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?

   $$D = \frac{1}{2}\frac{\Delta x^2}{\Delta t}$$

   Here we have,

   $$\begin{aligned} D &= 10^{-5}cm^2/sec = 10^{-9}m^2/sec \\ \Delta x &= 3\times 10^{-10}m \\ \\ \Delta t &= \frac{1}{2}\times\frac{3\times 10^{-20}m^2}{10^{-9}m^2/sec} = 4.5\times 10^{-11}\text{ sec} = 45\text{ psec} \end{aligned}$$

   (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?

   $$R(t)^2 = 2Dt$$

   Where $R(t)$ is the diffusion space. Here,

   $$\begin{aligned} R(t) &= 5\mu m \\ D &= 10^{-6}cm^2/sec = 10^{-10}m^2/sec \\ \\ t &= \frac{R(t)^2}{2D} = \frac{25\times 10^{-12}m}{2\times 10^{-10}} = 125\text{ msec} \end{aligned}$$

   (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?
   We will use X_* to denote the paterning distance, and T as the lifetime. We will use the

equation used in previous parts as:

$$
\begin{aligned}
D &= \frac{1}{2}\frac{X_*^2}{T} \\
X_*^2 &= 2DT = 2\times10^{-6}\times10^{-4}\mathrm{m}^2/\mathrm{sec}\times3600\mathrm{sec} \\
X_* &\approx 8.5\times10^{-4}\ \mathrm{m} = 0.85\ \mathrm{mm}
\end{aligned}
$$

Check Wikipedia for the developmental stage.

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 $\hat{\rho}(k,t)$.

$$
\begin{aligned}
\dot{\rho}(k,t) &= D(ik)^2\rho(k,t) - \alpha\rho(k,t) \\
\dot{\rho}(k,t) &= -Dk^2\rho(k,t) - \alpha\rho(k,t)
\end{aligned}
$$

(b) Evaluate $\hat{\rho}(k,t=0)$ in terms of model parameters.
Given the problem set-up, $\hat{\rho}(k,t=0)$ is the number of particles released at the origin at $t=0$.

$$\rho(k,t=0^+) = n_0$$

More specifically,

$$
\begin{aligned}
\rho(x,t=0) &= n_0\delta(x) \\
\rho(k,t=0) &= \int_{-\infty}^{\infty} dx e^{-ikx}\rho(x,t=0) \\
&= \int_{-\infty}^{\infty} dx e^{-ikx} n_0\delta(x) \\
&= n_0
\end{aligned}
$$

(c) Solve the ODE to obtain $\hat{\rho}(k,t)$ in terms of model parameters.
We will find $\hat{\rho}(k,t)$ for $t>0$ by considering the ODE derived in part (a). For $t>0$,

$$\dot{\rho}(k,t) = -(Dk^2+\alpha)\rho(k,t)$$

The following solution satisfies the ODE, and the initial condition $\rho(k,t=0)$:

$$\begin{aligned}\rho(k,t) &= \rho(k,t=0)e^{-(Dk^2+\alpha)t} \\ &= n_0 e^{-(Dk^2+\alpha)t}\end{aligned}$$

(d) Use an inverse Fourier transform to obtain $\rho(x,t)$.
We will use the formula below to derive the inverse Fourier transform integral:

$$\int_{-\infty}^{\infty} e^{-ax^2+bx}dx = \sqrt{\pi/a}e^{b^2/4a}$$

Now we take the inverse Fourier transform of $\rho(k,t)$ as:

$$\begin{aligned}\rho(x,t) &= \int_{-\infty}^{\infty} \frac{dk}{2\pi} e^{ikx} n_0 e^{-(D*k^2+\alpha)t} \\ &= \frac{n_0 e^{-\alpha t}}{2\pi} \int_{-\infty}^{\infty} e^{(-Dt)k^2+(ix)k} dk \\ &= \frac{n_0 e^{-\alpha t}}{2\pi} \sqrt{\frac{\pi}{Dt}} e^{\frac{-x^2}{4Dt}}\end{aligned}$$

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

$$\frac{d\rho(x,t)}{dt}|_{t=t^\star} = 0$$

With $\alpha = 0$ and some simplification:

$$\frac{1}{\sqrt{t}}[\frac{x^2}{4Dt^2}e^{\frac{-x^2}{4Dt}}] + \frac{-1}{2}\frac{1}{t\sqrt{t}}e^{\frac{-x^2}{4Dt}} = 0$$

$$\frac{x^2}{4Dt^2\sqrt{t}} - \frac{1}{2t\sqrt{t}} = 0$$

$$2Dt = x^2$$

$$t^\star = \frac{x^2}{2D}$$

(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?

