Chapter 6: Applications of Reaction Mechanisms

Calculate the maximum flux of CO_2 into the ocean by assuming the bulk concentration of CO_2 in seawater is zero and the interfacial concentration of CO_2 is in equilibrium with the atmosphere.

Chemical reaction **networks** are defined by complex systems of coupled rate laws for homogeneous and heterogeneous chemical reactions. The processes can include photochemical reactions and surface catalysis. Understanding reaction networks is necessary for solving many practical problems. Problems in nature often involve spatial separation; chemical concentrations are often not uniform. In this chapter we apply our basic theoretical understanding of chemical kinetics to systems that couple chemical reactions with concentration gradients. Global climate change is a pressing issue that is informed by chemical kinetics. As an example of the coupling of chemical processes and concentration gradients, we discuss the exchange of carbon dioxide across the air/sea interface. The theory that we develop is also applicable to active transport across membranes, which is an important consideration in living cells. **Pharmacokinetics** is the study of the absorption, disposition, metabolism, and excretion of drugs in living organisms. Pharmacokinetics also involves the coupling of concentration gradients and chemical reactions. We will use pharmacokinetics to motivate and illustrate our discussion of spatially dispersed networks. We conclude this chapter with a general discussion of box models, which are a useful way of visualizing spatial and chemical relationships in chemical reaction networks.

6.1 Spatial Variation has an Important Influence on Chemical Kinetics

Detailed balance requires that all reactions run to equilibrium. This necessity creates problems for living systems. The equilibrium states for the production of many biochemicals are not favorable at the levels required for the proper functioning of the cell. The presence of enzyme catalysis does nothing more than hasten the approach to equilibrium. To avoid detailed balance, living cells depend on compartmentalization and active transport processes. In other words, to avoid the equilibrium state, the cell is engineered to support concentration gradients. The proper functioning of cells depends on spatial variations in concentration. Concentration gradients also play an important role in biogeochemical processes.

One of the critical issues in the development of sound energy policies is understanding global CO_2 dynamics. How rapidly will global CO_2 levels adjust to decreases in CO_2 production? The oceans and other surface waters are primary sinks for CO_2. CO_2 enters aquatic systems by diffusion across the concentration gradients at the air/water interface. The CO_2 may then be consumed by chemical reactions and eventually by photosynthesis. Taken together, processes in living cells and global climate change require an understanding of the coupling of chemical kinetics and concentration gradients. With this goal in mind, we first derive Fick's Second Law of diffusion, which determines the change of concentration with time for a system with concentration gradients. We then add in the additional concentration changes that arise from chemical reactions. Using CO_2 transfer across the air/water interface as an example, we then develop a simple model of interfacial diffusion, and then compare the simple model to a model that includes coupled diffusion and chemical reactions.

Diffusion Changes the Concentration: Fick's First Law of diffusion, Eq. 2.3.4, relates the molar flux of a substance to the concentration gradient, $J_m = -D\, dc/dx$. The flux is the time rate of change of the amount of substance across a surface of unit area per unit time. However, we often need to know how the concentration at some point in the solution changes because of the flux. Consider a thin slice of solution, with cross-sectional area A, of thickness dx, Figure 6.1.1. The volume of this thin slice is dV = Adx. Assume a concentration gradient across the sample with a decrease in concentration with increasing x, from left to right. The number of moles in this thin slice, at position x, will increase by diffusion of the substance into the slice from the left over a time interval dt, as given by $J_m(x)$ Adt. Dividing by the volume of the slice gives the change in concentration with time:

$$\frac{dc}{dt} = \frac{J_m(x)A}{Adx} = \frac{J_m(x)}{dx} \qquad 6.1.1$$

where $J_m(x)$ is the flux at position x in the solution.

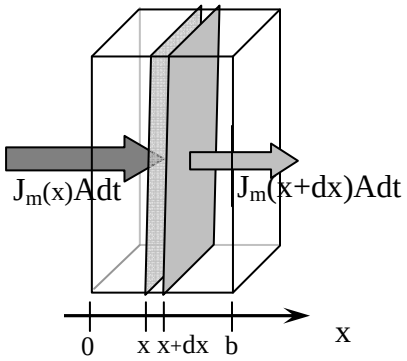


Figure 6.1.1: Diffusion into and out of a thin slice of solution. Fluxes into and out of a thin slice of thickness dx.

The flux leaving the thin slice at (x+dx) is given by:

$$\frac{dc}{dt} = \frac{J_m(x+dx)A}{Adx} = \frac{J_m(x+dx)}{dx} \qquad 6.1.2$$

The net change in concentration is then given by the difference between Eqs. 6.1.2 and 6.1.1:

$$\frac{dc}{dt} = \frac{J_m(x) - J_m(x+dx)}{dx} \qquad 6.1.3$$

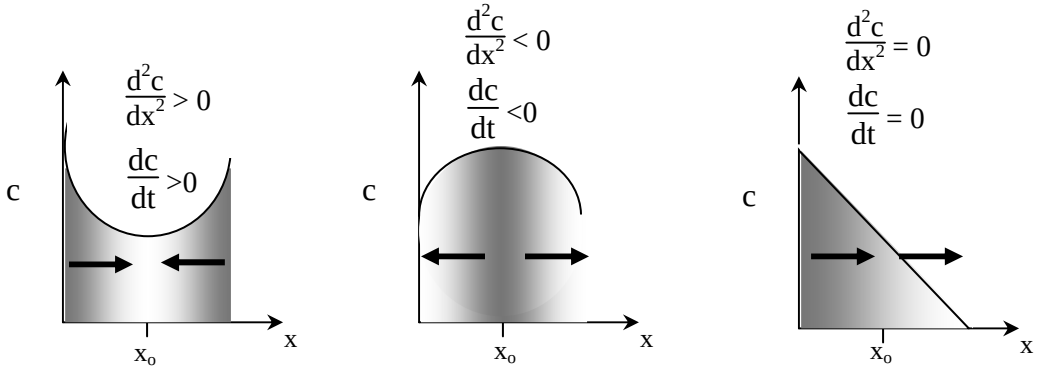
The definition of the derivative of J_m with respect to x is $dJ_m/dx = [J_m(x+dx) - J_m(x)]/dx$. With this definition Eq. 6.1.3 gives:

$$\frac{dc}{dt} = -\frac{dJ_m}{dx} \qquad 6.1.4$$

As a simple starting example, consider the case with no change in flux with distance: $dJ_m/dx = 0$. As you step along the x-axis in Figure 6.1.1, if the flux remains the same, the flux in and out of each slice remains the same giving no net change in concentration: dc/dt = 0. We can obtain a relationship directly in terms of concentration by substitution of $J_m = -D\, dc/dx$ into Eq. 6.1.4:

$$\frac{dc}{dt} = D\frac{d^2c}{dx^2} \qquad 6.1.5$$

The second derivative with respect to distance is the curvature. Remember that a function with a minimum has a positive curvature, and that the flux is from regions of high concentration to regions of low concentration. Consider the point x_o in Figure 6.1.2. The positive curvature at x_o in Figure 6.1.2a causes an increase in concentration with time. Functions with a maximum have negative curvature, Figure 6.1.2b, causing a decrease in concentration. Functions with a constant slope have no curvature; the flux into and out of the region near x_o will be the same, giving no net change in concentration: $d^2c/dx^2 = dJ_m/dx = 0$, Figure 6.1.2c. In other words, in this last case, the flux is uniform because of a purely linear concentration gradient. In Figure 6.1.2a we find that holes fill in and in 6.1.2b we find that peaks spread. In 6.1.2c we note that linear concentration gradients tend to stay linear.



(a) positive curvature (b) negative curvature (c) zero curvature

Figure 6.1.2: The curvature at a point and the concentration change with time have the same sign. (a) If the concentration profile has a minimum, the fluxes from the left and right of x_o increase the concentration. (b) If the concentration profile has a maximum, the fluxes from the left and right of x_o decrease the concentration. (c) For a linear concentration profile, the gradient is linear, and the fluxes are equal.

To be careful we should use the partial derivative symbol $(\partial c/\partial t)_x$ instead of dc/dt to remind us that the concentration is a function of both x and t when we take the derivative with respect to time at a specific position, x. We also need to point out that the derivatives of the concentration with respect to x are taken at constant t:

$$\left(\frac{\partial c}{\partial t}\right)_x = D\left(\frac{\partial^2 c}{\partial x^2}\right)_t \qquad \text{(uniform in y and z)} \quad 6.1.6$$

We will deal more with partial derivatives in the next chapter, if you haven't seen them before. For now, just note that they simply point out the variable that is held constant for the derivative. Eq. 6.1.6 is called **Fick's Second Law** of diffusion, or sometimes just the **diffusion equation**. Eq. 6.1.6 assumes the concentration gradient exists in only the x direction. The y and z directions are assumed to be uniform. Fick's Second Law can be easily generalized to the case with concentration gradients in all three directions. Eq. 6.1.6 is often solved numerically; however

diffusion away from a planar surface can be solved analytically. This planar diffusion model is particularly useful for understanding gas transfer across an air/water interface and other interfacial and chromatographic processes.

Consider a sheet of filter paper coated with a thin layer of a compound immersed in a beaker filled with water. Assume that there are n_o moles on the surface with area A. The compound dissolves and then diffuses into the water, Figure 6.1.3. The x-direction is chosen perpendicular to the sheet with x = 0 at the plane of the sheet. The concentration profile is given as a function of distance and time by:

$$c(x,t) = \frac{n_o}{A\sqrt{4\pi Dt}} e^{-x^2/4Dt} \qquad 6.1.7$$

We will prove that this result is a solution to Eq. 6.1.6. However, first we should understand the behavior of this concentration profile. Figure 6.1.3 shows the profile as a function of time. As time progresses the compound diffuses further into the solution. Eq. 6.1.7 is a specific example of a Gaussian distribution.

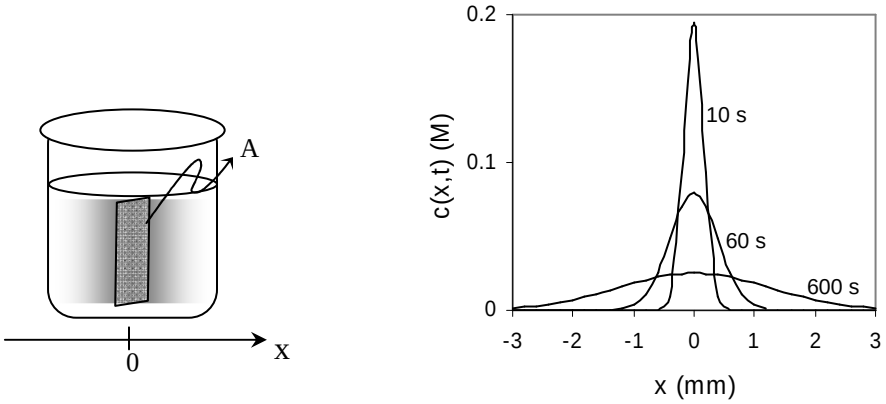


Figure 6.1.3: Concentration profile as a function of time for diffusion from a planar surface for CO_2 in sea water, $D_{CO_2} = 1.35 \times 10^{-9}$ m^2 s^{-1}.

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General Pattern 5: Gaussian Distribution, $e^{-x^2/2\sigma^2}$

The Gaussian distribution, also called the normal distribution, is the classic "bell-shaped" curve that is common in statistics. The general form of a Gaussian distribution is given as:

$$g(x) = \frac{1}{\sigma\sqrt{2\pi}} e^{-(x-\mu)^2/2\sigma^2} \qquad 6.1.8$$

where μ is the average or mean value of x and σ is the standard deviation of the distribution. For a series of measurements, x_i, the mean is given by:

$$\mu = \frac{1}{n}\sum_{i=1}^{n} x_i \qquad 6.1.9$$

and the standard deviation is a measure of the spread of the distribution:

$$\sigma = \left(\frac{1}{n} \sum_{i=1}^{n} (x_i - \mu)^2 \right)^{1/2} \qquad (n \to \infty) \qquad 6.1.10$$

where n is the number of measurements. The standard deviation is an example of a **root-mean-square**. In other words, the standard deviation is the square root of the average of a value that is squared. The square in $(x_i - \mu)^2$ prevents positive and negative deviations from the mean from canceling, which would otherwise give a sum of zero. To obtain a truly representative value for the mean and standard deviation, the number of measurements for the sums in Eqs. 6.1.9 and 6.1.10 must be very large. The resulting statistics are called the **population mean** and **population standard deviation**. If n is small, an estimate of the mean is obtained, which is denoted $\bar{x}$ and is called the **sample mean**. For small n, an estimate of the standard deviation is obtained by the **sample standard deviation**, s, which is defined by:

$$s = \left(\frac{1}{n-1} \sum_{i=1}^{n} (x_i - \bar{x})^2 \right)^{1/2} \qquad (n \text{ small}) \qquad 6.1.11$$

As the number of measurements increases, the sample average and standard deviation approach the underlying population average and standard deviation: as $n \to \infty$, $\bar{x} \to \mu$ and $s \to \sigma$.

