Diffusion-controlled ligand binding to spheres partially covered by receptors: An effective medium treatment

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ABSTRACT   An effective medium treatment is used to extend Berg and Purcell's theory of diffusion-controlled ligand binding to a sphere partially covered by receptors. This treatment takes into account more completely the effects of interference between receptors. The results are in excellent agreement with computer simulations by Northrup.

A mathematical problem that arises in many contexts is to determine the diffusion-controlled rate of irreversible binding of ligands to receptors on the surface of a sphere. Long ago this problem was solved by Smoluchowski in the limit where the surface is completely covered by receptors. Berg and Purcell (1) solved it in another limit, where there are many receptors but the size of a single receptor is much smaller than the typical distance between receptors. They found that even in this limit the Smoluchowski result is recovered if the number of receptors is large enough. Berg and Purcell used an electrostatic analogy to obtain their final results; an intuitively appealing re-derivation was given by Shoup and Szabo (2).

Northrup (3) reported Brownian dynamics simulations of this problem. At low coverage, the agreement with the Berg–Purcell result was good. But small discrepancies were found at higher coverage; for example, when about one-fourth of the sphere's surface was covered by receptors, the simulation results were about 5% higher than the Berg–Purcell prediction.

I present here an approximate treatment of this problem that takes into account more completely the effects of cooperative interactions between receptors. The result agrees with Northrup's simulations at all coverages to within their experimental error (S. H. Northrup, personal communication).

The problem is as follows. N receptors are placed at random on the surface of a sphere of radius R and area $4\pi R^2$. A single receptor is treated as a disk of radius a and area πa^2. The radius of the disk is assumed to be much smaller than that of the sphere, but if there are enough receptors, the total area $N\pi a^2$ of the disks can be comparable with the area $4\pi R^2$ of the sphere. The fraction of the sphere's surface that is covered by disks is

$$p_A = N\pi a^2 / 4\pi R^2. \qquad [1]$$

The ligands have a diffusion coefficient D, and their concentration C at position r is maintained at the constant value $C = 1$ far from the sphere. On the surface of the sphere, C vanishes if r is inside any disk, and the normal gradient $\partial C/\partial r$ vanishes if r is outside all disks. That is, the disks are perfectly absorbing, and otherwise the surface is perfectly reflecting. The problem is to determine the steady-state flux

K of ligands into the absorbing disks. This is given by the surface integral

$$K = \oint dS \, D \, [\partial C/\partial r]_{r=R}. \qquad [2]$$

Smoluchowski's result, K_{SM}, applies when the entire surface is absorbing,

$$K_{SM} = 4\pi DR. \qquad [3]$$

The result found by Berg and Purcell, for partial coverage, is

$$K_{BP} = K_{SM} \frac{Na}{Na + \pi R}. \qquad [4]$$

This reduces to the Smoluchowski K_{SM} when Na is much larger than πR, and to $4DNa$ when πR is much larger than Na. My modification of the Berg–Purcell formula is

$$K_E = K_{SM} \frac{Na}{Na + \pi R(1 - p_A)}. \qquad [5]$$

The extra factor in the denominator is the fraction of the sphere's surface that is not occupied by absorbing disks. (The subscript E stands for "effective medium.") This is the formula that agrees well with Northrup's simulations.

As a beginning, it will be useful to review the derivation of the Berg–Purcell formula due to Shoup and Szabo. The steady-state diffusion equation is

$$D\nabla^2 C = 0. \qquad [6]$$

This is to be solved with appropriate boundary conditions on the surface of the sphere. To an observer far from the sphere, the surface appears to be uniform but neither perfectly reflecting nor perfectly absorbing. This suggests use of a "radiation boundary condition,"

$$D\frac{\partial C}{\partial r} = kC \text{ on } r = R. \qquad [7]$$

If $k = 0$, the surface is perfectly reflecting, and if $k \to \infty$, the surface is perfectly absorbing. Then the appropriate solution of the diffusion equation is

$$C = 1 - \frac{\alpha}{r}, \qquad [8]$$

and the boundary condition on R determines the coefficient

$$\alpha = \frac{k}{k/R + D/R^2}. \qquad [9]$$

The total flux into the sphere is obtained by integrating the normal gradient of C over the surface, Eq. 2,

$$K_{SM} = 4\pi D\alpha = \frac{4\pi Dk}{k/R + D/R^2}. \qquad [10]$$

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Shoup and Szabo suggest an approximation for k, based on the observation (4) that the flux into a single isolated hole or absorbing disk of radius a in an infinite flat plane is $4Da$. It is reasonable to expect that the flux into a single disk on the sphere is also $4Da$, as long as the radius of the disk is much smaller than the radius of the sphere, so that its environment is locally flat. The number of disks per unit area is $N/4\pi R^2$. Then Shoup and Szabo use the intuitively plausible guess that k is the product of the flux into one disk times the number of disks per unit area,

$$k \approx 4Da\frac{N}{4\pi R^2}. \qquad [11]$$

This guess can be good only if the disks are far enough apart. The reason is that a single absorbing disk produces a change of the concentration C that extends a distance of the order of many disk radii. This complicates the fitting of boundary conditions on the reflecting region and on the other disks.

