Problem Set 5   **Assigned: 11.17.04**
Due in class   **Due: 11.30.04**

Do either problem 1 or 2, and do problem 3.

1.   Concentration gradient due to a pipette tip.

A pipette is connected to a reservoir of cAMP at concentration c_p, and its tip is placed in a beaker of water. cAMP begins to diffuse from regions of high concentration to those of low concentration, creating a total flux F out of the reservoir; the resulting drop in the reservoir concentration of cAMP is negligible. Meanwhile, a concentration gradient is set up in the beaker, with [cAMP] = c_p at the pipette tip, and zero far from the tip. The purpose of this problem is to calculate the resulting concentration profile.

(10)   *a.*   Consider a spherical surface of radius r, centered at the pipette tip, through which there flows a flux per unit area $J(r)$ (see Fig. 1). What is the total flux $F(r)$ through this surface?

(10)   *b.*   Since cAMP is neither created nor degraded in the beaker, the total flux through a sphere at any radius must be a constant; that is, $F(r) = F$. What does this imply about $J(r)$?

(20)   *c.*   Fick's first law (with diffusion coefficient set to unity) states that $J(r) = -\partial c(r)/\partial r$. Integrate your answer from part (*b*) to calculate $c(r)$. If r_P is the radius of the pipette tip, then $c(r_p) = c_p$, and $c(\infty)=0$. Calculate the value of F required for $c(r)$ to satisfy these boundary conditions. Give expressions for $c(r)$ and $J(r)$ in terms of c_p, r_p, and r.

(10)   *d.*   A spherical cell of radius ρ_0 is placed a distance R from the pipette tip, with $\rho_0 \ll R$. The flux is therefore nearly constant near the cell, and the concentration changes linearly from the leading edge to the trailing edge of the cell. That is, $J(r) \approx J(R)$, and $c(r) \approx c(R) - J(R) \cdot (r - R)$. We now change coordinates, measuring the distance ρ from the center of the cell and the angle θ from its leading edge (see Fig. 2). Calculate the concentration distribution along the cell surface. You should find

$$c(\rho_0,\theta) = c_p \left[\frac{r_p}{R} + \frac{r_p \rho_0}{R^2} \cos(\theta) \right].$$
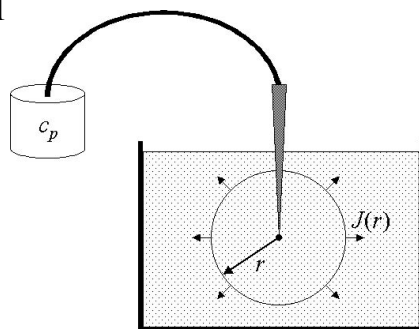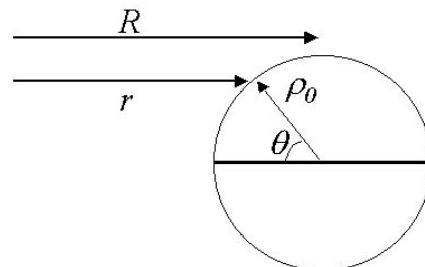
Fig. 1   Fig. 2

2. Cell in a linear concentration gradient

The purpose of this problem is to show how the presence of a cell can influence the distribution of a chemical around it. Consider a linear concentration gradient of some chemical, specified by $c(x, y, z) = c_0 - J_0 x$.

(5) *a.* Using $\vec{J} = -\vec{\nabla}c$, calculate the flux throughout space.

(5) *b.* Consider a spherical surface of radius ρ_0 centered at the origin (see Fig. 2). Show that the concentration along this surface is given by $c(\rho_0, \theta) = c_0 + J_0\rho_0\cos(\theta)$.

(10) *c.* Now introduce a cell of radius ρ_0 centered at the origin. If the cell membrane is impermeable to the chemical under consideration, there will be no radial flux at the cell surface. That is, $\hat{\rho} \cdot \vec{J}(\rho_0, \theta) = -\partial c(\rho,\theta)/\partial\rho\,|_{\rho_0} = 0$. Assuming that the concentration distribution far from the cell remains unchanged, make a sketch comparing the lines of flux before and after the cell is introduced.