In statistics, the probability of occurrence of a given experimental result, x_i, is given by a probability distribution, $P(x_i)$. For example, consider the set of five observations:

Observations: 4, 3, 4, 4, 2

The probability of occurrence of the results is given by the probability distribution, $P(x_i)$:

x_i	$P(x_i)$
0	0/5
1	0/5
2	1/5
3	1/5
4	3/5
5	0/5
sum	5/5

and the probability for any other result is 0/5. The sum of the probabilities is equal to one. Using a probability distribution, the mean and standard deviation in Eqs. 6.1.9 and 6.1.10 can be equivalently calculated by:

$$\mu = \langle x \rangle = \sum_{x_i = -\infty}^{\infty} x_i \, P(x_i) \qquad \sigma = \langle (x - \mu)^2 \rangle^{1/2} = \left(\sum_{x_i = -\infty}^{\infty} (x_i - \mu)^2 \, P(x_i) \right)^{1/2} \qquad 6.1.12$$

where the sum now runs over all possible values of x_i. The brackets, $\langle\rangle$, indicate an average. The sum is appropriate for a discreet set of results. For a continuous variable, the summations in Eqs. 6.1.12 are replaced by integrals, over all possible values of x from $x = -\infty$ to ∞. In particular, assuming a Gaussian distribution, the mean and standard deviation are averages over the probability distribution given by the integrals:

$$\mu = \langle x \rangle = \int_{-\infty}^{\infty} x\, g(x)\, dx \qquad \sigma = \langle (x-\mu)^2 \rangle^{1/2} = \left(\int_{-\infty}^{\infty} (x-\mu)^2\, g(x)\, dx \right)^{1/2} \qquad 6.1.13$$

x is averaged — *$(x-\mu)^2$ is averaged*

The constant, $1/\sigma\sqrt{2\pi}$, in Eq. 6.1.8 is the normalization constant; the constant is specified so that the area under the curve is equal to one:

$$\int_{-\infty}^{\infty} g(x)\, dx = \int_{-\infty}^{\infty} \frac{1}{\sigma\sqrt{2\pi}} e^{-(x-\bar{x})^2/2\sigma^2}\, dx = 1 \qquad 6.1.14$$

In probability applications, normalization just means that the sum of all the probabilities is 100%. Eq. 6.1.8 is plotted in Figure 6.1.4 to highlight the relationship of the standard deviation to the area under the curve and the full-width at half maximum. Integrating g(x) between $x = -2\sigma$ to 2σ gives 0.9544 or 95.44% of the area under the full distribution.

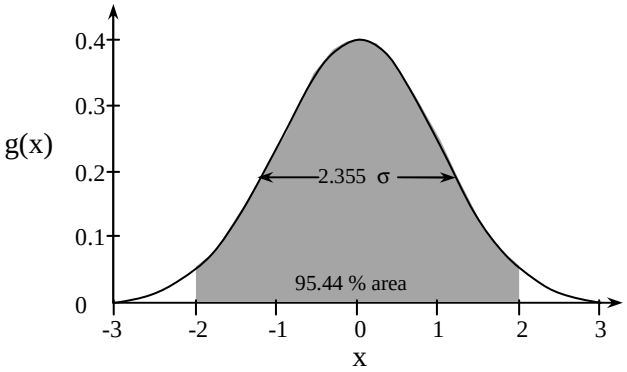


Figure 6.1.4: Gaussian distribution with $\mu = 0$ and $\sigma = 1$.

The maximum value of the distribution, g_{max}, is at the center of the distribution: $g_{max} = g(\mu)$. The half-width at half-maximum, *hwhm*, is given by solving for x from $g(x) = g_{max}/2$:

$$hwhm = \sqrt{2 \ln 2}\ \sigma \qquad 6.1.15$$

and the full-width at half-maximum, *fwhm*, is just twice this value:

$$fwhm = 2\sqrt{2 \ln 2}\ \sigma = 2.355\, \sigma$$
6.1.16

Often the first and second derivatives of the Gaussian function are needed, as in Eq. 6.1.6. Taking the first derivative with respect to x of Eq. 6.1.8 and choosing a zero mean gives:

$$\frac{dg}{dx} = \frac{1}{\sigma\sqrt{2\pi}} \frac{d\left(e^{-x^2/2\sigma^2}\right)}{dx} = \frac{1}{\sigma\sqrt{2\pi}} \left(\frac{-2x}{2\sigma^2}\right) e^{-x^2/2\sigma^2} \qquad 6.1.17$$

This last equation can be written more simply by using the definition of g(x) from Eq. 6.1.8:

$$\frac{dg}{dx} = \left(\frac{-x}{\sigma^2}\right) g \qquad 6.1.18$$

and then the derivative of Eq. 6.1.18 gives the second derivative, using the product rule:

$$\frac{d^2g}{dx^2} = \frac{d\left(\frac{-x}{\sigma^2}g\right)}{dx} = \left[\left(\frac{-x}{\sigma^2}\right)\left(\frac{-x}{\sigma^2}\right)g + \left(\frac{-1}{\sigma^2}\right)g\right] = \left[\left(\frac{x^2}{\sigma^4}\right) - \left(\frac{1}{\sigma^2}\right)\right]g \qquad 6.1.19$$

The Gaussian, or normal, distribution is a very commonly occurring function for several reasons. One reason is the **central limit theorem**, which states that the probability of occurrence of a given value from a continuous, random, and independent set of observations approaches a Gaussian distribution as the number of observations goes to infinity. In other words, for independent, continuous measurements all distributions approach a Gaussian distribution for large data sets. The other reason that the Gaussian distribution is so common is that it is the solution to the diffusion equation, Eq. 6.1.6, and equations of similar form.

How far do molecules move by diffusion? One rough way to answer this question is to determine the width of the concentration profile. Comparing Eq. 6.1.7 to the general form in Eq. 6.1.8, the standard deviation of the concentration profile is related by $2\sigma^2 = 4Dt$, or $\sigma = \sqrt{2Dt}$. The full-width at half-height of the diffusion region is, using Eq. 6.1.15, *fwhm* = $2.355\sqrt{2Dt}$. The Gaussian distribution shows that, in a given time period, most molecules move a short distance and a few move longer distances. So to get a better idea of the distance traveled, we need to take an average. The best way to find the distance traveled is the root-mean-squared, or rms, displacement. Given the probability distribution for the displacement, g(x), the rms displacement is defined as:

$$x_{rms} = \langle x^2 \rangle^{1/2} = \left(\int_{-\infty}^{\infty} x^2\, g(x)\, dx\right)^{1/2} \qquad 6.1.20$$

where the integral calculates the average value of the squared distance traveled. However, we note that this value is just the standard deviation as defined by Eq. 6.1.13, given that the center of the distribution is at x = 0. Using the concentration profile from Eq. 6.1.7 as the probability distribution, the rms displacement is calculated as:

$$x_{rms} = \sigma = \sqrt{2Dt} \qquad 6.1.21$$

Now that we have a better understanding of the result, we now wish to prove that Eq. 6.1.7 is a solution to Eq. 6.1.6. The general approach to such problems is to work on the part of the differential equation to the left of the "=" sign first and then the part to the right. Then we need to show that the result from the left-hand side equals the result from the right-hand side. So starting with the left-hand side of Eq. 6.1.6 (or equivalently 6.1.5) we take the time derivative, keeping x constant. Factoring out the constants and using the product rule:

$$\left(\frac{\partial c}{\partial t}\right)_x = \frac{n_o}{A\sqrt{4\pi D}} \frac{d\left(\frac{1}{t^{1/2}} e^{-x^2/4Dt}\right)}{dt} = \frac{n_o}{A\sqrt{4\pi D}}\left[\left(\frac{1}{t^{1/2}}\right)\left(\frac{x^2}{4Dt^2}\right)e^{-x^2/4Dt} - \left(\frac{1}{2\,t^{3/2}}\right)e^{-x^2/4Dt}\right] \qquad 6.1.22$$

We can simplify the appearance of this equation by substituting in the original definition of the concentration from Eq. 6.1.7:

$$\left(\frac{\partial c}{\partial t}\right)_x = \left[\left(\frac{x^2}{4Dt^2}\right) - \left(\frac{1}{2\,t}\right)\right] c \qquad \text{(lhs)} \quad 6.1.23$$

Now we need to work separately on the right-hand side. Taking the second derivative of Eq. 6.1.7 with respect to distance while keeping t constant, using Eq. 6.1.19 with $2\sigma^2 = 4Dt$, gives:

$$\left(\frac{\partial^2 c}{\partial x^2}\right)_t = \left[\left(\frac{x^2}{4D^2t^2}\right) - \left(\frac{1}{2Dt}\right)\right] c \qquad 6.1.24$$

To find the right-hand side of Eq. 6.1.6, all we need to do is multiply by the diffusion coefficient:

$$D\left(\frac{\partial^2 c}{\partial x^2}\right)_t = \left[\left(\frac{x^2}{4D\,t^2}\right) - \left(\frac{1}{2\,t}\right)\right] c \qquad \text{(rhs)} \quad 6.1.25$$

If Eq. 6.1.7 is a solution to Eq. 6.1.6 then the result of the left-hand side should equal the result of the right-hand side, which we see is the case. Eqs. 6.1.23 and 6.1.25 are equal. Eq . 6.1.7 is a valid solution to the diffusion equation for this problem. Note that we will draw on this general left-hand side then right-hand side then compare procedure many times throughout this course.

Eq. 6.1.7 is useful for a wide variety of problems. The same profile results from chromatography experiments, including gas chromatography, HPLC, and electrophoresis. A small plug of a compound in a chromatography columnl diffuses during the separation according to Eq. 6.1.7. As time progresses, the band spreads in a Gaussian distribution.

Example 6.1.1:
Calculate the distance that a molecule with a diffusion coefficient of $2.0\text{x}10^{-9}$ m^2 s^{-1} travels in 10 minutes.

Answer: Using $2\sigma^2 = 4Dt$ and that the standard deviation is the rms distance:

$$x_{rms} = \sigma = (2Dt)^{½} = (2\,(2.0\text{x}10^{-9}\ m^2\ s^{-1})(600\ s))^{½} = 1.55\text{x}10^{-3}\ m = 1.55\ mm$$

Diffusion is a very slow process, which is why vigorous stirring is required for solution preparation and other lab activities.

Now that we know how to work with diffusion, we can tie together what we know about diffusion and chemical kinetics.

Diffusion and Chemical Reactions Both Change the Concentration. At any point in a system, the net change in concentration for a species is just the sum of the change due to diffusion and any chemical reactions. All we need to do is to add the rate law to Eq. 6.1.6. For species i with stoichiometric coefficient ν_i and reaction rate υ:

$$\left(\frac{\partial c_i}{\partial t}\right)_x = \underbrace{D\left(\frac{\partial^2 c_i}{\partial x^2}\right)_t}_{\textit{diffusion}} + \underbrace{\nu_i\,\upsilon}_{\textit{reactions}} \qquad 6.1.26$$

For example, for a first-order reaction with the species of interest as a reactant, the reaction rate is $\upsilon = -dc_i/dt = k_1 c_i$ and ν_i is -1:

$$\left(\frac{\partial c_i}{\partial t}\right)_x = D\left(\frac{\partial^2 c_i}{\partial x^2}\right)_t - k_1 c_i \qquad \text{(first-order reaction)} \quad 6.1.27$$

diffusion *reactions*

where the concentration now depends on the position and time: $c_i(x,t)$. Note that we have neglected any convection and bulk flow for this equation, but they can be added in if necessary. The absorption of CO_2 by surface waters, other than the obvious importance, is an excellent example of the use of this equation. But, as a point of comparison, we first consider interfacial transfer in the absence of chemical reactions.

Interfacial Diffusion is Determined by the Boundary Conditions: We first need to develop a simple, but very useful, model for the flux of a substance near an interface. For convenience, we will focus on the air-water interface, but the result is also applicable to gas-solid and liquid-solid interfaces as well, under similar conditions. Consider a solution in contact with air. We assume that the gas phase and the bulk of the solution are each well mixed. Let the x-direction be perpendicular to the solution surface with x = 0 at the interface, Figure 6.1.5.

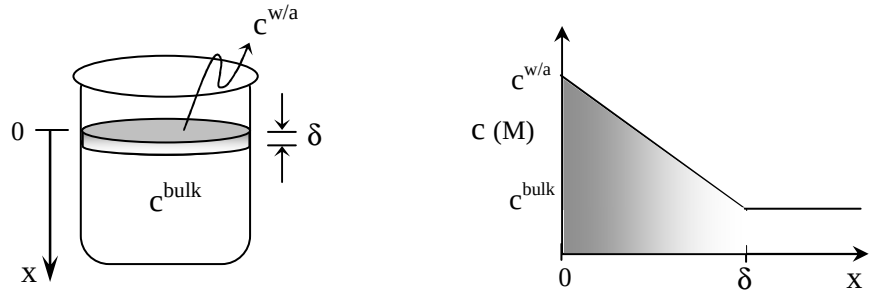


Figure 6.1.5: Stagnant boundary layer model for interfacial gas exchange. The thickness of the boundary layer is δ, the concentration of the solution at the water/air interface is $c^{w/a}$.

