1. Diffusion.

   (a) The diffusion constant of water in water is $D = 10^{-5}\text{cm}^2/\text{sec}$. We have interpreted D as $(1/2)\Delta x^2/\Delta t$, where Δx is diffusive step and Δt is the typical time between steps. For water, a typical step will be the diameter of a water molecule, about 0.3 nm. What is the corresponding Δt in picoseconds?

   (b) Suppose a hormone has to diffuse through a cell to activate a gene in the nucleus. A typical diffusion constant for small peptides or drugs is $D = 10^{-6}\text{cm}^2/\text{sec}$. If the diffusion distance is 5 μm, approximately how much time does the hormone require to diffuse to the nucleus?

   (c) Suppose a morphogen has a diffusion constant of $D = 10^{-6}\text{cm}^2/\text{sec}$ and has a lifetime of 1 hr. The distance over which patterning can occur is about equal to its root-mean-square diffusion length over its lifetime. What is this distance? At what developmental stage does a human embryo have this diameter, and how many cells does it have at this point?

2. Morphogen gradient patterning, transient solution. Suppose a morphogen diffuses in one dimension according to the partial differential equation

$$\dot{\rho}(x,t) = D(d/dx)^2\rho(x,t) - \alpha\rho(x,t).$$

   At time 0, the density is concentrated at the origin, $\rho(x,t=0) = n_0\delta(x)$.

   (a) Convert the PDE for $\rho(x,t)$ into an ODE for $\hat{\rho}(k,t)$.

   (b) Evaluate $\hat{\rho}(k,t=0)$ in terms of model parameters.

   (c) Solve the ODE to obtain $\hat{\rho}(k,t)$ in terms of model parameters.

   (d) Use an inverse Fourier transform to obtain $\rho(x,t)$.

   (e) For no decay, $\alpha = 0$, find the time $t^\star(x)$ when $\rho(x,t)$ has its maximum value.

   (f) Whenever you have a diffusion problem, $R^2 = 2Dt$ is a good guess for relating time, distance, and diffusion constant. For the previous problem, a reasonable guess would therefore be $t^\star(x) = x^2/2D$. How does this guess compare to to the analytical answer?

   (g) Evaluate the maximum morphogen density at position x, equal to $\rho(x,t^\star(x))$.

   (h) For threshold K, find the patterning length $x^\star$ defined as $\rho(x^\star,t^\star(x^\star)) = K$.

3. Morphogen gradient patterning, method of images for an absorbing barrier. Suppose a morphogen diffuses in one dimension according to the partial differential equation

$$\dot{\rho}(x,t) = D(d/dx)^2\rho(x,t).$$

   At time 0, the density is concentrated at the origin, $\rho(x,t=0) = n_0\delta(x)$. The cell membrane is at $x = L$. Suppose that morphogens are absorbed and degraded at the cell membrane so that

$\rho(x,t) = 0$ for $x \geq L$. We could model this with an ODE that includes a loss term. Instead, a simpler approach is to consider anti-particles emitted by a source symmetrically located on the other side of the membrane at $x = 2L$. Each time a particle hits the membrane, an anti-particle also hits the membrane and cancels it.

(a) Calculate the density of particles assuming that no membrane exists, $\rho'(x,t)$.

(b) Show that the density of anti-particles assuming that no membrane exists is $\rho''(x,t)$, is

$$(4\pi Dt)^{-1/2} \exp[-(x-2L)^2/4Dt]$$

.

(c) With a membrane, the method of images suggests that the true density $\rho(x,t) = \rho'(x,t) - \rho''(x,t)$ for $x \leq L$, and $\rho(x,t) = 0$ for $x \geq L$. We can use the equality for both parts of the solution because the values should match at both sides of the boundary. Show that this solution satisfies (i) the initial condition; (ii) the diffusion equation for $x < L$; (iii) the boundary condition $\rho(L,t) = 0$.

(d) Define the number of particles remaining at time t as $n(t) = \int_{-\infty}^{\infty} dx\, \rho(x,t)$. What is $\lim_{t\to\infty} n(t)$?