It's the same!

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

$$\begin{aligned} t^\star(x) &= x^2/2D \\ \rho(x) &\equiv \rho[x, t^\star(x)] \\ &= n_0\sqrt{1/4\pi D t^\star}\exp[-x^2/4Dt^\star] \\ &= n_0\sqrt{1/2\pi x^2}\exp(-1/2) \\ &= n_0/|x|\sqrt{2\pi e} \end{aligned}$$

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

$$\begin{aligned} \rho(x^\star) &= n_0/|x^\star|\sqrt{2\pi e} = K \\ |x^\star| &= n_0/K\sqrt{2\pi e} \end{aligned}$$

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, $\rho'(x,t)$.

$$\rho'(x,t) = \sqrt{1/4\pi Dt}\exp[-x^2/4Dt]$$

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

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

This is the standard result: for an initial density of $\rho''(x,t=0) = \delta(x - x_0)$, the solution to the diffusion equation is

$$\rho''(x,t) = \sqrt{1/4\pi Dt}\exp[-(x-x_0)^2/4Dt].$$

(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 $\rho(L,t) = 0$. (i) The initial condition is satisfied because $\rho'(x,t=0)$ is the delta function and $\rho''(x,t=0)$ is entirely focused on the other side of the barrier and doesn't contribute for $x < L$. (ii) Since ρ' and ρ'' both satisfy the diffusion equation, and diffusion is a linear operator, any linear combination satisfies the diffusion equation. (iii) Notice that $\rho'(x=L,t) = \rho''(x=L,t)$. This means that the difference has to be 0.

(d) Define the number of particles remaining at time t as $n(t) = \int_{-\infty}^{\infty} dx\, \rho(x,t)$. What is $\lim_{t\to\infty} n(t)$? Since the density is 0 beyond the barrier,

$$n(t) = \int_{-\infty}^{L} dx\, \rho(x,t) = \int_{-\infty}^{L} dx, \rho'(x,t) - \rho''(x,t).$$

You should then be able to find using a change of variables for $\rho''(x,t)$ that

$$n(t) = \int_{-L}^{L} dx (1/\sqrt{4\pi Dt}) \exp[-x^2/2Dt],$$

which can be expressed in terms of the error function. Since $\exp[-x^2/2Dt] \leq 1$, and upper limit is

$$n(t) \leq \int_{-L}^{L} dx (1/\sqrt{4\pi Dt}) = 2L/\sqrt{4\pi Dt}.$$

As $t \to \infty$, the remaining density goes to 0 as $1/\sqrt{t}$. For two-dimensional diffusion, I think $n(t)$ also goes to 0. For three-dimensional diffusion and higher, some particles escape.

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 $x < L$. See the previous question; it's all about linear combinations of solutions being solutions also.

(b) Define $n(t) = \int_{-\infty}^{\infty} dx, \rho(x,t)$. Show that $n(t) = n_0$. This is like the preceding questions, except that now we get the full integral rather than just $-L$ to $+L$.

(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. You should see that $(d/dx)\rho'(x = L,t) = -(d/dx)\rho''(x = L,t)$, which means that the derivative of $\rho(x = L,t) = 0$. In general, the derivative of the density is 0 at a reflecting barrier.

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, $\hat{\rho}(k)$.
At steady state:

$$\begin{aligned} \dot{\rho}(x,t) &= \beta\delta(x) + D(d/dx)^2\rho(x,t) - \alpha\rho(x,t). = 0 \\ 0 &= \beta + D(ik)^2\hat{\rho}(k) - \alpha\hat{\rho}(k) \end{aligned}$$

$$\hat{\rho}(k) = \frac{\beta/D}{k^2 + \frac{\alpha}{D}} = \frac{\beta/D}{\left(k + i\sqrt{\frac{\alpha}{D}}\right)\left(k - i\sqrt{\frac{\alpha}{D}}\right)}$$

(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? The poles are $k = \pm i\sqrt{\frac{\alpha}{D}}$.
We will need to calculate the inverse Fourier transform integral as:

$$\rho(x) = \int_{-\infty}^{\infty} \frac{dk}{2\pi} e^{ikx} \frac{\beta/D}{\left(k + i\sqrt{\frac{\alpha}{D}}\right)\left(k - i\sqrt{\frac{\alpha}{D}}\right)}$$

Closing the loop and performing the contour integral implies that we are substituting the integration variable k by $a+ib$ in points outside the real axis.
For the contour integral to remain finite, we will need to have finite e^{ikx} term; the imaginary part of the exponent will be oscillatory. We need to control the real part of the exponent to be negative.

$$e^{ikx} = e^{i(a+ib)x} = e^{iax} \times e^{-bx}$$

For $x > 0$, we will need to close contour integral so that $bx > 0$. Therefore, we will have $b > 0$ which means closing the contour integral in upper half-plane.
For $x < 0$, we will need to close contour integral so that $bx > 0$ again. Thus, we will close the contour integral in the lower half plain to satisfy $b < 0$.