Under many circumstances a good approximation is to assume that the solution interfacial region is a thin stagnant layer of thickness δ. It is also often a good approximation to assume that the concentration gradient across this so-called boundary layer is linear, with endpoints between the concentration in solution at the water/air interface at x = 0, $c^{w/a}$, and the concentration of the well-mixed bulk of the solution, c^{bulk}. The concentration gradient is then given by Eq. 2.3.3 as:

$$\frac{dc}{dx} = \frac{c^{bulk} - c^{w/a}}{\delta} \qquad 6.1.28$$

Fick's First Law of diffusion, Eq. 2.3.4, relates the molar flux of a substance to the concentration gradient:[1]

$$J_m = -D\frac{dc}{dx} = -\left(\frac{D}{\delta}\right)(c^{bulk} - c^{w/a}) \qquad 6.1.29$$

where D is the diffusion coefficient for the gas species in the solvent. This model is often called the **stagnant boundary layer** model or the **film diffusion** model. The diffusion coefficient for

CO_2 in the ocean is $D_{CO_2} = 1.35x10^{-9}$ m^2 s^{-1}.[2] For surface waters, the stagnant layer thickness depends on wind velocity, surface state, and convective currents; however, a reasonable range is 600 ± 400 μm for fresh water and about 50 μm on average for the ocean.[3] In the laboratory the thickness of the boundary layer depends on stirring speed; the faster the stirring speed, the thinner the boundary layer, and the larger the flux.

Example 6.1.2:
Calculate the maximum flux of CO_2 into the ocean by assuming the bulk concentration of CO_2 in sea-water is zero and the interfacial concentration of CO_2 is in equilibrium with the atmosphere. To find the interfacial concentration note that the atmosphere is 0.030% by volume CO_2 and the equilibrium solubility of CO_2 in water at 25°C is $3.39x10^{-2}$ M atm^{-1}. Assume the atmospheric pressure is 1.00 atm.[1] A box model representing the process is in Figure 6.1.6.

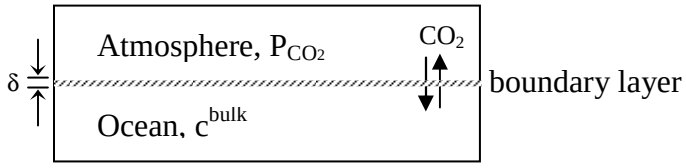


Figure 6.1.6: Box model or reservoir model for CO_2 exchange across the air/sea interface.

Answer: The concentration of CO_2 at the water/air interface in equilibrium with the atmosphere is: $[CO_2]_{eq}^{w/a} = 1.00$ atm $(0.00030)(3.39x10^{-2}$ M $atm^{-1}) = 1.0x10^{-5}$ M

and in mol m^{-3}: $c_{eq}^{w/a} = [CO_2]_{eq}^{w/a} = 1.0x10^{-5}$ M $(1000$ L/1 $m^3) = 1.0x10^{-2}$ mol m^{-3}

The flux is then given by Eq. 6.1.29 using $D_{CO_2} = 1.35x10^{-9}$ m^2 s^{-1} and δ = 50 μm:

$$J_m = -D\left(\frac{c^{bulk} - c^{w/a}}{\delta}\right) = -1.35x10^{-9}\ m^2\ s^{-1}\left(\frac{0 - 1.0x10^{-2}\ mol\ m^{-3}}{50.x10^{-6} m}\right) = 2.7x10^{-7}\ mol\ m^2\ s^{-1}$$

On a yearly basis this flux corresponds to 8.4 mol m^2 yr^{-1}. We can use this flux to find the time necessary on average to exchange all the CO_2 in the atmosphere into the oceans. There are about 100 mol of CO_2 in the column of air above each square meter of the surface of the ocean. Then about (100 mol m^{-2})/(8.4 mol m^2 yr^{-1}) or 12 years are required to exchange all of the CO_2 in the atmosphere with the ocean. Note, however, that when the bulk concentration of CO_2 in the ocean approaches the equilibrium CO_2 solubility, the net flux will drop to zero. At equilibrium the flux into the oceans will be equal to the flux leaving the ocean. Our calculation, so far, neglects any chemical reactions that consume $[CO_2]$ in the boundary layer.

The neglect of chemical reactions in the boundary layer works fairly well for CO_2 absorption by the oceans. However, for accurate predictions and surface waters at higher pH, we also need to consider the effects of chemical reactions.

CO_2 Transport Across the Air/water Interface Couples Diffusion and Chemical Reactions:
When CO_2 dissolves in surface waters the following hydration reaction occurs:

$$CO_2\,(aq) + H_2O \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} HCO_3^- + H^+ \qquad 6.1.30$$

The result is that CO_2 is converted into HCO_3^- in the stagnant boundary layer and the total flux of CO_2 into solution is increased. The contribution of this reaction is dependent on pH. The reverse reaction slows as the pH increases, increasing the net rate of CO_2 hydration. The rate of hydration of CO_2 is then:

$$\upsilon = -\frac{d[CO_2]}{dt} = \frac{d[HCO_3^-]}{dt} = k_1\,[CO_2] - k_{-1}\,[H+][HCO_3^-] \qquad 6.1.31$$

with $\nu_{CO_2} = -1$ and $\nu_{HCO_3^-} = 1$. To determine the steady state fluxes, we can use our old friend the steady state approximation by setting Eq. 6.1.26 equal to zero for both CO_2 and HCO_3^-:

$$D_{CO_2}\left(\frac{\partial^2[CO_2]}{\partial x^2}\right)_t - k_1\,[CO_2] + k_{-1}\,[H+][HCO_3^-] = 0 \qquad \text{(steady state flux)} \quad 6.1.32$$

$$D_{HCO_3^-}\left(\frac{\partial^2[HCO_3^-]}{\partial x^2}\right)_t + k_1\,[CO_2] - k_{-1}\,[H^+][HCO_3^-] = 0 \qquad \text{(steady state flux)} \quad 6.1.33$$

Quinn and Otto[2] and Emerson[3] numerically evaluate these expressions for typical values for natural water. However, for our purposes, we will make simplifying assumptions that, while drastic, will allow us to explore the coupling of diffusion and the chemical reactions in a general way. We assume a stagnant boundary layer model with a constant pH. We assume that the constant pH is maintained by a buffer that does not involve HCO_3^-.

Eqs. 6.1.32 and 6.1.33 show that, at steady state for the fluxes, any increase or decrease in concentration caused by chemical reactions must be countered by diffusion. Since the rate of consumption of CO_2 and the rate of production of HCO_3^- are the same but opposite in sign, adding these last two equations gives:

$$D_{CO_2}\left(\frac{\partial^2[CO_2]}{\partial x^2}\right)_t + D_{HCO_3^-}\left(\frac{\partial^2[HCO_3^-]}{\partial x^2}\right)_t = 0 \qquad \text{(steady state flux)} \quad 6.1.34$$

or rearranging: $$D_{CO_2}\left(\frac{\partial^2[CO_2]}{\partial x^2}\right)_t = -D_{HCO_3^-}\left(\frac{\partial^2[HCO_3^-]}{\partial x^2}\right)_t \qquad \text{(steady state flux)} \quad 6.1.35$$

The only way for Eq. 6.1.35 to hold for this system is if the curvatures for both CO_2 and HCO_3^- are zero. Otherwise, the HCO_3^- concentration would need to drop below the bulk concentration to have opposite curvature from the CO_2 concentration (if not zero, one progresses towards a minimum while the other progresses to a maximum). Zero curvature corresponds to a linear gradient; we then assume a linear concentration gradient for both CO_2 and HCO_3^-. The boundary conditions at the water/air interface are $[CO_2](0) = [CO_2]^{w/a}$ and $[HCO_3^-](0) = [HCO_3^-]^{w/a}$. However, we don't know $[HCO_3^-]^{w/a}$. Since the curvature is zero in Eq. 6.1.32, the reaction rate term must also be zero. In this approximation, then, the reaction is also found to be at steady state for all values of x. Therefore, at the water/air interface:

$$k_1\,[CO_2]^{w/a} - k_{-1}\,[H^+][HCO_3^-]^{w/a} = 0 \qquad \text{(steady state reaction)} \quad 6.1.36$$

giving: $$\frac{[HCO_3^-]^{w/a}}{[CO_2]^{w/a}} = \frac{k_1}{k_{-1}\,[H^+]} \qquad \text{(steady state reaction)} \quad 6.1.37$$

The total flux of CO_2 from the atmosphere, J_T, is the sum of the terms for CO_2 and HCO_3^- since both result from absorption of CO_2 from the gas phase. The flux for each species is calculated from Fick's First Law, $J_m = -D\, dc/dx$, and Eqs. 6.1.29 for each species:

$$J_T = J_{CO_2} + J_{HCO_3^-}$$
$$= -\frac{D_{CO_2}}{\delta}([CO_2]^{bulk} - [CO_2]^{w/a}) - \frac{D_{HCO_3^-}}{\delta}([HCO_3^-]^{bulk} - [HCO_3^-]^{w/a})$$

(steady state flux) 6.1.38

In the absence of the chemical reaction the flux, J_o, is given by just the first term:

$$J_o = -\frac{D_{CO_2}}{\delta}([CO_2]^{bulk} - [CO_2]^{w/a}) \qquad \text{(steady state flux)} \quad 6.1.39$$

To find the maximum flux, we set the bulk concentrations to zero as we did in Example 6.1.2. The enhancement of the total flux by the chemical reaction is then defined as:

$$\frac{J_T - J_o}{J_o} = \frac{D_{HCO_3^-}[HCO_3^-]^{w/a}}{D_{CO_2}[CO_2]^{w/a}} \qquad \text{(steady state flux, max)} \quad 6.1.40$$

using Eqs. 6.1.38 and 6.1.39. Substitution of Eq. 6.1.37 for the concentration ratio then gives the maximum enhancement as:

$$\frac{J_T - J_o}{J_o} = \frac{D_{HCO_3^-}}{D_{CO_2}} \frac{k_1}{k_{-1}[H^+]} \qquad \text{(steady state, max)} \quad 6.1.41$$

The diffusion coefficients of CO_2 and HCO_3^- are approximately the same.[4] The ratio k_1/k_{-1} is the acid dissociation constant for CO_2:[3] $K_1 = 4.45 \times 10^{-7}$. The predicted pH dependence agrees with our reasoning from reaction Eq. 6.1.30; the enhancement increases with increasing pH. At neutral pH the enhancement predicted by this simple model is significant, ~4.45. However, more complete numerical calculations for natural waters predict the enhancement at pH 7 to be smaller, in part because the pH is not constant across the boundary layer if the system is not buffered by a non-carbonate buffer.[5] For natural waters we also need to consider the additional equilibrium,[2] $CO_2\,(aq) + OH^- \rightleftarrows HCO_3^-$. However, our model for CO_2 transfer across the air/water interface is a good first step in understanding the coupling of chemical reaction rates with concentration gradients.

For membrane systems, the membrane is completely analogous to the boundary layer in these models. Therefore, similar models can be constructed to explain CO_2, O_2, and CO exchange into the blood.[5,6] Such models are useful in understanding lung function. Membrane transport in batteries and fuel cells as well as surface catalysis can be handled in an analogous fashion.

Diffusion in Discontinuous Systems Can Be Approximated As a First-Order Process: The study of chemical reaction models is greatly simplified if all processes can be written as first-order processes. We now show that diffusion can often be adequately approximated as a first-order reversible process, which allows diffusive mass transport to be easily included in reaction models. Consider two well-stirred compartments with concentrations c_1 and c_2 that are separated by a membrane or an interfacial boundary layer, Figure 6.1.7. The flux through the boundary layer, assuming a linear gradient, is given either by Eq. 2.3.4 or analogously with Eq. 6.1.29:

$$J_m = -D\frac{dc}{dx} = -\left(\frac{D}{\delta}\right)(c_2 - c_1) \qquad \text{(linear gradient)} \quad 6.1.42$$

with D the diffusion coefficient in the boundary layer or membrane.

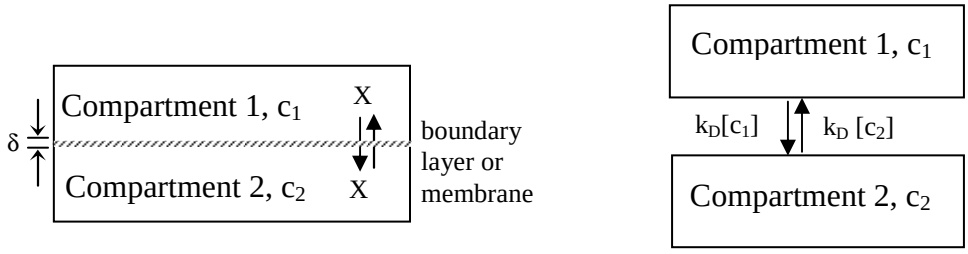


Figure 6.1.7: Equivalent ways of illustrating diffusive transport. From the point of view of the compartments, diffusion can be treated as a first-order process, assuming a boundary layer model and the compartments are well-mixed.

