

BIOREPS Problem Set #9

The Physics of Chemoreception

1 Background

Microorganisms such as bacteria live their in a soup of all sorts of vital nutrients and deadly toxins. In order to survive in such a world, a bacteria needs to spend a majority of its time in a nutrient rich environment free of any toxins. This is not something that exists everywhere so in order to survive, bacteria need to be able to move toward high concentrations of food and away from toxins. But how does it know which way to go? The only way for our heroic bacteria to learn anything about the locations and densities of any relevant molecules in its neighborhood is to bring information about the environment around it inside the cell.

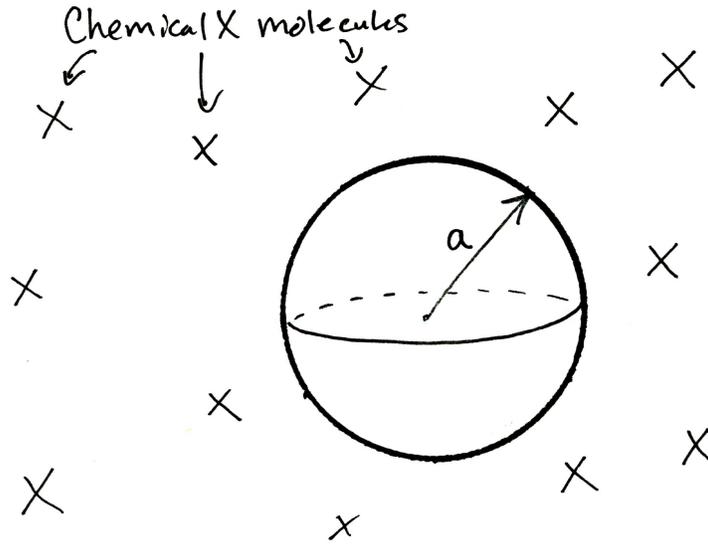
Therefore, in order to survive, these microorganisms need to be able to transfer signals (about fuel, toxins, predators, etc.) across the cell membrane. However, the small scale of the system makes the logistics of these sensory problems significantly different than the ones larger organisms – such as humans – have to face. Information for a cell can only come from the area right next to the membrane itself and the timescales of when your information becomes obsolete are much shorter than the time scales that larger organisms have to deal with.

An object pushed by a human hand continues to move away due to the object's inertia. A human eye receives visual information from photons at a rate of about 10^{15} photons/s. A microorganism, on the other hand, lives in a world governed by a very different set of rules. Since on this scale the motion of particles is governed by diffusion, changes in direction occur randomly, reflective of the myriad solvent interactions more than any Newtonian Force. Similarly, the relative viscosity of a cell's environment brings any motion to a stop almost immediately after you stop applying a force—there is no costing on inertia on the cellular scale. Even random thermal fluctuations – hardly a consideration on macroscopic scales – have a significant influence on the behavior at a cellular and molecular level.

But Bacteria need information in order to survive and so they turn to a very different sort of carrier: molecules. By counting individual packets of information - whether a molecule has or has not been bound to a receptor protein—the cell can navigate its environment. This has its limitations as well: the only part of the environment a bacterium can see is the area right around its surface. The rate at which information is brought into a cell is a matter of literal life and death, and yet it exists in this world of random motion and thermal fluctuations.

So how *does* a cell get information from outside the cell into the cell as quickly as possible to survive in the cell eat cell world?

1.1 Model



The full problem of an irregularly shaped bacteria lost and alone in the world doesn't give us immediate insight into this question, so instead consider a spherical cell of radius a immersed in an unbounded medium. Let's say the medium contains some molecules of chemical X in low concentration c , expressed in molecules per cubic centimeter, with diffusion constant D . The variation of c in space and time is given by the diffusion equation:

$$D\nabla^2 c = \frac{\partial c}{\partial t} \quad (1)$$

We'll start by assuming that the cell is a perfect sink for X molecules, that is an X molecule touches the membrane it is sucked inside the cell instantaneously, effectively removing it from our model. This gives us a boundary condition of $c = 0$ for the above differential equation. Finding a solution to this equation as a spherically symmetric system yields a constant molecular flux across the membrane.

$$J = 4\pi a D c_\infty$$

This is indeed a solution to the problem presented, however it does not reflect the reality experienced by the bacteria. In assuming spherical symmetry and total absorption everywhere on the surface, we have created a simple, solvable problem that grants us no insight into the underlying mechanisms of the cell. (Though as we will see the solution is still useful in establishing an upper limit on the cell's information current.)

