{Ns + \pi R^2 \xi (d/D_T) \exp(E/k_B T)\} e^{\delta R}}{\pi R + \{Ns + \pi R^2 \xi (d/D_T) \exp(E/k_B T)\} (R/\delta) (e^{\delta R} - 1)}$$  (7.19)

which reduces to (4.19) when two-stage capture is switched off.
By way of illustration consider the following examples. A cell is involved in chemoreception under the following conditions:

(a) No charge; only one-stage capture; infinitely many receptors. The flux is found by taking the limit $N \to \infty$ in (4.17). This gives the saturation value $J_\infty = 4\pi R D_T c(\infty)$.

(b) As case (a), but with finite $N$. In order to get 50% of the maximum flux one has to choose $N = \pi R/s \approx 3100$ with the estimates (4.1), and $J_N = 2\pi R D_T c(\infty)$.

(c) Electrostatic attraction; only one-stage capture; $N = \pi R/s$. For a charge such that $\delta/R = 1$ the flux is twice its value under conditions (b): $J_N = 4\pi R D_T c(\infty)$.

(d) No electrostatic attraction, but both one-stage and two-stage capture processes are permitted. Eq. (7.18) shows that the ratio of the contribution of the non-specific to the direct paths enters through the dimensionless parameter

$$
\kappa = \frac{\pi R^2 d D_T'}{Ns^2 D_T} \exp(E/k_B T) \frac{\xi^2(Ns^2/2R^2)}{2R^2},
$$

(7.20)

where the dependence of $\xi$ on $Ns^2/2R^2$ was denoted explicitly. Now, as $Ns$ is of order $R$, $d$ of order $s$ and $\xi^2(Ns^2/2R^2)$ of order $Ns^2/R^2$ one finds that $\kappa$ will typically be of order $(D_T'/D_T) \exp(E/k_B T)$. Typical values of $D_T'/D_T$ are in the range $10^{-2}$ to $10^{-3}$. It has been argued by Wiegel and DeLisi [67] that $\exp(E/k_B T)$ has values in the range $10$ to $100$. The main conclusion is that $\kappa$ will usually be small as compared to unity, which implies that two-stage capture processes are usually unimportant as compared to one-stage capture processes.

8. Chemoreception by a swimming cell

In many cases of biological interest the cell which is involved in chemoreception is in a state of uniform motion with respect to the surrounding extracellular fluid. This situation would describe a swimming bacterium, for example. If the cell is described by the standard spherical model with $N$ binding sites, as discussed in section 4, one can ask for the effect of swimming on the rate of ligand capture. Up till now this question has not yet been studied theoretically in a satisfactory way. It is the aim of this section to formulate the problem as far as possible, to identify the dimensionless parameters which occur in it, and to solve it in some limiting cases.

The problem of chemoreception by a swimming bacterium was first noted by Berg and Purcell [16] (also cf. [33]). It should not be confused with the problem of chemoreception by a cell in shear flow, for which a theoretical analysis is lacking altogether, although some elegant experiments by Purcell [71] have clarified the situation.

Before turning to the details of the calculation some general remarks are appropriate. First, it should once more be stressed that our “standard” model is quite realistic in the sense that chemoreception by a swimming bacterium occurs in a finite number of specific receptor sites rather than continuously everywhere on the cell’s surface. This latter case, in which the whole cell surface acts as a perfect ligand absorber, has been studied analytically by Acrivos and Taylor [72]; numerical results can be found in ref. [16].

Second, it should be noted that for a bacterium that swims through water with a speed $v_0 \approx 15 \times 10^{-3}$ cm s$^{-1}$ the Reynolds number $Rv_0\rho_0/\eta$ is of order $10^{-3}$. Hence, just as in section 2, the Navier–Stokes equation can be linearized and the fluid velocity field is the Stokes flow.
\[ v_r = -v_0 \cos \theta \left( 1 - \frac{3R}{2r} + \frac{R^3}{2r^3} \right), \]  
(8.1) 
\[ v_\theta = +v_0 \sin \theta \left( 1 - \frac{3R}{4r} - \frac{R^3}{4r^3} \right). \]  
(8.2)

Third, one should note that the ligand current density is now given by

\[ j = -D_T \nabla c + cv, \]  
(8.3)

so the diffusion equation has the form

\[ \frac{\partial c}{\partial t} = D_T \Delta c - v \cdot \nabla c, \]  
(8.4)

provided the flow is incompressible, which is the case for Stokes flow.