We have been focusing on the flux within the boundary layer. Now we shift our focus to the concentrations of the two compartments. The flux acts over the surface area of the boundary layer, $\mathcal{A}$, giving the changes in moles as:

$$\frac{dn_1}{dt} = -J_m \mathcal{A} = \left(\frac{D}{\delta}\right)\mathcal{A}\,(c_2 - c_1) \qquad \text{and} \quad \frac{dn_2}{dt} = J_m \mathcal{A} = -\left(\frac{D}{\delta}\right)\mathcal{A}\,(c_2 - c_1)$$

(discontinuous, linear interface) 6.1.43

The overall signs are opposite because as the flux depletes compartment 1, the concentration increases in compartment 2. Defining the effective mass transport coefficient as $k_D = D\mathcal{A}/\delta$ and using $n_1 = X_1$, $n_2 = X_2$, $c_2 = [X_2]$ and $c_1 = [X_1]$, as is conventional in chemical rate laws, allows these last equations to be written as reversible first-order processes that are in the same form as chemical rate laws:

$$\frac{dX_1}{dt} = -k_D [X_1] + k_D [X_2] \qquad \text{and} \quad \frac{dX_2}{dt} = k_D [X_1] - k_D [X_2]$$

(discontinuous, linear interface) 6.1.44

In working with heterogeneous systems or systems in several compartments, it is often preferable to work with moles directly instead of concentrations. Given the volumes of the two compartments V_1 and V_2, the corresponding changes in terms of moles from Eqs. 6.1.43 are:

$$\frac{dX_1}{dt} = \left(\frac{D}{\delta}\right)\mathcal{A}\left(\frac{X_2}{V_2} - \frac{X_1}{V_1}\right) \qquad \text{and} \quad \frac{dX_2}{dt} = -\left(\frac{D}{\delta}\right)\mathcal{A}\left(\frac{X_2}{V_2} - \frac{X_1}{V_1}\right)$$

(discontinuous, linear interface) 6.1.45

Defining the effective mass transport coefficients as:

$$k_{D1} \equiv D/\delta\,(\mathcal{A}/V_1) \qquad \text{and} \qquad k_{D2} \equiv D/\delta\,(\mathcal{A}/V_2) \qquad 6.1.46$$

recasts these last equations into a form that is analogous with chemical reaction rate laws:

$$\frac{dX_1}{dt} = -k_{D1} X_1 + k_{D2} X_2 \qquad \text{and} \quad \frac{dX_2}{dt} = -k_{D2} X_2 + k_{D1} X_1$$

(discontinuous, linear interface) 6.1.47

Note that $k_{D2}/k_{D1} = V_1/V_2$. All the standard chemical kinetics methods that we have developed can then be applied to problems that couple interfacial diffusion and chemical kinetics. Notice the $\mathcal{A}/V$ term is analogous to the a/V, A/V, and σ/V terms in bulk flow, photochemical, and heterogeneous catalysis rates, Eqs. 6.2.5, 5.1.6, 5.1.10, and 5.5.6. These A/V terms allow the conversion of flux units to concentration units.

Fick's Second Law is often difficult to solve analytically. The approximation that we used in Eqs. 6.1.43-6.1.47 avoids explicitly solving Fick's Second Law within the compartments by assuming uniform concentrations separated by a boundary layer. Such a system is called a **discontinuous system**, since the concentration changes abruptly across the interface between the two solutions. We still need to solve Fick's Second Law within the boundary layer, but first-order, reversible, mass transfer between compartments is a good approximation if the concentrations are uniform in the compartments. The assumption of a discontinuous system is a common trick for simplifying systems governed by linear flux-force relationships.

Figures 6.1.6 and 6.1.7 are represented as box models. Box models help us visualize complex systems and can be useful for representing systems that couple spatial separation with chemical reactions.

6.2 Box Models

Box models are commonly used tools for visualizing the relationships represented by systems of differential equations, Figure 4.4.1. As we have seen, a reaction mechanism can be pictured as a series of reservoirs, one for each reactant or product, that fill and empty as the reaction progresses. These models are examples of box models. However, the true utility of box models arises when chemical reactions are subject to spatial separations. We will highlight some of the general principles in using box models to understand complex series of chemical reactions in spatially dispersed systems. We start by discussing a few specific examples in the context of the drug discovery process. We then present a general pattern that summarizes some of the properties of box models. Box models are applicable to a wide variety of fields.

Pharmacokinetics: **Pharmacokinetics** is the study of the absorption, disposition, metabolism, and excretion (**ADME**) of drugs in living organisms.[7] Pharmacokinetics uses chemical kinetics and chemical transport properties as tools to predict the time variation of drug levels in the body. The prediction of the ADME properties of new candidate drugs (pharmaceutical **lead compounds**) is used to anticipate drug distribution problems. For example, if a compound is poorly soluble in water, getting the drug to the desired tissues in the body will be a difficult problem. The principal purpose is to shorten the drug discovery and development process.

A little of the terminology of pharmacology will be helpful for our examples. A **bolus dose** is a drug given in a single time-point addition, for example by intravenous injection or oral tablet administration. **Infusion** is the administration of a drug at a constant rate over a long period of time, for example by an intravenous drip. A system with a continuous input is called an open system. A **compartment** is a portion of the body that acts as a homogeneous reservoir for a particular drug. The mixing time within the compartment is assumed to be short compared to the flow of the drug into or out of the compartment. The components of a given compartment can vary from drug to drug. Common components include the blood plasma, extracellular water, liver, kidneys, and adipose tissue, which may combine or act separately. The boundaries between the compartments are membranes or flow restrictions. Alternate names for compartments in drug discovery applications are organs and tissues. In other fields compartments may be called

reservoirs, beakers, flow reactors, and most generally **boxes**, hence the name **box models**. Drug **disposition** is characterized by the amount of drug or concentration in each of the compartments. The disposition is determined by the balance of **distribution** of the drug after absorption from the site of administration and **elimination**. Elimination occurs through excretion and metabolism. Metabolism is where chemical reaction kinetics interfaces with pharmacokinetics. A major metabolic site in the body is the liver.

In multi-compartment problems, for consistency with mass transport processes (Section 6.1), the rate laws are usually written in terms of moles instead of concentrations. The typical first-order rate law:

$$\upsilon = \frac{1}{V}\frac{d\xi}{dt} = k_1 [X] \qquad 6.2.1$$

is multiplied by the volume of the solution in the compartment:

$$\frac{d\xi}{dt} = \frac{1}{\nu_x}\frac{dX}{dt} = k_1 V\left(\frac{X}{V}\right) = k_1 X \qquad \text{or} \quad v = \frac{1}{\nu_x}\frac{dX}{dt} = k_1 X \qquad 6.2.2$$

which is <u>independent</u> of the volume of the solution. We use "v" for the rate expressed in moles. The rate law can be written in terms of concentrations or moles directly, as we did with diffusion in Eq. 6.1.47. In pharmacokinetics, the volume of a compartment is often not known. Working with moles avoids needing to know the volume of a given compartment. In the equations that follow, we will continue to use [X] when writing rate laws. Just remember that for single compartment systems or compartments with equal volumes, you can work with concentrations, but for multi-compartment systems just switch the units to moles. A pseudo-first order rate law results from $dX_1/dt = (k_2[X_2])\, X_1$, with $k_{eff} = k_2[X_2]$.

Most drug absorption, disposition, metabolism, and excretion processes can be adequately modeled by first-order or pseudo-first order kinetics. In other words, the mass transfer and metabolic chemical reactions are taken to be first-order processes (see Problem 3.10). Mixing within each compartment and mass transfer between compartments is by bulk flow driven by blood circulation, diffusion, and/or convection. The mass transfer fluxes into and out of each compartment are considered to be slow compared to mixing within each compartment, so the compartments maybe considered as discontinuous.

Steady state Box Models: A one-compartment model for drug disposition is shown in Figure 6.2.1a. Box models can be visualized more generically as flows into and out of reservoirs, as in Figure 6.2.1b. There are two types of box models, dynamic and static, or steady state. Let's begin with a very simple steady state model. Assume that the flow of drug into the compartment, υ_+, is constant. This could be arranged by intravenous infusion. The net change of concentration of the drug, d[X]/dt, in the compartment is the difference in the rate due to flow into the compartment, υ_+, and flow out of the compartment, υ_-:

$$\upsilon = \frac{d[X]}{dt} = \upsilon_+ - \upsilon_- \qquad 6.2.3$$

For a steady state, the flow into the compartment must be equal to the total flow out of the compartment, υ_+:

$$\upsilon_+ = \upsilon_- \qquad \text{(steady state)} \qquad 6.2.4$$

Steady state means that the concentration of all species in the compartment remain constant, d[X]/dt = 0. However, it is important to remember that the system is not at equilibrium, since the input process is not the exact reverse of the output process (water doesn't flow back up the inlet pipe in Figure 6.2.1). The system is in a metastable, steady state. A very commonly used characteristic of steady state systems is the residence time. The **residence time** is the average time that a species spends in the compartment. The residence time can be calculated by:

$$\tau_{res} = \frac{[X]}{\upsilon_-} \qquad 6.2.5$$

To help with this concept, consider the following analogy, which is taken from the excellent introduction to environmental modeling by John Harte.[8] Assume the graduation rate on average for a college is 400 students yr^{-1} and the total enrollment at the school is 1600 students. What is the average residence time for the school? Eq. 6.2.5 gives τ_{res} = enrollment/graduation rate = 4 years. Note that the exchange time for CO_2 in the atmosphere that we calculated in Example 6.1.2 is, in fact, a residence time.

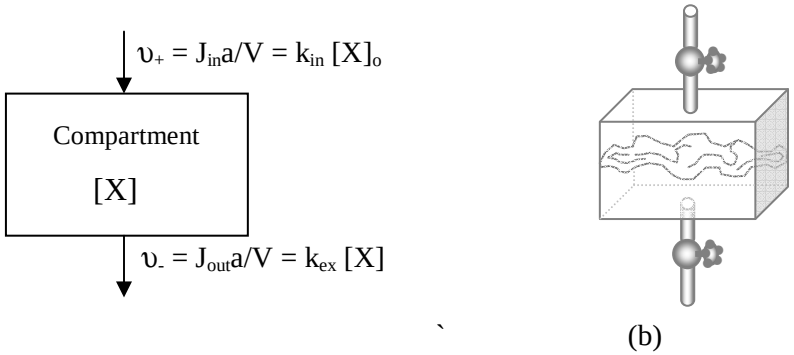


Figure 6.2.1: Box model for drug disposition assuming no metabolic reactions. (a) J_{in} is the input flux and J_{out} is the output flux. (b) The concentration of the drug can be represented as the level of fluid in a reservoir.

For the single-box model in Figure 6.2.1, assume that the flux into the compartment is constant, J_{in}. If the effective cross-sectional area for the flux into the compartment is "a" and the volume of the compartment is V, then the rate of change of the concentration from the inflow is given by $J_{in}a/V$. The input can alternately be written as a rate constant for mass transfer multiplied by the concentration of the drug, $[X]_o$, in the stream flowing into the compartment:

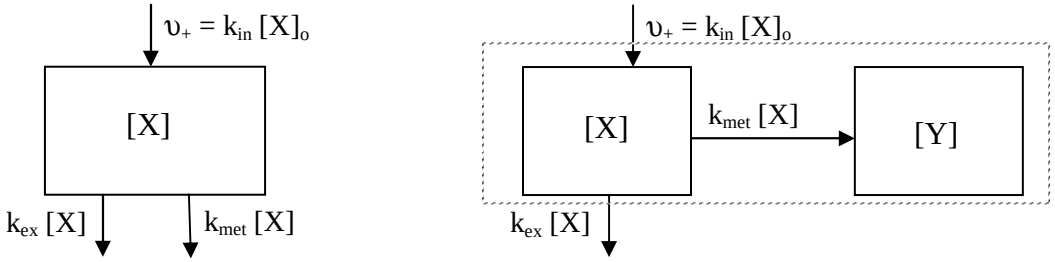
$$\upsilon_+ = J_{in}a/V = k_{in}[X]_o \qquad 6.2.6$$

We often use the "$k_{in}[X]_o$" form for the mass transfer fluxes because of the similarity to the terms in a chemical rate law. The flux out of the compartment, excretion, is also by bulk flow and $\upsilon_- = J_{out}a/V = k_{ex}[X]$. The differential equation is then:

$$\frac{d[X]}{dt} = k_{in}[X]_o - k_{ex}[X] \qquad 6.2.7$$

where [X] is the concentration in the compartment. At steady state, d[X]/dt = 0, $[X] = [X]_{ss}$ and the steady state concentration of the drug is $[X]_{ss} = k_{in}[X]_o/k_{ex}$.

Now let's combine the spatial aspects of the one compartment box model with a metabolic chemical reaction, $X \rightarrow Y$ with rate constant k_{met}. The decrease in concentration of the drug in the single compartment is by bulk flow and through the metabolic reaction, Figure 6.2.2.