Stepping back for a moment, consider the time-independent formulation of the diffusion equation instead:

$$\nabla^2 c = 0 \quad (2)$$

Solving this equation gives us any steady state solutions to the system. However, more suggestively, it also looks *very* similar to another, perhaps more familiar expression, Laplace's Equation

for electrostatic potential in a vacuum:

$$\nabla^2\phi = 0 \tag{3}$$

This problem has already been solved! Laplace's equation is one of those things that some one has worked on solving for almost any potential geometry because of its usefulness in electrostatics. By drawing out the analogy between molecular concentration in a diffusive medium and electrical potential around a conductor we can take advantage of this pre-existing math to find solutions to our own system. Ideally we want to derive an expression for J , the total information current across the cell membrane, which determines the life or death of the bacteria. To do this, we need to first define something called the diffusive current density, which parallels the electric field.

$$\begin{aligned}\vec{F} &= -D\nabla c \\ \vec{E} &= -\nabla\phi\end{aligned}$$

This is a basic measure of the motion of molecule X to maintain the steady state concentration. We can therefore define the total flux of X through a surface as an integral similar to Gauss's Law:

$$\begin{aligned}J &= \int_S \vec{F} \cdot ds \\ Q &= \int_S \vec{E} \cdot ds\end{aligned}$$

Where J becomes an analogous to charge. This grants us a good intuitive framework to consider the relationship between the concentration and the current by looking at the relationship between potential and charge. The amount of potential generated for a given amount of charge is determined by the geometry of the charge distribution. In general we represent this geometrical dependance through a value called *capacitance* defined by the following:

$$C = \frac{Q}{\phi}$$

This is a more general construction than the standard two plate capacitor model and applies to any geometry. It is sometimes called self-capacitance for stand alone conductors. Since in electrostatics Capacitance defines the proportionality of potential and charge, in our biophysical system it gives us the relationship between concentration and current. In general the steady state diffusion current to a totally absorbing body of any shape and size can be written as:

$$J = 4\pi CDc_\infty$$

Where C is the "capaticance" of the analogous conductor in electrostatics and c_∞ is the concentration far away from the cell.

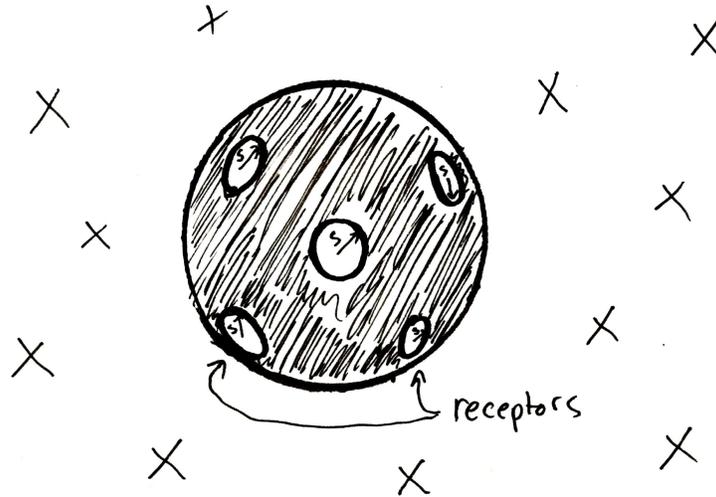
Using this new framework, let us return to the problem of a Cell's chemoreception.

References

- [1] Berg, H. C. and Purcell, E. M. Physics of Chemoreception. *Biophysics Journal* **20**, 193–219 (1977).

2 Questions

2.1 Multi Receptor Electrostatic Model



a) To begin, let us return to the spherical model of a cell with radius a . Suppose there are N circular receptors are distributed over the surface of the cell, each of radius s . Find the ratio of the receptor area to the total surface area of the cell.

b) Consider one of these receptors. If the receptor is small enough, the area around it on the sphere is locally flat so we can model the system as a thin disk embedded on the surface of an insulating sphere. The capacitance of a thin disk sitting out in space is given as $C = \frac{2r}{\pi}$. What is the current through one receptor?

c) The current across the membrane will be maximized if the entire surface is covered by receptors, given that the self-capacitance of a sphere in cgs units is just $C = r$, where r is the radius of the sphere. What is J_{max} ? (Note that it should match the solution to the spherically symmetric diffusion equation we derived earlier)

d) Now consider a system where we treat N receptors on the surface of the cell as N circular conductors embedded on an insulating sphere. Each of the disks has a charge of q_i and a potential of ϕ_i for $i = 1, 2, \dots, N$. These charges and potentials are related by the linear equation

$$\phi_j = \sum_k h_{jk} q_k \quad (4)$$

where h_{jk} is a constant measuring the strength of the interaction of charge k on potential j .