(c) Perform the inverse Fourier transforms to calculate $\rho(x)$ for positive and negative x.
For $x > 0$, we will use contour integration in the upper half-plane, and apply the residue theorem. The integration path forms a counter clock-wise loop around the $k = i\sqrt{\frac{\alpha}{D}}$ pole.

$$\begin{aligned}
\rho(x) &= \int_{-\infty}^{\infty} \frac{dk}{2\pi} e^{ikx} \frac{\beta/D}{\left(k+i\sqrt{\frac{\alpha}{D}}\right)\left(k-i\sqrt{\frac{\alpha}{D}}\right)} \\
&= \frac{1}{2\pi} \times 2\pi i \times \text{res}\left(k = i\sqrt{\frac{\alpha}{D}}\right) \\
&= \frac{\beta/D}{2\sqrt{\frac{\alpha}{D}}} e^{-\sqrt{\frac{\alpha}{D}}x} \\
&= \frac{\beta}{2\sqrt{D\alpha}} e^{-\sqrt{\frac{\alpha}{D}}x}
\end{aligned}$$

Similarly for $x < 0$, we close the contour in the lower half-plane. Please note that this forms a clock-wise loop around the $k = -i\sqrt{\frac{\alpha}{D}}$ pole. Thus, The value of the contour integral will have a sign opposite to that of the residue at the pole.

$$\begin{aligned}
\rho(x) &= \int_{-\infty}^{\infty} \frac{dk}{2\pi} e^{ikx} \frac{\beta/D}{\left(k+i\sqrt{\frac{\alpha}{D}}\right)\left(k-i\sqrt{\frac{\alpha}{D}}\right)} \\
&= \frac{1}{2\pi} \times (-2\pi i) \times \text{res}\left(k = -i\sqrt{\frac{\alpha}{D}}\right) \\
&= \frac{\beta/D}{2\sqrt{\frac{\alpha}{D}}} e^{\sqrt{\frac{\alpha}{D}}x} \\
&= \frac{\beta}{2\sqrt{D\alpha}} e^{\sqrt{\frac{\alpha}{D}}x}
\end{aligned}$$

Notice that the answers for $x > 0$ and $x < 0$ can be summarized as

$$\rho(x) = (\beta/2\sqrt{D\alpha})\exp[-|x|/\sqrt{D/\alpha}].$$

It is good to see that $\rho(x) = \rho(-x)$.

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

$$K = \frac{\beta}{2\sqrt{D\alpha}} e^{-\sqrt{\frac{\alpha}{D}}x^\star}$$
$$x^\star = \sqrt{\frac{D}{\alpha}} \ln\left(\frac{2K\sqrt{\alpha D}}{\beta})\right)$$

(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? We see that the density decays exponentially with length constant $\sqrt{D/\alpha}$. This length scale is close to the root mean square diffusion during lifetime $1/\alpha$.

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 $x(t) = x_n$.

$$n = kt.$$

(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.

$$\mu = (1-p)(-\Delta x) + p(\Delta x) = (2p-1)\Delta x.$$

$$n(2p-1)\Delta x = vt$$
$$v = k(2p-1)\Delta x$$

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

$$\sigma^2 = (\Delta x)^2 - \mu^2 = (\Delta x)^2[1-(2p-1)^2] = (\Delta x)^2[4p(p-1)].$$

The maximum variance is Δx^2 at $p = 1/2$, pure diffusion without drift. The minimum variance is 0 at $p = 0$ or 1, pure drift without diffusion.

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

(e) The remaining parts of this question are challenging and will not be on the final exam. Returning to the general case, we still can use the Central Limit Theorem. Since we know $\langle x(t) \rangle$ and $\mathrm{Var}[x(t)]$, we know that the probability distribution for diffusion with drift for a particle at the origin at time 0 must approach the form

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

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 $\rho(x,t)$.