When Eq. 11 is put into K_{SM}, one gets the Berg–Purcell formula. My result is equivalent to replacing k by $k/(1 - p_A)$, where p_A is the fraction of the surface area that is absorbing. This takes into account at least approximately the effects on k of interference between disks.

The derivation to be presented here uses an "effective medium" approximation. (Effective medium arguments are hardly ever exact but they are often surprisingly accurate, and they provide results with a minimum of labor.) The sphere having N absorbing disks on a reflecting surface is replaced by a sphere with one disk-shaped region, which can be either perfectly absorbing or perfectly reflecting, surrounded by a uniform partially absorbing surface of the sort used by Shoup and Szabo. The probability that the special region is perfectly absorbing is p_A, and the probability that it is perfectly reflecting is $p_R = 1 - p_A$.

Now consider the three cases E (for effective), A (for absorbing), and R (for reflecting). In case E, the entire surface is uniformly partially absorbing; the total flux into the sphere is K_E. In case A, the special region is perfectly absorbing and the rest of the surface is partially absorbing; the total flux is K_A. In case R, the special region is perfectly reflecting and the rest of the surface is partially absorbing; the total flux is K_R. The effective medium approximation is found by requiring that K_E is the average of K_A and K_R,

$$K_E = p_A K_A + p_R K_R. \qquad [12]$$

This determines the degree to which the surface is partially absorbing. Now the three fluxes are needed.

At this point it appears to be necessary to solve Laplace's equation for the three cases E, R, and A; however, most of the work has already been done, and only some careful organization is needed. Spherical polar coordinates (r, θ, ϕ) are used; the surface is $r = R$. In all cases, $C(r, \theta, \phi)$ is fully determined by the boundary conditions. Far from the sphere, $C = 1$. On the surface of the sphere, the boundary conditions

may involve either the value $C(R, \theta, \phi)$ or the normal derivative

$$\gamma(\theta, \phi) = \left[\frac{\partial}{\partial r} C(r, \theta, \phi)\right]_{r = R}. \qquad [13]$$

The part of the surface lying inside the chosen disk is denoted by [in], the rest of the surface is [out], and the entire surface is [all] = [in] + [out]. Then the three cases may be summarized as follows:

E [all] $C_E = 1 - \gamma R$; $\gamma_E = \gamma$

R [in] $C_R = ?$; $\gamma_R = 0$

[out] $C_R = ?$; $\gamma_R = \gamma$

A [in] $C_A = 0$; $\gamma_A = ?$

[out] $C_A = ?$; $\gamma_A = \gamma$.

The question marks indicate values or derivatives that are to be determined by solving Laplace's equation, using the boundary conditions that are explicitly stated. One more case, S, is needed. This is a single absorbing disk on a reflecting sphere:

S [in] $C_S = 0$; $\gamma_S = ?$

[out] $C_S = ?$; $\gamma_S = 0$.

In case E, the solution is known. In case R, it is not really needed, because the flux is fully determined by $\gamma(\theta, \phi)$ and this is given. In case S, the solution is nearly that of a hole in a flat plate, which is known. As observed earlier, the total flux into the hole is $4Da$. So only case A remains. But there is a simple identity connecting A to E and S:

$$C_A(r, \theta, \phi) = C_E(r) + C_E(R)[C_S(r, \theta, \phi) - 1]. \qquad [14]$$

This may be verified by observing that it solves Laplace's equation and fits all the boundary conditions, far from the sphere and on [in] and [out]. The radial derivative is

$$\gamma_A(\theta, \phi) = \gamma + C_E(R)\gamma_S(\theta, \phi). \qquad [15]$$

Now it is easy to find the three fluxes. They are $K_E = 4\pi R^2 D\gamma$, $K_R = (4\pi R^2 - \pi a^2)D\gamma$, $K_S = 4Da$, and $K_A = K_E + C_E(R)4Da$. After some algebraic rearrangement, the effective medium self-consistency condition, Eq. 12, leads to Eq. 5 for K_E. This concludes the derivation.

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