The Peclet number \( P \) is defined as the ratio between the order of magnitude of the convective term, \( v \cdot \nabla c \approx v_0 c(\infty)/R \), and of the diffusion term \( D_T \Delta c \approx D_T c(\infty)/R^2 \)

\[ P = v_0 R / D_T. \]  
(8.5)

Using the expression (2.12) for the translational diffusion coefficient and substituting typical orders of magnitude for the various parameters one finds

\[ P = 6 \pi \eta a R v_0 / k_B T \approx 17. \]  
(8.6)

For \( P \ll 1 \) the total ligand current will be close to the limiting form (4.17) derived before. In the rest of this section we consider the asymptotic limit of large Peclet numbers, which is typical for various biophysical situations.

For the stationary state (8.4), when transformed to spherical coordinates, becomes

\[ D_T \left\{ \frac{\partial^2 c}{\partial r^2} + \frac{2}{r} \frac{\partial c}{\partial r} + (r^2 \sin \theta)^{-1} \frac{\partial}{\partial \theta} \left( \sin \theta \frac{\partial c}{\partial \theta} \right) \right\} = v_r \frac{\partial c}{\partial r} + v_\theta \frac{\partial c}{\partial \theta}, \]  
(8.7)

where \( v_r \) and \( v_\theta \) are given by the formulae (8.1, 2). The various terms have different orders of magnitude. For a fixed value of \( r \) the concentration will drop from the value \( c(\infty) \) at \( \theta = 0 \) to a value close to 0 for \( \theta = \pi \), hence

\[ \frac{1}{r} \frac{\partial c}{\partial \theta} \approx c(\infty)/R. \]  
(8.8)

A fluid element close to the cell membrane will need a time of the order \( R/v_0 \) to flow around the sphere. During this time the ligands will diffuse over distances of order \( (RD_T/v_0)^{1/2} \), so

\[ \frac{\partial c}{\partial r} \approx c(\infty) (v_0/RD_T)^{1/2}. \]  
(8.9)

This shows that for \( P \gg 1 \) the third term on the left hand side of (8.7) can be neglected with respect to
the second term. In the same way one shows that the second term is negligible with respect to the first, so the convection-diffusion equation simplifies to

$$D \frac{\partial^2 c}{\partial r^2} = \nu_r \frac{\partial c}{\partial r} + \nu_\theta \frac{c}{r \frac{\partial}{\partial \theta}}, \quad (P \gg 1).$$

(8.10)

Note that in the layer of thickness \((RD_\tau/v_0)^{1/2}\) in which the ligand concentration is substantially depleted as a result of ligand diffusion and capture, \(v_\theta\) will be large compared to \(v_r\), so both terms on the right hand side have to be retained.

In the method of Levich [73] one introduces the function

$$\psi(r, \theta) = \frac{1}{2}v_0 \sin^2 \theta \left( r^2 - \frac{3rR}{2} + \frac{R^3}{2r} \right),$$

(8.11)

which has the property

$$\left( \frac{\partial \psi}{\partial r} \right)_r = r v_\theta \sin \theta,$$

(8.12)

$$\left( \frac{\partial \psi}{\partial \theta} \right)_r = -r^2 v_r \sin \theta,$$

(8.13)

and which, therefore, equals minus the stream function for Stokes flow. Writing the ligand concentration as a function \(c(\psi, \theta)\) of the independent variables \(\psi\) and \(\theta\) (8.10) takes the form

$$\frac{\partial c}{\partial \theta} = D \frac{\partial^2}{\partial \psi \partial \theta} \left( r v_\theta \frac{\partial c}{\partial \psi} \right),$$

(8.14)

where \(r\) now denotes the function \(r(\psi, \theta)\) which is uniquely defined by inverting (8.11). For \(P \gg 1\) the factor \(r^2\) on the right hand side of this equation can be replaced by \(R^2\) and the factor \(rv_\theta\) by \((3v_0\psi)^{1/2}\), so the previous equation simplifies further to

$$\frac{\partial c}{\partial \theta} = D \frac{\partial^2}{\partial \psi \partial \theta} \left( (3v_0\psi)^{1/2} \frac{\partial c}{\partial \psi} \right).$$

(8.15)

A second coordinate transformation pertinent to this problem consists of replacing \(\theta\) by

$$\tau = \frac{1}{2}D_\tau R^2 (3v_0)^{1/2} \left( \theta - \frac{1}{2} \sin 2\theta \right), \quad (0 < \theta < \pi).$$