(a). One-box model (b). Two-box model

Figure 6.2.2: Equivalent box models for drug disposition with a metabolic reaction. The total loss rate for the drug is given by $\upsilon_- = k_{ex}[X] + k_{met}[X]$.

Either a one-box or a two-box model can be used to visualize this system. In general, an output sink, as in Figure 6.2.1a, or a receiving box with a unidirectional input gives the same underlying differential equation for the central box. The differential equation with the chemical reaction is, assuming all first-order processes:

$$\frac{d[X]}{dt} = k_{in}[X]_o - k_{ex}[X] - k_{met}[X] \qquad 6.2.8$$

At steady state the concentration of the drug is constant and:

$$\frac{d[X]}{dt} = k_{in}[X]_o - k_{excretion}[X]_{ss} - k_{met}[X]_{ss} = 0 \qquad \text{(steady state)} \quad 6.2.9$$

or $$k_{in}[X]_o = k_{ex}[X]_{ss} + k_{met}[X]_{ss} \qquad \text{(steady state)} \quad 6.2.10$$

which is to say that the drug inflow is equal to the total drug outflow:

$$\upsilon_+ = \upsilon_- \qquad \text{(steady state)} \quad 6.2.11$$

Solving Eq. 6.2.10 for $[X]_{ss}$, the steady state concentration of the drug is:

$$[X]_{ss} = \frac{k_{in}}{(k_{ex} + k_{met})}[X]_o \qquad \text{(steady state)} \quad 6.2.12$$

The residence time can be calculated by substitution of this last equation into Eq. 6.2.5 and noting that at steady state, $\upsilon_+ = \upsilon_- = k_{in}[X]_o$:

$$\tau_{res} = \frac{[X]}{\upsilon_-} = \frac{\left(\frac{k_{in}[X]_o}{k_{ex} + k_{met}}\right)}{k_{in}[X]_o} = \frac{1}{(k_{ex} + k_{met})} \qquad \text{(steady state)} \quad 6.2.13$$

In other words, the steady state concentration of the drug is decreased and its residence time is shortened by the metabolic removal of the drug, as you might expect. Just as for a competitive chemical reaction, comparing Eqs. 4.1.14 and 6.2.13 gives $1/\tau_{res} = k_{ex} + k_{met} = 1/\tau_{ex} + 1/\tau_{met.}$ The important conclusion is that we can model mass transport in a way analogous to chemical

reactions. All the methods that we have developed for chemical reaction kinetics can be used for modeling spatial dependence.

Dynamic Box Models: There are two general types of dynamic models. The first type corresponds to a bolus dose; in other words, the normal kind of kinetics experiment that we have been considering in the previous sections for non-flowing systems. For a bolus-dose the differential equation in Eq. 6.2.8 reduces to:

$$\frac{d[X]}{dt} = -k_{ex}[X] - k_{met}[X] \qquad 6.2.14$$

with the initial concentration of the drug, $[X]_o$, as determined by the single time-point dose. This rate law is equivalent to a parallel reaction mechanism with time course given by Eq. 4.1.5:

$$[X] = [X]_o e^{-kt} = [X]_o e^{-(k_{ex}+k_{met})t} \qquad 6.2.15$$

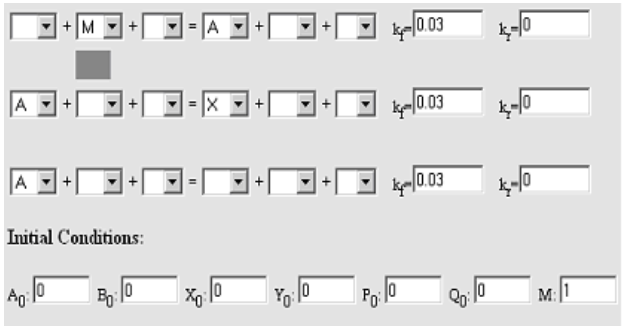
Box models with rate laws that have only first-order terms are called **linear** models. The time course for a linear single-box model is a simple exponential decay with a single time constant, which in our example is $\tau = 1/(k_{ex} + k_{met})$. Notice that this result is analogous to the lifetime for a purely chemical, parallel mechanism, Eq. 4.1.14, and also a parallel photochemical process, Eq. 5.1.31.

The second type of dynamic experiment is an open system with constant inflows. These dynamic systems often evolve towards a steady state.

Example 6.2.1:
Find the steady state concentration of a drug and the residence time for the model in Figure 6.2.2 if $k_{in} = k_{ex} = k_{met} = 0.030\ min^{-1}$, and $[X]_o = 1.00\ \mu M$. Use the "Kinetics Mechanism Simulator" or other simultaneous differential equations solver utility. What would the steady state concentration of the drug be if there was no metabolic process?

Answer: To find the steady state concentration we run the simulation until the concentration of the drug is constant.

www Using the "Kinetics Mechanism Simulator," we need to use a constant concentration source for the inflow, which is signified as "M" in this applet (and "N" if you need two constant concentration sources). Let the drug be represented by species A and the metabolite by X. Flow out of the box is represented by the third reaction, which has no product. We will start with $[A]_o$= 0 and let the system come into steady state. The settings are shown below:



After 150 min with 7500 steps, the concentration of [A] reaches 0.500 μM. The residence time using Eq. 6.2.13 is:

$$\tau_{res} = \frac{1}{(k_{ex} + k_{met})} = \frac{1}{(0.03\ min^{-1} + 0.03\ min^{-1})} = 17\ min$$

If $k_{met} = 0$, then $[A]_{ss} = [M]$.

6.3 Linear Multiple-Box Models

Let's return to spatial dispersion only, and consider another important pharmacokinetic model. Consider the case where disposition of a drug takes place between two compartments.[9] Compartment 1 is the plasma and compartment 2 is filled slowly and reversibly from the plasma, Figure 6.3.1. This second compartment might be the liver. Environmental examples of a similar two-reservoir model are the carbon dioxide distribution at the air/water interface or alternatively the transport of moisture and pollutants across the planetary boundary layer.

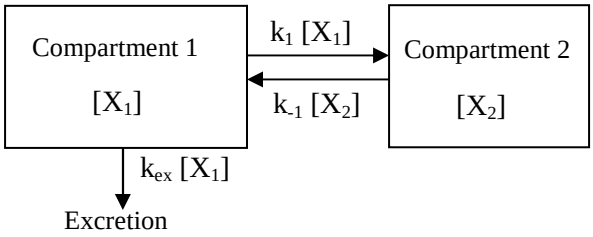


Figure 6.3.1: Two-compartment box model for drug disposition.

The concentration of the drug in compartment 1 is $[X_1]$ and in compartment 2 is $[X_2]$. The rate constant for mass transfer from compartment 1 to 2 is k_1, for transfer from compartment 2 to 1 is k_{-1}, and for excretion is given by k_{ex}. Excretion only occurs from compartment 1. We consider a dynamic model that corresponds to the response after a bolus dose, with the initial concentration in compartment 1 given by $[X_1]_o$ with compartment 2 having $[X_2]_o = 0$.

The rate laws for this model are:

$$\upsilon_1 = \frac{d[X_1]}{dt} = -k_{ex}[X_1] - k_1[X_1] + k_{-1}[X_2] \qquad 6.3.1$$

$$\upsilon_2 = \frac{d[X_2]}{dt} = k_1[X_1] - k_{-1}[X_2] \qquad 6.3.2$$

The response of a linear single-box model is an exponential decay with a single time constant. Is the response of a two-box model given by the sum of two exponential terms? For linear systems, the answer is yes. As we have seen, integrating complex rate laws can be cumbersome. A method has been developed by Wei and Prater that allows the straightforward and automatic integration of simultaneous linear kinetic equations.[10-12] Matrix algebra comes to the rescue.

The Wei-Prater Method for Multiple Box Models: The method is essentially based on a Taylor expansion. The first step is to rewrite Eqs. 6.3.1 and 6.3.2 as a matrix equation. The rate matrix,

$\underset{\approx}{K}$, is defined as the matrix of rate constants, where the rows label the rate law and the columns label the chemical species. For our example, from Eq. 6.3.1 and 6.3.2:

$$\underset{\approx}{K} = \begin{pmatrix} -(k_{ex} + k_1) & k_{-1} \\ k_1 & -k_{-1} \end{pmatrix} \qquad 6.3.3$$

The rates and concentrations can be formed into corresponding vectors. Using the same symbols as is Section 5.2:

$$\left(\frac{d[\underset{\sim}{X}]}{dt}\right) = \begin{pmatrix} \frac{d[X_1]}{dt} \\ \frac{d[X_2]}{dt} \end{pmatrix} \quad \text{and} \quad [\underset{\sim}{X}] = \begin{pmatrix} [X_1] \\ [X_2] \end{pmatrix} \qquad 6.3.4$$

and then the simultaneous first-order equations in Eq. 6.3.1 and 6.3.2 can be written:

$$\left(\frac{d[\underset{\sim}{X}]}{dt}\right) = \underset{\approx}{K}\,[\underset{\sim}{X}] \qquad 6.3.5$$

The formal solution to this equation is:[10-12]

$$[\underset{\sim}{X}] = [\underset{\sim}{X}]_o\, e^{\underset{\approx}{K}t} \qquad 6.3.6$$

which is analogous to the integrated rate law for simple first-order kinetics. At first this equation might look a bit confusing, because of the matrix in the exponent. However, remember that the exponential function is just a nickname for the power series:

$$[\underset{\sim}{X}] = [\underset{\sim}{X}]_o\left(\underset{\approx}{I} + \underset{\approx}{K}\,t + \frac{\underset{\approx}{K}^2 t^2}{2!} + \ldots\right) \qquad 6.3.7$$

The first two terms of the series, $[\underset{\sim}{X}]_o(\underset{\approx}{I} + \underset{\approx}{K}\,t)$, are just the finite difference approximation, in matrix form, that we used earlier in Eq. 4.1.19. For linear systems Eq. 6.3.7 can be rearranged and recast as a sum of exponentials:

$$[\underset{\sim}{X}] = [\underset{\sim}{X}]_o(\alpha_1 \underset{\sim}{C}_1 e^{\lambda_1 t} + \alpha_2 \underset{\sim}{C}_2 e^{\lambda_2 t} + \ldots) \qquad 6.3.8$$

where the λ_i values are composite rate constants and the $1/\lambda_i$ values give the time constants for the course of the reaction. The α_i are scalar coefficients (in other words, they are not vectors) that are fixed by the boundary conditions. When $t = 0$, $[\underset{\sim}{X}] = [\underset{\sim}{X}]_o$, and Eq. 6.3.8 reduces to:

$$[\underset{\sim}{X}]_o = \alpha_1 \underset{\sim}{C}_1 + \alpha_2 \underset{\sim}{C}_2 + \ldots \qquad 6.3.9$$

The formulation in Eq. 6.3.8 conveniently allows us to model complicated processes as a sum of a few exponential processes. The number of required terms and corresponding time constants is dependent on the problem; however, we might anticipate that we will need two terms for our two-box model. The alternative approach is to use finite difference simulations; however, the analytical solution in Eq. 6.3.8 is chemically more intuitive than the tables of concentrations output from numerical simulations. Mathematically the λ_i are calculated as the eigenvalues and the $\underset{\sim}{C}_i$ are the eigenvectors of the rate matrix. Eigenvalue and eigenvector problems may be new

to you; however, understanding these general problems greatly simplifies many chemical models. Let's change to more general notation to highlight the general utility of the eigenvalue-eigenvector formulation.

℘6

General Pattern 6: Eigenvalue-Eigenvector Equations

Eigenvalue-eigenvector problems are quite common in economics, psychology, sociology, statistics, ecology, business applications, and of course in chemistry and physics. To introduce the general concept, we start with the example matrix and vectors:

$$\underset{\approx}{M} = \begin{pmatrix} 2 & 4 \\ 4 & 2 \end{pmatrix} \qquad \text{and vectors} \qquad \underset{\sim}{X}_1 = \begin{pmatrix} 1 \\ 1 \end{pmatrix} \text{ and } \underset{\sim}{X}_2 = \begin{pmatrix} 1 \\ -1 \end{pmatrix} \tag{6.3.10}$$

Consider the multiplications:

$$\underset{\approx}{M}\underset{\sim}{X}_1 = \begin{pmatrix} 2 & 4 \\ 4 & 2 \end{pmatrix}\begin{pmatrix} 1 \\ 1 \end{pmatrix} = \begin{pmatrix} 6 \\ 6 \end{pmatrix} = 6\begin{pmatrix} 1 \\ 1 \end{pmatrix} = 6\,\underset{\sim}{X}_1 \tag{6.3.11}$$

and:
$$\underset{\approx}{M}\underset{\sim}{X}_2 = \begin{pmatrix} 2 & 4 \\ 4 & 2 \end{pmatrix}\begin{pmatrix} 1 \\ -1 \end{pmatrix} = \begin{pmatrix} -2 \\ 2 \end{pmatrix} = -2\begin{pmatrix} 1 \\ -1 \end{pmatrix} = -2\,\underset{\sim}{X}_2 \tag{6.3.12}$$

Notice that the vector multiplications return the same vector multiplied by a constant. A vector with this property is a special vector and is called an **eigenvector**. The constants that multiply the vector after the multiplication are called **eigenvalues**. The eigenvalues of our example matrix are 6 and –2. Eigen means "the same" in German; the same thing, $\underset{\sim}{X}_i$, appears on both sides of the equations. If the matrix is an NxN matrix and has this property, there are N eigenvalues and vectors. The eigenvalues are often given the symbol λ_i for each of the N possible eigenvectors:

$$\underset{\approx}{M}\underset{\sim}{X}_i = \lambda_i \underset{\sim}{X}_i \tag{6.3.13}$$

The eigenvectors are specific to the given matrix. Not all matrices have eigenvectors. Sometimes some of the eigenvalues are identical. When two eigenvalues have the same value they are said to be **degenerate**. In Problems 2.24 and 2.25 we saw that matrix multiplication can be thought of as a transformation like a rotation in computer graphics. One interpretation of eigenvalue equations is that the transformation of the eigenvectors stretches or shrinks the eigenvector, but the direction remains unchanged. In other words, the eigenvectors have a special direction that corresponds to a special relationship between the variables.