i) If only one of the disks is contains a charge, such that $q_i = \begin{cases} q, & \text{if } i = k \\ 0, & \text{otherwise} \end{cases}$, what is the potential on the charged disk?

ii) What is the total potential on all of the uncharged disks?

iii) If the charges are sufficiently spread apart, then the capacitance of the single disk on the insulating sphere is $\frac{s}{\pi}$, which gives $h_{kk} = \frac{\pi}{s}$. If we assume that N is large,

$$\sum_{j \sim k} h_{jk} = \frac{N}{a}$$

What is the sum of all of the potentials on all disks?

iv) What is the total capacitance over the sphere?

e) Using equation for current again

$$J = 4\pi CDc_{\infty} \quad (5)$$

where C is the conductance, and the result derived in part c, write J in terms of J_{max} .

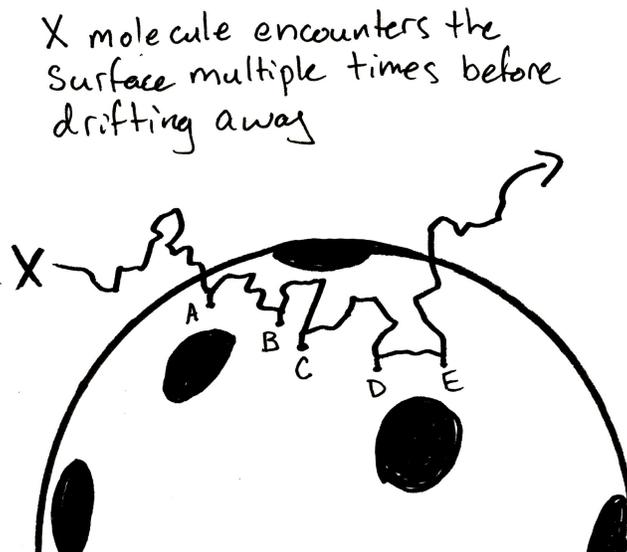
f) From your results in part d, you should find that as $N \rightarrow \infty$, $J \rightarrow J_{max}$. It does not take infinitely many receptors for $J \approx J_{max}$. Using the values $s = 10\text{\AA}$ and $a = 1\mu\text{m}$.

i) How many receptors are needed for $J = \frac{1}{2}J_{max}$?

ii) What fraction of the surface area is needed to be covered by the receptors for $J = \frac{1}{2}J_{max}$?

iii) Plot $\frac{J}{J_{max}}$ as a function of N.

2.2 Probabilistic Model of Molecule Capture



Our results show that J approaches J_{max} without devoting the majority of the cell surface to receptor sites. At $J = \frac{1}{2}J_{max}$ we have less than 1 percent of the cell's surface covered in receptors! How can it be that such a small fraction of receptor area can work so efficiently? The answer lies

in the diffusive nature of the X molecules' motion.

a) Consider particles of species X diffusing in the vicinity of a spherical cell of radius a with N receptor sites of radius s . A particle may hit the surface many times over a given time interval, we will only consider jumps where the particles moves a distance s away from the surface of the cell for simplicity. For a particle at a distance r from the center of the cell, the probability of hitting the cell is

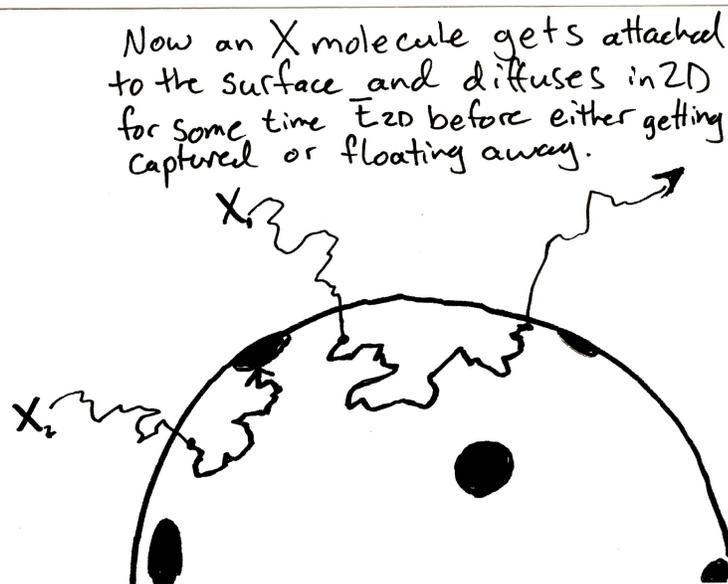
$$P_c = \frac{a}{r}. \quad (6)$$

Find the probability for a particle at $r = a + s$ to hit the cell n times before diffusing to infinity. Using this result, find the average number \bar{n} of times a particle bounces off of the cell's surface before diffusing away.