(8.16)

This transforms (8.15) into

$$\frac{\partial c}{\partial \tau} = \frac{\partial}{\partial \psi} \left( \psi^{1/2} \frac{\partial c}{\partial \psi} \right).$$

(8.17)

Hence \(\tau\), which essentially measures the azimuthal angle from the direction in which the cell swims, plays the role of time and \(\psi\) plays the role of coordinate in a one-dimensional diffusion problem with a \(\psi\)-dependent diffusion coefficient \(\psi^{1/2}\). The maximum physically meaningful \(\tau\)-value is
\[ \tau_0 = \frac{\pi}{2} D_T R^2 (3v_0)^{1/2}. \] (8.18)

The boundary condition at infinity on the function \( c(\psi, \tau) \) is

\[ c(\psi, \tau) = c(\psi), \quad (0 < \tau < \tau_0). \] (8.19)

We also require the concentration to equal \( c(\psi) \) on the whole line \( \theta = 0, \ R < r < \infty \) in the forward direction; this leads to the initial condition

\[ c(\psi, 0) = c(\psi), \quad (0 < \psi < \infty). \] (8.20)

Finally, at the surface of the cell one imposes the boundary condition (4.14), with \( V = 0 \) because of the absence of external forces. Transformation to the \( \psi, \tau \) coordinates gives the boundary condition

\[ c = \epsilon' \sin \theta \psi^{1/4} (\partial c / \partial \psi)_\tau, \quad (\psi = 0, 0 < \tau < \tau_0), \] (8.21)

in the limit \( \psi \to 0 \); here \( \sin \theta \) should be interpreted as a function of \( \tau \) through (8.16) and \( \epsilon' \) denotes the constant

\[ \epsilon' = \frac{4\pi R^2}{\alpha N_s} (3v_0)^{1/2}. \] (8.22)

The general solution of (8.17) can be expanded in Bessel functions of the first kind and has the form

\[ c(\psi, \tau) = c(\psi) + \psi^{1/4} \int_0^{\infty} \left[ A(\lambda) J_{1/3}(\frac{1}{3} \lambda^{1/2} \psi^{3/4}) + B(\lambda) J_{-1/3}(\frac{1}{3} \lambda^{1/2} \psi^{3/4}) \right] \exp(-\lambda \tau) d\lambda. \] (8.23)

The boundary condition (8.19) shows that the functions \( A(\lambda) \) and \( B(\lambda) \) vanish for \( \lambda < 0 \). The initial condition (8.20) is satisfied provided these functions are related by

\[ \int_0^{\infty} \left[ A(\lambda) J_{1/3}(\frac{1}{3} \lambda^{1/2} \psi^{3/4}) + B(\lambda) J_{-1/3}(\frac{1}{3} \lambda^{1/2} \psi^{3/4}) \right] d\lambda = 0, \quad (0 < \psi < \infty). \] (8.24)

The boundary condition (8.21) becomes

\[ c(0, \tau) = c(\psi) + \Gamma^{-1}(2/3)(2/3)^{-1/3} \int_0^{\infty} B(\lambda) \lambda^{-1/6} e^{-\lambda \tau} d\lambda \]

\[ = \frac{1}{2} \epsilon' \sin \theta \Gamma^{-1}(4/3)(2/3)^{1/3} \int_0^{\infty} A(\lambda) \lambda^{1/6} e^{-\lambda \tau} d\lambda, \quad (0 < \tau < \tau_0). \] (8.25)
Although the two unknown functions $A(\lambda)$ and $B(\lambda)$ are in principle determined by the last two equations their explicit evaluation has not yet been possible. These equations show that, as $\psi$ is of order $v_0 R^2$ and $\partial c / \partial \psi$ of order $c(\infty) R^{-3/2} D_T^{-1/2} v_0^{-1/2}$, the solution will depend not on $e'$ but on the dimensionless combination

$$e = \frac{R}{N_s} P^{1/2}$$  \hspace{1cm} (8.26)

of the Peclet number $P$ which determines the convection-diffusion problem and the parameter $R/N_s$ which determines chemoreception by a cell at rest.