The eigenvectors for a given problem group the original variables in a special way. Consider a complex reaction mechanism. Some concentrations increase and some decrease over time. The eigenvectors for the problem group together those species that have the same time profiles. The process of finding the eigenvectors "sorts" through the variables and puts similar variables in the same eigenvector. Then the resulting groups, or eigenvectors, are as different as possible from each other. For examples in chemical kinetics, each eigenvector has a distinct time signature. Each time signature is characterized by an exponential time constant, which is the reciprocal of the eigenvalue that corresponds to the group behavior. Similar interpretations can be placed on other types of eigenvalue problems. Vibration normal mode coordinates are eigenvectors. These special characteristics are very useful, but how do you find the eigenvalues and vectors?

Eigenvalue equations are just a special case of simultaneous homogeneous linear equations. Subtracting $\lambda_i \underset{\sim}{X}_i$ from both sides of Eq. 6.3.13 and factoring out the common factor of $\underset{\sim}{X}_i$ gives:

$$(\underset{\approx}{M} - \lambda_i \underset{\approx}{I})\,\underset{\sim}{X}_i = 0 \qquad 6.3.14$$

where $\underset{\approx}{I}$ is just the unit matrix. This looks a little abstract, but we can do the multiplications to explicitly write the equivalent set of simultaneous equations. Let X_{1i} be the value for variable 1 that corresponds to eigenvalue i and X_{2i} the value for variable 2 for eigenvalue i. Variables 1 and 2 are the concentrations in two different boxes or for two different chemical species in our problems. For the example of a 2x2 matrix and for eigenvalue i the matrix operations give:

$$(\underset{\approx}{M} - \lambda_i \underset{\approx}{I})\underset{\sim}{X}_i = \left[\begin{pmatrix} M_{11} & M_{12} \\ M_{21} & M_{22} \end{pmatrix} - \begin{pmatrix} \lambda_i & 0 \\ 0 & \lambda_i \end{pmatrix}\right]\begin{pmatrix} X_{1i} \\ X_{2i} \end{pmatrix} = \begin{pmatrix} M_{11}-\lambda_i & M_{12} \\ M_{21} & M_{22}-\lambda_i \end{pmatrix}\begin{pmatrix} X_{1i} \\ X_{2i} \end{pmatrix} = 0 \qquad 6.3.15$$

which upon multiplication gives:

$$\begin{aligned} (M_{11}-\lambda_i)\,X_{1i} \;+\; & M_{12}\,X_{2i} = 0 \\ M_{21}\,X_{1i} \;+\; & (M_{22}-\lambda_i)\,X_{2i} = 0 \end{aligned} \qquad 6.3.16$$

The solution to this set of homogeneous equations will be the trivial solution, which is $\underset{\sim}{X}_i = 0$, unless the determinant of the matrix of coefficients vanishes:

$$|\underset{\approx}{M} - \lambda_i \underset{\approx}{I}| = 0 \qquad 6.3.17$$

This last equation is called the **characteristic equation**. To help you remember this fact about homogeneous linear equations, take the two simple examples:

Example 1, which only has the trivial solution:

$$\begin{aligned} x + 2\,y &= 0 \\ 2x + 3\,y &= 0 \end{aligned} \quad \text{gives:} \quad \det\begin{vmatrix} 1 & 2 \\ 2 & 3 \end{vmatrix} = 1\,3 - 2\,2 = -1 \quad \text{so only } x = y = 0 \qquad 6.3.18$$

Example 2, which has a non-trivial set of solutions:

$$\begin{aligned} x + 2\,y &= 0 \\ 2x + 4\,y &= 0 \end{aligned} \quad \text{gives:} \quad \det\begin{vmatrix} 1 & 2 \\ 2 & 4 \end{vmatrix} = 1\,4 - 2\,2 = 0 \quad \text{so } x = -2\,y \qquad 6.3.19$$

Now only a bit of algebra stands between us and the eigenvalues. For a general 2x2 matrix, $\underset{\approx}{M}$, the determinant in Eq. 6.3.17 is given by:

$$\begin{vmatrix} M_{11}-\lambda_i & M_{12} \\ M_{21} & M_{22}-\lambda_i \end{vmatrix} = (M_{11}-\lambda_i)\,(M_{22}-\lambda_i) - M_{21}\,M_{12} \qquad 6.3.20$$

$$= \lambda_i^{\,2} - (M_{11} + M_{22})\,\lambda_i + (M_{11}\,M_{22} - M_{21}\,M_{12}) = 0 \qquad 6.3.21$$

This polynomial is called the **characteristic polynomial**. We can now solve the second-order characteristic polynomial in Eq. 6.3.21 for the eigenvalues using the quadratic formula:

$$\lambda_i = \frac{(M_{11} + M_{22}) \pm \sqrt{(M_{11} + M_{22})^2 - 4\,(M_{11}\,M_{22} - M_{21}\,M_{12})}}{2} \qquad 6.3.22$$

which simplifies to:

$$\lambda_i = \frac{(M_{11} + M_{22}) \pm \sqrt{(M_{11} - M_{22})^2 + 4\,M_{21}\,M_{12}}}{2} \qquad 6.3.23$$

For larger matrices the algebra is a bit cumbersome, but quite analogous.

Now, how can we find the eigenvectors? There is a straight-forward algorithm to find the eigenvectors. However, the calculations are a bit long. Luckily, there are many different computer based eigenvalue-eigenvector programs available, see Problem 6.7 and Example 6.3.3. Notice, however, that for the non-trivial case, Eq. 6.3.19, there are many possible solutions. For example x = 2, y = -1 is a solution as is x = -2, y = 1; any solution set can be multiplied by -1 and still be a solution. Correspondingly, any multiple is also a solution, so x = 4, y = -2 and x = 6, y = -3 are also solutions. The lack of a unique, single solution for a homogeneous set of linear equations is the reason that normalization is necessary, for example the α terms in Eq. 6.3.8. The boundary conditions fix the multiplier for the eigenvectors.

$\wp 6$

We can now solve for the integrated time course for the two-box model in Eq. 6.3.3. Using Eq. 6.3.23, the full analytical solution is:

$$\lambda_i = \frac{-(k_{ex} + k_1 + k_{-1}) \pm \sqrt{(-k_{ex} - k_1 + k_{-1})^2 + 4\, k_1\, k_{-1}}}{2} \qquad 6.3.24$$

Let λ_1 be the eigenvalue that corresponds to the negative sign in this last equation and λ_2 the eigenvalue that corresponds to the positive sign. The λ_1 value corresponds to the faster decay. The integrated rate law is, using Eq. 6.3.8:

$$[X_1] = [X_1]_o \left[\frac{(k_{-1} + \lambda_1)}{(\lambda_1 - \lambda_2)} e^{-\lambda_1 t} - \frac{(k_{-1} + \lambda_2)}{(\lambda_1 - \lambda_2)} e^{-\lambda_2 t} \right] \qquad 6.3.25$$

See Problems 6.11 and 6.13 for the derivation of the coefficients. This general type of bi-exponential form is quite commonly encountered.

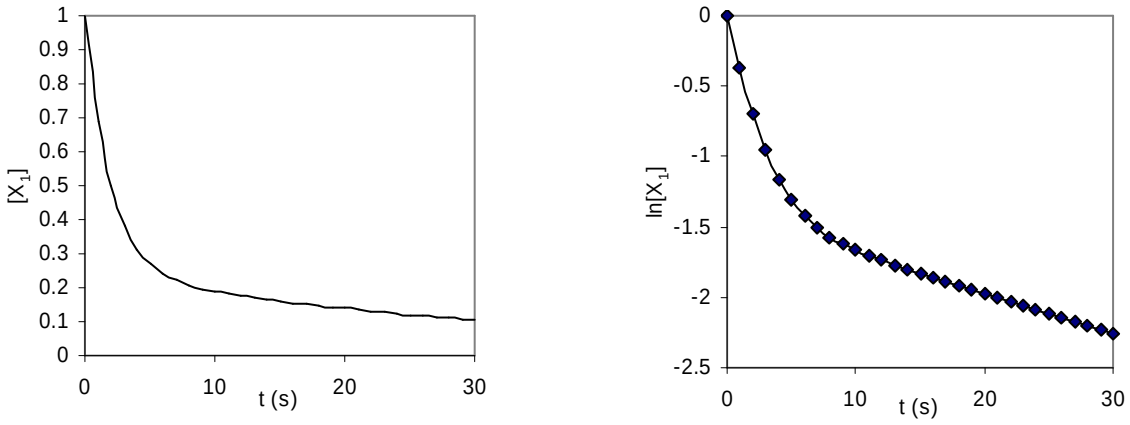
Example 6.3.1

Using Eqs. 6.3.24 and 6.3.25, calculate the time course of the two-box model for $k_1 = 0.3\ s^{-1}$, $k_{-1} = 0.15\ s^{-1}$, and $k_{ex} = 0.1\ s^{-1}$, with initial conditions $[X_1]_o = 1.0$ M and $[X_2]_o = 0$. Plot both $[X_1]$ vs. t and $\ln[X_1]$ vs. t for a maximum time of 30 s.

Answer: The first few lines of the Excel spreadsheet to evaluate Eqs. 6.3.24 and 6.3.25 are:

λ_1=	-0.52122	s-1
λ_2=	-0.02878	s-1
c_1=	0.753837	M
c_2=	0.246163	M
t (s)	$[X_1]$ (M)	$\ln[X_1]$
0	1	-1.1E-16
1	0.686804	-0.37571
2	0.498192	-0.69677
3	0.383631	-0.95807
4	0.313115	-1.16119
5	0.268822	-1.31371

where $c_1$and c_2 are the coefficients multiplying the exponential terms, Eq. 6.3.25. The plots are:



(a) (b)

Figure 6.3.2: Integrated time course for the reversible two-box model, Eq. 6.3.25. The logarithmic plot shows two linear portions indicating a bi-exponential process.

In many cases the concentration plot with a linear axis for a bi-exponential process is hard to distinguish from a single exponential function. Notice that the logarithmic plot, however, consists of two straight-line segments separated by a transition region between. This bi-linear log plot is diagnostic for bi-exponential processes. Curve fitting for bi-exponential processes is discussed in Problem 5.29.

Example 6.3.2
The first-order consecutive mechanism from Chapter 4, Eq. 4.1.24, is a good first example for using Eqs. 6.3.8 and 6.3.9. Solve for the exponential time constants and draw the mechanism as a box model. Compare the results to Eqs. 4.1.28-4.1.31.

Answer: Using Eqs. 4.1.25-4.1.27 the rate matrix and corresponding secular matrix are:

$$\underset{\approx}{K} = \begin{pmatrix} -k_1 & 0 & 0 \\ k_1 & -k_1' & 0 \\ 0 & k_1' & 0 \end{pmatrix}$$

and:

$$\underset{\approx}{M} = \begin{pmatrix} -k_1-\lambda_i & 0 & 0 \\ k_1 & -k_1'-\lambda_i & 0 \\ 0 & k_1' & -\lambda_i \end{pmatrix}$$

Expanding the determinant across the first row gives:

$$(-k_1 - \lambda_i)(-k_1' - \lambda_i)(-\lambda_i) = 0$$

which is already factored giving:

$$(-k_1 - \lambda_i) = 0, \quad (-k_1' - \lambda_i) = 0, \quad \text{and } (-\lambda_i) = 0$$

The roots are then: $-k_1$, $-k_1'$, and 0. In other words, there are only two exponential terms, which are in the form $e^{-k_1 t}$ and $e^{-k_1' t}$, just as in Eqs. 4.1.28-4.1.31. The exponential time constants for this mechanism are then $\tau_1 = 1/k_1$ and $\tau_2 = 1/k_1'$.

We can draw the box model corresponding to this mechanism in two ways, Figure 6.3.2.