(25) *d.* Calculate the new concentration distribution $c(\rho, \theta)$.

Hint: the diffusion equation in steady state gives $0 = \partial c/\partial t = \nabla^2 c$. That is, the concentration distribution $c(\vec{r})$ satisfies Laplace's equation. The problem is therefore analogous to one in electrostatics, with $c \leftrightarrow \varphi$, and $\vec{J} \leftrightarrow \vec{E}$. Outside the sphere, the potential must satisfy Laplace's equation, and reduce to a linear potential at large distances. Inside the sphere, we must add some charge distribution so that the boundary conditions are satisfied. Convince yourself that the introduction of a dipole at the origin provides the right kind of corrrection, and calculate the resulting potential.

(5) *e.* Show that the new concentration distribution along the cell surface has the form $c(\rho_0, \theta) = c_0 + \alpha J_0\rho_0\cos(\theta)$, with some $\alpha > 1$. The cell thus experiences a greater concentration difference across its length than we might have guessed from the unperturbed concentration distribution. Sketch the new concentration distribution along the line $\theta = 0$ to illustrate this effect.

(0) *f.* CHALLENGE. From problem 1 we find that the concentration distribution due to a pipette tip can be written as the potential due to a point charge with $q = c_p r_p$. If the cell is small compared with its distance from the pipette tip, this potential can be approximated as linear, providing the starting point for problem 2. If, however, the cell is large or close to the pipette tip, this approximation does not hold. Calculate the exact concentration distribution due to a pipette tip in the presence of a cell.

3.   Gradient sensing

In problems 1 and 2, we argued that the concentration distribution along the surface of a cell in a linear chemical gradient has the general form $c(\theta) = c_0 + c_1 \cos(\theta)$, with the angle θ measured from the cell's leading edge. We now calculate how the cell might respond to such a stimulus, based on the receptor activation/inactivation model of Levchenko and Iglesias.

This model assumes that two biochemical species, *A* and *I*, are produced in the cell membrane at rates linearly proportional to the extracellular signal concentration $c(\theta)$. The levels of these biochemicals are "read out" by a receptor *R* whose steady state concentration is given by $r_{ss} \approx a/i$ (where lower case letters represent normalized concentrations). Both *A* and *I* undergo first-order decay, and both diffuse along the membrane. The equations describing this system are:

$$\frac{\partial a}{\partial t} = \gamma_a(c(\theta) - a) + D_a \frac{\partial^2 a}{\partial \theta^2} \qquad\qquad \frac{\partial i}{\partial t} = \gamma_i(c(\theta) - i) + D_i \frac{\partial^2 i}{\partial \theta^2}.$$

(15)   *a.*   First assume a uniform concentration situation: $c(\theta) = c_0$. In this case, *a* and *i* will be independent of θ. Calculate the steady state values of *a*, *i*, and $r_{ss} = a/i$. Now suddenly double the signal concentration to $2c_0$. Show that the following expressions satisfy the dynamical equations with the correct initial conditions:

$$a(t) = c_0(2 - e^{-\gamma_a t}) \qquad\qquad i(t) = c_0(2 - e^{-\gamma_i t}).$$

For $\gamma_a = 5$ and $\gamma_i = 1$, plot $r_{ss}(t) = a(t)/i(t)$. Is the system perfectly adapting?

(20)   *b.*   Now assume a linear concentration gradient, so $c(\theta) = c_0 + c_1 \cos(\theta)$. Guess a solution of the form

$$a(\theta, t) = c_0 + \beta_a(t)\cos(\theta) \qquad\qquad i(\theta, t) = c_0 + \beta_i(t)\cos(\theta).$$

Substitute these guesses into the dynamical equations and calculate the steady state values of β_a and β_i. Also write down an expression for $r_{ss}(\theta)$.

(10)   *c.*   Suppose that *A* diffuses very slowly, while *I* diffuses fast. That is,

$$D_a/\gamma_a \ll 1, \qquad\qquad\qquad D_i/\gamma_i \gg 1.$$

What is $r_{ss}(\theta)$ in this limit?

(5)   *d.*   These calculations show that the system is perfectly adapting in uniform concentrations, but polarized in a concentration gradient, matching exipermental observations. Explain in words how this behavior comes about.