b) Treating each collision as an independent attempt to find a receptor site, find the probability for a particle to avoid a receptor on every bounce before diffusing away, P_{esc} . [Hint: Express the probability to survive a collision in terms of the ratio of the total area covered by receptor sites to the total surface area of the cell. Then, just use the usual product of probabilities for independent events.]

c) Finally, use P_{esc} to find the ratio J/J_{max} . You should find the results is almost identical to that of the previous calculation! [Hint: Start by finding $P_{capture}$ and work from there.]

2.3 Two-stage Capture Model



A more realistic model of absorption might include X molecules loosely binding to the surface of the cell instead of bouncing away when they do not encounter a receptor. In this scenario, molecules attached to the cell will perform a 2-dimensional random walk until either they hit one of the X-receptors or they detach from the surface.

a) We will begin by calculating the capture time of an X molecule in the vicinity of a circular X-receptor. For concreteness, consider the X particle to be released in the region between two concentric circles: the X-receptor (radius s) and a larger bounding circle (radius b).

Using the diffusion equation $D'\nabla^2\tau_c(\vec{r}) = -1$, where D' is the 2-dimensional diffusion constant and $\tau_c(\vec{r})$ is the mean capture time for an X molecule released from the point \vec{r} , show that

$$\tau_c(r) = \frac{1}{2D'} \left[b^2 \ln\left(\frac{r}{s}\right) + \frac{r^2 - s^2}{2} \right]. \quad (7)$$

[Hint: The rotational symmetry in the problem suggests the use of polar coordinates. In polar coordinates, τ_c depends only on r , not on θ , and the Laplace operator can be given by $\nabla^2 = \frac{1}{r}\partial_r(r\partial_r)$.]

b) This gives the average capture time for a particle released at the point \vec{r} . We are interested in the mean capture time over all points in the donut shaped region, $\bar{t}_{c,\text{annul}}$. Calculate the mean value of τ_c over the annular area. Simplify this expression under the assumption that $s \ll b$. You should find that

$$\bar{t}_{c,\text{annul}} \approx \frac{b^2}{4D'} \ln\left(\frac{b^2}{4s^2}\right). \quad (8)$$

[Hint: You may approximate $\exp(3/4) \approx 2$.]

c) In the cellular system we are considering, there are N receptors on the surface of a sphere of radius a . Derive an expression for b , so that there is only one receptor in each region of area πb^2 . Use this expression to calculate the average capture time for X-molecules bound to the surface of a cell, \bar{t}_c .

d) Now let us calculate the quantity \bar{m} , the mean number of molecules on the surface of the cell at any given time. To do this, make the approximation that X molecules bound to the surface are in equilibrium with X molecules in the extracellular solution with concentration c_∞ . In addition, consider the cellular surface as a spherical shell of radius a and thickness d , chosen so that only a single layer of X molecules may lie in the shell. Finally, assume that the adsorption of X onto the cell releases an adsorption energy E_A .

e) Let us define the average current of X molecules into the cell as $J' \equiv \frac{\bar{m}}{\bar{t}_c}$. Show that

$$J' \approx 4\pi N D' d c_\infty \frac{\exp(E_A/k_b T)}{\ln(a^2/Ns^2)} \quad (9)$$

f) Assuming that the current absorbed by the cell is small compared to the current of X that hits the cell, we know from above that the one stage capture mechanism admits a current into the cell

of $J \approx 4NDsc_\infty$. If two-stage capture is to be beneficial, then $J' > J$. What does this condition imply about the adsorption energy?

g) Typical values of $\ln\left(\frac{a^2}{Ns^2}\right)$ and $\frac{\pi d}{s}$ are approximately 10 and 1, respectively. Let us consider the case of $\frac{D'}{D} \approx 0.1$; what value must E_A take for the two-stage capture mechanism to improve the current of X-molecules into X-receptors? Compare this energy to the energy of a hydrogen bond (ranging from 0.04 to 0.22 eV). Would you expect the two stage capture mechanism to improve cell capture rates of certain molecules X?