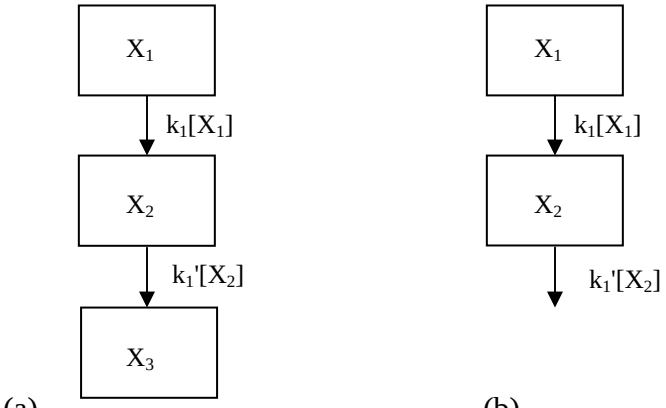


Figure 6.3.2: Consecutive unidirectional reaction mechanism. Model (a) and (b) are equivalent from the point of view of the resulting number of exponential time constants and the concentrations of X_1 and X_2.

Both box models work because there are only two exponential terms, even though there are three species. The reason is that the terminal receiving box is connected by a unidirectional input. Therefore, the concentration of the product in this terminal box does not enter into any of the rate laws. Three explicit boxes are used if you want to solve for $[X_3]$. However, if you don't need to know the integrated time course for X_3, then two boxes and a unidirectional sink are sufficient to determine the properties of the system and are more easily algebraically handled.

Example 6.3.3

Use *Maple* or *Mathematica* to find the integrated time course for the first-order consecutive mechanism:

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

Compare to Eqs. 4.1.28-4.1.31. The α_i values can be arranged as a vector and found by solving Eq. 6.3.9 using General Pattern ***℘3***:

$$\underset{\sim}{\alpha} = C^{-1} \underset{\sim}{X}_o \qquad 6.3.26$$

Answer: Let K be the rate matrix, L be the vector of eigenvalues, and C be the matrix of eigenvectors with each eigenvector corresponding to a column. The set of initial conditions is given by the vector X_o and A is the vector of the α_i values. The *Maple* input is:

with(LinearAlgebra) ;
K := Matrix([[–k₁ , 0 , 0], [k₁ , – k₂ , 0], [0 , k₂ , 0]]) ;
X_o := Vector([1,0,0]) ;
(L,C) := Eigenvectors(K) ;
A := MatrixInverse(C).X_o *;*
A[1] ·C[1..3,1] ;
A[2] ·C[1..3,2] ;
A[3] ·C[1..3,3] ;

The last three lines list the constants that multiply the exponential terms. Note that the "." symbol is the matrix multiplication operator, which is typed as a period, and the "·" symbol is scalar multiplication, which is typed as a "*" in Maple.

The corresponding eigenvalues, vectors, and α_i values are listed:

$$L = \begin{bmatrix} -k_1 \\ 0 \\ -k_2 \end{bmatrix} \qquad C = \begin{bmatrix} \frac{k_1 - k_2}{k_2} & 0 & 0 \\ \frac{-k_1}{k_2} & 0 & -1 \\ 1 & 1 & 1 \end{bmatrix} \qquad A := \begin{bmatrix} \frac{k_2 X_o}{k_1 - k_2} \\ X_o \\ -\frac{k_1 X_o}{k_1 - k_2} \end{bmatrix}$$

Notice, in the terminology we have used for box models, the product C is a terminal species, or box, connected with a unidirectional input. As expected, one of the eigenvalues is correspondingly zero, and the corresponding eigenvector only involves the terminal concentration [0,0,1]. Note that the order of the listing of the eigenvalues is arbitrary. Doing the multiplications in Eq. 6.3.8 gives the results shown in Figure 6.3.3. These equations are equivalent to Eqs. 4.1.28-4.1.31.

coefficients for1st eigenvalue *coefficients for2nd eigenvalue* *coefficients for 3rd eigenvalue*

A[1] ·C[1..3,1] = *A[2] ·C[1..3,2] =* *A[3] ·C[1..3,3] =*

$$\begin{bmatrix} X_o \\ -\frac{k_1 X_o}{k_1 - k_2} \\ \frac{k_2 X_o}{k_1 - k_2} \end{bmatrix} \qquad \begin{bmatrix} 0 \\ 0 \\ X_o \end{bmatrix} \qquad \begin{bmatrix} 0 \\ \frac{k_1 X_o}{k_1 - k_2} \\ -\frac{k_1 X_o}{k_1 - k_2} \end{bmatrix}$$

$$[X_1] = X_o\, e^{-k_1 t} + 0 + 0$$

$$[X_2] = -\frac{k_1 X_o}{k_1 - k_2}\, e^{-k_1 t} + 0 + \frac{k_1 X_o}{k_1 - k_2}\, e^{-k_2 t}$$

$$[X_3] = \frac{k_2 X_o}{k_1 - k_2}\, e^{-k_1 t} + X_o - \frac{k_1 X_o}{k_1 - k_2}\, e^{-k_2 t}$$

Figure 6.3.3: The correspondence of the vector results with the final integrated rate law for the Wei-Prater matrix method.

The Wei-Prater method is restricted to first-order systems; however, the method also applies to the response of a system near steady state or equilibrium following a perturbation.[13] In other words, parallel to what we saw for relaxation kinetics in Section 3.6, even complex systems relax toward equilibrium following a perturbation by a sum of first-order processes that are characterized by a set of exponential time constants. The Wei-Prater method may also be extended to non-first order systems.[10]

We introduced the Wei-Prater matrix method using box models, however, the method was originally developed for purely chemical mechanisms. Within the context of generalized box models, the matrix method provides a convenient means of analyzing complex networks of spatial and chemical processes. The examples that we have discussed can be summarized into a few general principles.

℘7

General Pattern 7: First-Order Box Models

Box models are routinely used by environmental chemists, medicinal chemists, chemical engineers, ecologists, systems biologists, and others in a wide variety of disciplines. It is important for chemists in general to be comfortable with box models since we often work in interdisciplinary teams. Box models are useful tools for displaying important interrelationships and simplifying communication about important systems. On the other hand, it is important to realize that there is nothing mathematically unique or particularly special about box models. Box models are simply a visual representation of the underlying differential equations. The properties of box models are determined by the properties of the underlying set of simultaneous differential equations. Box models are particularly useful for displaying networks of first-order or pseudo-first-order processes. Here is a summary of the general characteristics of first-order box models, assuming constant volumes in the compartments.

1. First-order, pseudo-first-order, and zeroth-order chemical reactions, photochemical reactions, surface reactions, and mass transport in discontinuous systems can be combined in first-order box models.
2. Primary photochemical processes are essentially always unidirectional. The “k” in a photochemical rate law is often written as a “j” to emphasize the relationship to the light flux. The production of secondary photo-products in optically thin systems is first order, Eq. 5.1.17.
3. Surface reactions for rapid, reversible, weak, reactant adsorption can be expressed in the form of first-order processes, Eq. 5.5.8, or pseudo-first-order processes, Eq. 5.5.17, under appropriate conditions.
4. Zeroth-order processes can be handled using the same mathematical machinery as first-order processes by introducing a constant concentration, that is by setting $\upsilon = k_o[M]$ with $[M] = 1$. Zeroth-order processes include photochemical reactions in optically thick systems, Eq. 5.1.14, and strong surface adsorption and catalysis, Eq. 5.5.9.
5. For multi-compartment systems, the amount or concentration of each chemical species in each compartment is handled as a separate variable. For example, for component X, $[X_i]$ is the concentration and X_i is the molar amount in each compartment i.
6. For multi-compartment systems, the rate laws are best written in terms of moles instead of concentration changes, as in Eqs. 6.1.47 and 6.2.2.

7. Mass transport can be by bulk flow, convection, and diffusion. Bulk flow is often represented by a unidirectional first-order process. For a source at constant concentration $[X]_o$ and a compartment of solution volume V:

   For inflow:

   In concentration terms: $\upsilon_+ = J_{in}a/V = k_{in}\,[X]_o$

   In moles: $v_+ = J_{in}a = k_{in}\,X_o$ where $X_o = V\,[X]_o$.

   For outflow:

   In concentration terms: $\upsilon_- = J_{out}a/V = k_{out}\,[X]$

   In moles: $v_- = J_{out}a = k_{out}\,X$

   where [X] is the concentration and X is the molar amount in the compartment. Each bulk flow rate constant is given by k = F/V, where F is the volumetric flow rate. Put succinctly, the rate laws for bulk flow can be expressed in either mole or concentration units using the same bulk flow rate constants. For a given compartment, k_{in} or k_{out} are the same for all species in the mobile phase.

8. The a/V terms for the bulk flow, diffusion, photochemical, and heterogeneous catalysis rates are analogous, Eqs. 5.1.6, 5.1.10, 5.5.6, 6.1.47, and 6.2.6. The a/V term converts from flux to concentration units.

9. Assuming discontinuous systems with rapid mixing and uniform concentrations in each compartment avoids solving the diffusion equation <u>within</u> each compartment.

10. Mass transport by diffusion in discontinuous systems is a reversible first-order process, Eqs. 6.1.44 or 6.1.47. With concentrations in the rate law, the rate constant for a given species is the same in each transfer direction, that is $\upsilon_1 = -k_D\,[X_1] + k_D\,[X_2] = k_D\,([X_2] - [X_1])$. When moles are used in the rate law: $v_1 = -k_{D1}\,X_1 + k_{D2}\,X_2$ with $k_{D2}/k_{D1} = V_1/V_2$. Diffusion can be depicted with an explicit interface or with reversible arrows, Figure 6.1.7.

11. The steady state approximation can be used for transient intermediates in dynamic systems under the same conditions as for any general chemical mechanism. For meta-stable, steady state models and systems at equilibrium all time derivatives vanish, exactly.

12. At steady state, each species in each box is characterized by a residence time, $\tau_{res} = [X_i]/\upsilon_-$.

13. The integrated time course for networks of first-order processes is characterized by a small set of exponential time constants, which are related to the eigenvalues of the rate matrix, $\tau_i = 1/\lambda_i$ for each eigenvalue i.

14. If all processes are reversible, one of the eigenvalues is zero and the corresponding eigenvector is the set of equilibrium concentrations.

15. A terminal receiving box connected by a unidirectional input also gives a zero eigenvalue, if the concentration inside the box is included in the variables, Examples 6.3.2 and 6.3.3. This zero eigenvalue results because the concentration in the box does not enter into any of the rate laws. In other words, a unidirectional sink and a unidirectional terminal box are equivalent in their effect on the remainder of the network. The terminal box just continuously fills.

16. For some systems, the eigenvalues are complex numbers. Complex eigenvalues correspond to oscillatory concentration changes.

17. The mode of the process underlying the box model can be dynamic or static. For a static model with a constant inflow, the system is in a meta-stable, steady state. For a static model for a closed system, the system is at equilibrium.
18. For a dynamic system, the process can start far from equilibrium (left, below) or at equilibrium or in a steady state state (right, below). The process at t = 0 for a system starting far from equilibrium is to mix the reactants or start the flow, which is done by setting the initial conditions. The process for a system starting at equilibrium or steady state is to apply a perturbation. These relationships are diagrammed below:

closed, single-time-point addition:

initial state:	far from equilibrium:			equilibrium:
process:	mix reactants			perturbation
t = 0	$[X_i]_o$			$x_o = [X_i]_o - [X_i]_{eq}$
t = ∞		→	$[X_i]_{eq}$ ←	
final state:			equilibrium	

open, constant inflow:

initial state:	far from steady state:			steady state:
process:	start flow			perturbation
t = 0	$[X_i]_o$			$x_o = [X_i]_o - [X_i]_{ss}$
t = ∞		→	$[X_i]_{ss}$ ←	
final state:			steady state	

All closed systems approach equilibrium at long times. Most, but not all, constant inflow systems approach a steady state. A dynamic process for a system starting far from equilibrium with a single-time point addition corresponds to traditional chemical kinetics. A dynamic process for a system starting near equilibrium with a perturbation corresponds to chemical relaxation. Example 6.2.1 corresponds to a constant inflow starting far from steady state. In pharmacokinetics, a single-time point addition is called a bolus dose. A constant inflow system corresponds to infusion.

The general idea of box models and complex networks of simultaneous differential equations is further elaborated in network theory, biological systems theory, and systems chemistry.

6.4 Summary – Looking Ahead

Chemical kinetics is a wonderfully predictive tool that is indispensable in many areas of science. However, chemical kinetics does not answer some very central questions. Chemical kinetics tells us how a reaction progresses, but the theory does not tell us why:

1. Why do reactions run? What is the impetus for reactions? Do energy changes drive the reaction progress and if not what does?
2. Do reactions always progress towards equilibrium?

3. What is the position of equilibrium? In other words, kinetic arguments tell us that $K_{eq} = k_f/k_r$ but give us no theoretical method to determine K_{eq}, k_f, or k_r. Within chemical kinetics these important parameters can only be determined empirically (from experiment).

Our goal for the remainder of this text is to answer these central questions. In the next chapter we begin the study of thermodynamics, which specifically addresses these questions. In particular, our initial focus is to predict the equilibrium state.