4. Morphogen gradient patterning, method of images for a reflecting barrier. The problem is the same as the previous problem, with an initial density $\rho(x,t=0) = n_0 \delta(x)$, except that morphogens that hit the membrane at $x = L$ are reflected backwards. Here we imagine a second source at $x = 2L$ whose particles add to the density for $x < L$. Define $\rho'(x,t)$ and $\rho''(x,t)$ as before.

   (a) Show that $\rho(x,t) = \rho'(x,t) + \rho''(x,t)$ for $x < L$ and $\rho(x,t) = 0$ for $x > L$ satisfies (i) the initial condition; (ii) the diffusion equation for $x < L$.

   (b) Define $n(t) = \int_{-\infty}^{\infty} dx, \rho(x,t)$. Show that $n(t) = n_0$.

   (c) Evaluate $(d/dx)\rho(x,t)$ as $x \to L$ from the left. The derivative is ill-defined at $x = L$. Since $\rho(x,t) = 0$ for $x > L$, the derivative is 0 as $x \to L$ from the right.

5. Morphogen gradient patterning, two barriers. This is a challenge problem that will not be on an exam. Again the initial density is $\rho(x,t=0) = n_0\delta(x)$, but now there are two barrier, one at $x = L$ and the other at $x = -L$. The barriers are either both absorbing or both reflecting. Use the method of images to motivate a solution for the density $\rho(x,t)$ for $|x| < L$. The reflecting barriers act like mirrors: when you hold up two mirrors opposite each other, they create an infinite series of images.

6. Morphogen gradient patterning, steady-state solution. Suppose a morphogen diffuses in one dimension according to the partial differential equation

$$\dot{\rho}(x,t) = \beta\delta(x) + D(d/dx)^2\rho(x,t) - \alpha\rho(x,t).$$

The steady-state profile is $\rho(x)$ and satisfied the ODE

$$\beta\delta(x) + D(d/dx)^2\rho(x,t) - \alpha\rho(x) = 0.$$

Cells are activated if $\rho(x) > K$. The boundary conditions are that $\rho(x) = (d/dx)\rho(x) = 0$ as $x \to \pm\infty$.

(a) Calculate the Fourier transform of the steady-state profile, $\hat{\rho}(k)$.

(b) The inverse Fourier transform can be calculated using contour integrals closed in the upper or lower half-plane. What are the poles? For $x > 0$, which half-plane is used to close the contour? For $x < 0$, which half-plane?

(c) Perform the inverse Fourier transforms to calculate $\rho(x)$ for positive and negative x.

(d) Determine the patterning length $x^\star$, with $\rho(x^\star) = K$, in terms of model parameters.

(e) As usual, if pressed for time a good guess for the patterning length is to use the relationship $R^2 = 2Dt$. Here we associate t with the mean lifetime of a particle, $t \approx 1/\alpha$, suggesting that the patterning length should scale as $\sqrt{2D/\alpha}$. How does this compare with the analytical solution?

7. Diffusion with drift. Consider a particle that hops at rate k, with probability $1-p$ to hop to the left and probability p to hop to the right. The distance of each hop is always Δx, and the hops are independent and identically distributed. The location of the particle after n hops is $x_n = \sum_{i=1}^{n} \Delta x_i$, where $\Delta x_i = \pm\Delta x$ depending on the direction of the hop. The model parameters are $\{k, p, \Delta x, t\}$.

   (a) How many hops are expected during time t? Choose t so that n hops are expected, and define $x(t) = x_n$.

   (b) Since the hops are independent and identically distributed, $\langle x(t)\rangle = \langle \sum_{i=1}^{n} \Delta x_i\rangle = n\mu$, where $\mu = \langle \Delta x_i\rangle$ for $1 \le i \le n$. Calculate μ and $\langle x(t)\rangle = n\mu$. Redefine $n\mu$ as vt, where v is interpreted as a drift velocity.

   (c) The variance $\text{Var}[x(t)] = \sum_{i=1}^{n} \text{Var}(\Delta x_i) = n\sigma^2$, where $\sigma^2 = \text{Var}\,\Delta x_i$ for $1 \le i \le n$. Calculate σ^2 and $\text{Var}[x(t)]$. What values of p maximize and minimize σ^2?