If $e \ll 1$ the right hand side of (8.21, 25) can approximately be set equal to zero. In this case one can follow the much simpler method of Levich [73] who noticed that both the differential equation (8.17) and its boundary conditions are invariant under the substitutions

$$\psi = \mu \psi', \hspace{1cm} (8.27a)$$

$$\tau = \mu^{3/2} \tau'. \hspace{1cm} (8.27b)$$

This suggests looking for a solution which is a function $c(\eta)$ of the combination

$$\eta = \psi \tau^{-2/3}. \hspace{1cm} (8.28)$$

The convection-diffusion equation now becomes an ordinary differential equation

$$\frac{d}{d\eta} \left( \eta^{1/2} \frac{dc}{d\eta} \right) + \frac{2}{3} \eta \frac{dc}{d\eta} = 0, \hspace{1cm} (8.29)$$

with boundary conditions

$$c(\eta = 0) = 0, \hspace{1cm} c(\eta = \infty) = c(\infty). \hspace{1cm} (8.30a, b)$$

The solution is

$$c(\eta) = c(\infty) \int_0^{\eta^{1/2}} \frac{\exp(-\frac{1}{3} z^3) \, dz}{\int_0^{\infty} \exp(-\frac{1}{3} z^3) \, dz}. \hspace{1cm} (8.31)$$

The ligand current density is given by

$$j = D_T (3v_0)^{1/2} \sin \theta \lim_{\psi \to 0} \psi^{1/2} \left( \frac{\partial c}{\partial \psi} \right)_\tau$$

$$= K D_T c(\infty) \left( \frac{v_0}{D_T R^2} \right)^{1/3} \sin \theta \left( \theta - \frac{3}{2} \sin 2\theta \right)^{1/3}, \hspace{1cm} (8.32)$$

where the numerical constant has the value
Finally, the total ligand flux into the cell is found to equal
\[
J = \frac{3}{2} \pi^{5/3} K c(\infty) D^{2/3} R^{4/3} v_0^{1/3} = 7.849 \ c(\infty)D^{2/3} R^{4/3} v_0^{1/3}, \quad (P \gg 1, \ v \ll 1).
\] (8.34)

Comparing this flux with the ligand flux \(J_\infty\) into a perfectly absorbing cell at rest the ratio is proportional to the one-third power of the Peclet number \((J/J_\infty = \frac{3}{2} \pi^{1/3} KP^{1/3} = 0.4264P^{1/3})\). Hence swimming is of little help to improve the efficiency of chemoreception, unless the cell swims very fast, which will necessitate a very high rate of energy consumption.

9. Concluding remarks

In this final section we collect some general conclusions, some open problems which might be the subject of further research in the immediate future, and some other more speculative comments.

The main conclusion of section 4 is that the rate of ligand capture by means of one-stage processes can indeed be increased considerably by the presence of a weak, non-specific force which attracts ligands to the cell. The analysis of section 7 showed that two-stage capture processes are often unimportant as compared to one-stage processes. In the same way, the tentative result of section 8 is that swimming will also not help the cell to drastically increase its ligand intake. This unexpectedly high efficiency of one-stage chemoreception is due to the highly erratic, fractal nature of the ligand's paths.

Of course, various open problems remain. One of the more interesting ones is the problem of calculating the rate of capture by a spherical cell in shear flow. This problem is relevant to chemoreception by any cell in blood or lymphatic fluid. Another group of important and partly unsolved problems is related to cells with receptors which appear and disappear stochastically in the cell membrane, as is the case with basophils in the immune system. Somewhat related is the problem of taking into account the finite time after catching a ligand during which a binding site cannot catch another ligand.

Somewhat more poorly defined are problems related to the search for the optimal distribution of receptor complexes in the cell membrane given a certain shape of the cell, or inversely: given the local density of receptor complexes what shape of cell leads to a maximum ligand capture rate?

Even more speculative is the possible application of the ideas discussed in this review to the organization of memory. In this respect I should especially mention the concept of reduction in dimensionality: when the ligand "searches for a receptor site" this search can proceed first by diffusion in a three-dimensional space, followed by diffusion in a plane or along a one-dimensional DNA backbone as in the examples studied by Berg and Blomberg [68, 69]. In a similar way it is conceivable that our consciousness, when searching for a particular image in our memory, performs a trial-and-error search in some high-dimensional space, until it hits a lower-dimensional manifold in which a trial-and-error search leads to a still lower-dimensional manifold, and so on until this cascade ends at the image which was specifically required. But here we are way beyond what theoretical physics can adequately model to date, and this possibility belongs in the crystal ball.

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