   (d) For the choice $p = q = 1/2$, show that $\mu = 0$ and $\text{Var}[x(t)] = 2Dt$, where D is the collection of parameters that defines the diffusion constant. The variance is often written as $R^2(t) \equiv \text{Var}[x(t)]$, and we obtain the useful relationship that $R^2(t) = 2Dt$ that often provides a good approximation for solutions to diffusion-related problems.

   (e) Returning to the general case, we still can use the Central Limit Theorem. Since we know $\langle x(t)\rangle$ and $\text{Var}[x(t)]$, we know that the probability distribution for diffusion with drift for a particle at the origin at time 0 must approach the form

$$\begin{aligned}\rho(x,t) &= (2\pi\,\text{Var}[x(t)])^{-1/2}\exp[-(x-\langle x(t)\rangle)^2/2\,\text{Var}[x(t)]] \\ &= (4\pi Dt)^{-1/2}\exp[-(x-vt)^2/4Dt]\end{aligned}$$

as the number of hops becomes large, $kt \gg 1$. In other words, if $x(t=0) = 0$, the probability that $x \leq x(t) < x + dx$ is $\rho(x,t)dx$. Rewrite the solution $\rho(x,t)$ in terms of the model parameters.

(f) Show that in the limits that $p \to 0$ and $p \to 1$, with drift and no diffusion, $\rho(x,t) = \delta(x - vt)$, where $\delta(x - vt)$ is a form of the δ-function. For the purposes of this problem, a δ-function has unit area concentrated at the origin: for $\varepsilon \to 0$ from above, $\delta(x)$ satisfies the properties

$$\begin{aligned} \int_{-\infty}^{-\varepsilon} dx\,|\delta(x)| &= 0; \\ \int_{-\varepsilon}^{\varepsilon} dx\,\delta(x) &= 1; \\ \int_{\varepsilon}^{\infty} dx\,|\delta(x)| &= 0. \end{aligned}$$

(g) A challenge problem that will not be on the exam. Let $\rho(x,t)$ be the Greens function for diffusion with drift, $\rho(x,t) = (4\pi Dt)^{-1/2} \exp[-(x-vt)^2/4Dt]$. This Greens function should be the solution to a continuous-time differential equation,

$$(d/dt)\rho(x,t) = L(D,v)\rho(x,t),$$

where $L(D,v)$ is a linear operator that depends on the diffusion constant and the drift velocity. For this problem we assume that D and v are isotropic and time-independent.

i. Calculate $(d/dt)\rho(x,t)$ for the known form of $\rho(x,t)$.

ii. A formal solution is $\rho(x,t) = \exp[L(D,v)t]\rho(x,0)$. Show that $\rho(x,t)$ is identical to the solution of a two-step process, first diffusion without drift for time t, and then drift without diffusion for time t, or equivalently drift first and then diffusion. Describe how this implies that $\exp[L(D,v)t] = \exp[L(D,v=0)t]\exp[L(D=0,v)] = \exp[L(D=0,v)]\exp[L(D,v=0)t]$. Use this relationship to prove that $L(D,v) = L(D,v=0) + L(D=0,v)$.

iii. For $v = 0$, we know that $L(D,v=0) = D(d/dx)^2$. For $D = 0$, we know that $\rho(x,t)$ is the drift-only solution $\rho(x-vt,0)$ from the previous problem. We also know that $\rho(x-vt,0) = \exp[-vt(d/dx)]\rho(x,0)$ because the operator $\exp[-vt(d/dx)]$ is the exponential form of the spatial-shift operator, which when expanded gives the Taylor's series for $\rho(x-vt,0)$ in terms of derivatives of $\rho(x,0)$. Thus, for $D = 0$, we see that

$$\begin{aligned} (d/dt)\rho(x,t) &= (d/dt)\exp[-vt(d/dx)]\rho(x,0) \\ &= -v(d/dx)\exp[-vt(d/dx)\rho(x,0) \\ &= -v(d/dx)\rho(x,t). \end{aligned}$$

For $D = 0$, then, $L(D=0,v) = -v(d/dx)$. Provide $L(D,v)$ for the general case and show that $L(D,v)\rho(x,t) = (d/dt)\rho(x,t)$ for the known form of $\rho(x,t)$.