Chapter Summary

Diffusion:

1. Fick's Second Law of diffusion relates solution concentration to the gradient of the flux and the concentration curvature:

$$\left(\frac{\partial c}{\partial t}\right)_x = -\left(\frac{\partial J_m}{\partial x}\right)_t \qquad \text{and} \qquad \left(\frac{\partial c}{\partial t}\right)_x = D\left(\frac{\partial^2 c}{\partial x^2}\right)_t$$

2. Diffusion from a planar surface produces a Gaussian concentration profile:

$$c(x,t) = \frac{n_o}{A\sqrt{4\pi Dt}}\, e^{-x^2/4Dt} \quad \text{with} \quad \textit{fwhm} = 2.355\sqrt{2Dt} \quad \text{and} \quad x_{rms} = \sqrt{2Dt}.$$

3. Diffusion and chemical reactions both change the concentration at a given point x. For species i with stoichiometric coefficient ν_i and reaction rate υ:

$$\left(\frac{\partial c_i}{\partial t}\right)_x = D\left(\frac{\partial^2 c_i}{\partial x^2}\right)_t + \nu_i \upsilon$$

4. The stagnant boundary layer model for interfacial diffusion of a gas across the air/solution interface, assuming a linear gradient, gives:

$$J_m = -D\frac{dc}{dx} = -\left(\frac{D}{\delta}\right)(c^{bulk} - c^{w/a})$$

where D is the diffusion coefficient for the gas in the solvent, $c^{w/a}$ is the concentration in solution at the water/air interface, and c^{bulk} is the concentration of the well-mixed bulk of the solution.

5. Two well-stirred, uniform compartments separated by an interface is called a discontinuous system. The concentration changes abruptly across the interface between the two solutions. Within the interfacial region Fick's Second Law is used to determine the concentration gradient and the net flux across the interface.

6. Diffusion in discontinuous systems can be approximated as a first-order process for transfer between the compartments:

$$\frac{dX_1}{dt} = -k_D[X_1] + k_D[X_2] \quad \text{and} \quad \frac{dX_2}{dt} = k_D[X_1] - k_D[X_2]$$

with $k_D = D\mathcal{A}/\delta$ assuming a linear gradient in the interfacial region, and D the diffusion coefficient within the interfacial region. Using moles directly with the volumes of the two compartments V_1 and V_2:

$$\frac{dX_1}{dt} = -k_{D1} X_1 + k_{D2} X_2 \quad \text{and} \quad \frac{dX_2}{dt} = -k_{D2} X_2 + k_{D1} X_1$$

where the effective mass transport coefficients are: $k_{D1} = D/\delta\,(\mathcal{A}/V_1)$ and $k_{D2} = D/\delta\,(\mathcal{A}/V_2)$.

Box Models

7. In multi-compartment problems, for consistency with mass transport equations, the rates of chemical reactions are often expressed in moles. For first-order reactions:

$$\frac{1}{\nu_x}\frac{d[X]}{dt} = k_1 [X] \quad \text{and} \quad \frac{1}{\nu_x}\frac{dX}{dt} = k_1 X \quad \text{are interchangeable}$$

8. The residence time is the average time that a species spends in the compartment: $\tau_{res} = [X]/\upsilon$..

9. The matrix method of Wei and Prater is exact for networks of first-order differential equations. The rate matrix, $\underset{\approx}{K}$, is the matrix of rate constants where the rows label the rate law and the columns label the chemical species. The rate laws are written as:

$$\left(\frac{d[\underset{\sim}{X}]}{dt}\right) = \underset{\approx}{K}\,[\underset{\sim}{X}]$$

For first-order processes the solution is a sum of exponentials:

$$[\underset{\sim}{X}] = [\underset{\sim}{X}]_o(\alpha_1 \underset{\sim}{C}_1 e^{\lambda_1 t} + \alpha_2 \underset{\sim}{C}_2 e^{\lambda_2 t} + \ldots) \quad \text{with} \quad [\underset{\sim}{X}]_o = \alpha_1 \underset{\sim}{C}_1 + \alpha_2 \underset{\sim}{C}_2 + \ldots.$$

The λ_i values are the eigenvalues and the $\underset{\sim}{C}_i$ are the corresponding eigenvectors of the rate matrix. The α_i values are fixed by the boundary conditions, $\underset{\sim}{\alpha} = C^{-1}\,\underset{\sim}{X}_o$.

℘5 *General Pattern 5: Gaussian Distribution*: The general form of a Gaussian distribution is:

$$g(x) = \frac{1}{\sigma\sqrt{2\pi}}\, e^{-(x-\mu)^2/2\sigma^2}$$

where μ is the mean value of x and σ is the standard deviation of the distribution. For a large number of n measurements, x_i, the population mean and standard deviation are:

$$\mu = \frac{1}{n}\sum_{i=1}^{n} x_i \quad \text{and} \quad \sigma = \left(\frac{1}{n}\sum_{i=1}^{n}(x_i - \mu)^2\right)^{1/2}$$

For a continuous, Gaussian, random variable the corresponding averages are:

$$\mu = \langle x \rangle = \sum_{x_i=-\infty}^{\infty} x_i\, g(x_i) \quad \text{and} \quad \sigma = \langle (x-\mu)^2 \rangle^{1/2} = \left(\sum_{x_i=-\infty}^{\infty}(x_i - \mu)^2\, g(x_i)\right)^{1/2}$$

The distribution is characterized by the full-width at half-maximum: $fwhm = 2\sqrt{2 \ln 2}\ \sigma$

℘6 *General Pattern 6: Eigenvalue-Eigenvector Equations*: The eigenvalues, λ_i, and eigenvectors, $\underset{\sim}{X}_i$, for matrix $\underset{\approx}{M}$ are defined by: $\underset{\approx}{M}\underset{\sim}{X}_i = \lambda_i \underset{\sim}{X}_i$. The eigenvalues are given by the solution to the secular equations, $(\underset{\approx}{M} - \lambda_i \underset{\approx}{I})\,\underset{\sim}{X}_i = 0$. For a non-trival solution to the secular equations, the determinant of the matrix of coefficients must vanish, $|\underset{\approx}{M} - \lambda_i \underset{\approx}{I}| = 0$. For a 2x2 matrix the secular determinant gives the characteristic polynomial:

$$\begin{vmatrix} M_{11}-\lambda_i & M_{12} \\ M_{21} & M_{22}-\lambda_i \end{vmatrix} = \lambda_i^2 - (M_{11} + M_{22})\,\lambda_i + (M_{11} M_{22} - M_{21} M_{12}) = 0$$

Solving the characteristic polynomial for the eigenvalues gives:

$$\lambda_i = \frac{(M_{11} + M_{22}) \pm \sqrt{(M_{11} + M_{22})^2 - 4\,(M_{11}\,M_{22} - M_{21}\,M_{12})}}{2}$$

or:
$$\lambda_i = \frac{(M_{11} + M_{22}) \pm \sqrt{(M_{11} - M_{22})^2 + 4\,M_{21}\,M_{12}}}{2}$$

The eigenvectors are obtained by substitution of each corresponding eigenvalue into the secular equations. As with all homogeneous sets of linear equations, any multiple of an eigenvector is also an eigenvector.

℘*7 General Pattern 7: First-Order Box Models*: The properties of box models are determined by the properties of the underlying set of simultaneous differential equations. Box models are particularly useful for displaying networks of chemical and spatial processes. Zeroth-order, first-order, and pseudo-first-order chemical reactions, photochemical reactions for optically thick and thin systems, surface reactions for strong and weak reactant adsorption, and mass transport in discontinuous systems can be combined in first-order box models (see the summary points in Chapter 5: 4, 6, 7, 10, 19, 20, and point 6, above). For meta-stable, steady state systems, each species in each box is characterized by a residence time, $\tau_{res} = [X_i]/\upsilon_-$. The integrated time course for networks of first-order processes is characterized by a small set of exponential time constants, which are related to the eigenvalues of the rate matrix, $\tau_i = 1/\lambda_i$. If all processes are reversible, one of the eigenvalues is zero and the corresponding eigenvector is the set of equilibrium concentrations.

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Further Reading

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Problems

1. Qualitatively predict the effect of wind turbulence on the exchange of CO_2 across the air/sea interface.

2. Find the second derivative with respect to x of a Gaussian distribution for a non-zero mean. Use explicit differentiation of the general form of the Gaussian distribution in Eq. 6.1.8.

3. In deriving Eq. 6.1.24, we used Eq. 6.1.19 from *General Pattern* ***℘5***. Instead, derive Eq. 6.1.24 by explicit differentiation of Eq. 6.1.7.

4. Write an Excel spreadsheet that uses the finite difference approximation to solve Eq. 6.1.6 for the one-dimensional planar diffusion problem. The analytical solution is Eq. 6.1.7. To do this, first assume finite differences for Eq. 6.1.6 to give:

$$\Delta c(x) = D\left(\frac{\partial^2 c}{\partial x^2}\right)_t \Delta t$$

where this equation is applied at each point, x, on equally spaced intervals along the x-axis. We also need an approximation for the second derivative. Assume the concentrations along the x-axis are c_0, c_1, c_2, c_3, …., which are evaluated at points x = 0, dx, 2dx, 3dx,… The first derivative from c_0 to c_1 and the first derivative from c_1 to c_2 are:

$$\left(\frac{dc}{dx}\right)_{x=0.5\,dx} = \frac{c_1 - c_0}{dx} \qquad \text{and} \qquad \left(\frac{dc}{dx}\right)_{x=1.5\,dx} = \frac{c_2 - c_1}{dx}$$

The second derivative is the derivative of the first derivatives:

$$\left(\frac{d^2 c}{dx^2}\right)_{x=dx} = \frac{\left(\frac{c_2 - c_1}{dx}\right) - \left(\frac{c_1 - c_0}{dx}\right)}{dx} = \frac{c_2 - 2\,c_1 + c_0}{dx^2}$$

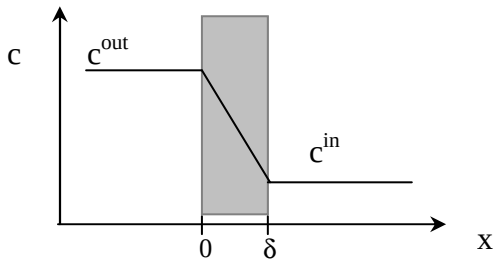
This result is then used to find the new value for the concentration at c_1 in the next time interval using the finite difference formula. Assume the diffusion coefficient is 1.0×10^{-9} m^2s^{-1}. Assume a time interval of $\Delta t = 0.01$ s and integrate to 0.3 s. Assume an x spacing of $dx = 1.0\times10^{-5}$m from 0 to 1×10^{-4}m. (In other words, use a range from 0 to 100 μm.) Assume the initial conditions are a concentration of 1.00 mol m^{-3} in the first x interval and zero at larger distances. One problem arises however. The second derivative can't be calculated at the very first or very last spatial point. For this problem, just set the value of the concentration at the largest value of x at zero. For the value of the concentration at x = 0, that is c_0, we can use conservation of mass. In other words find the sum of the concentrations: $c_1+c_2+c_3+c_4$… and then subtract from the initial concentration, c_0 at t = 0. Here is a start on how you might lay out the first few rows of your spreadsheet. The concentrations at equally spaced x are arranged across the columns and successive time points correspond to successive rows:

A1	B	C	D	E	F	G	H	I	J	K	L	M	N
2			dt=	0.01	s								
3			dx=	1.E-05	m								
4			D=	1.E-09	$m^2\ s^{-1}$								
5			c(0,0)=	1	mol m^{-3}								
6			x (m):										
7		t (s):	0	1.E-05	2.E-05	3.E-05	4.E-05	5.E-05	6.E-05	7.E-05	8.E-05	9.E-05	1.E-04
8		0	1.00	0	0	0	0	0	0	0	0	0	0
9		0.01											
10		0.02											

:

:

5. In this problem we will use Fick's Second Law to model diffusion through a membrane. Consider a membrane of thickness δ separating two well mixed solutions of concentration c^{out} and c^{in}. The origin of the x-axis is chosen to be at the interface between the membrane and the solution at concentration c^{out} as shown below:

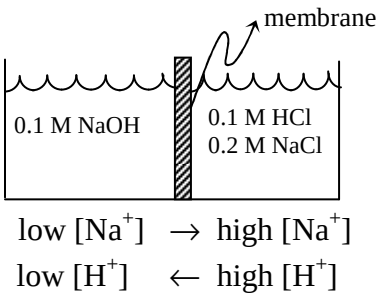


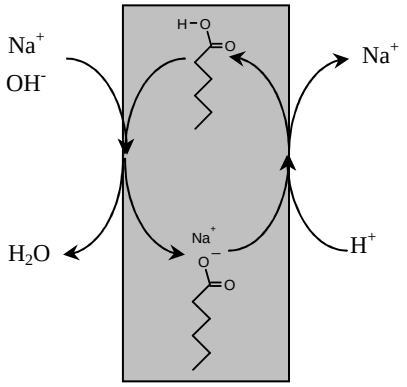
(a.) Show that the concentration profile:

$$c(x) = \left(\frac{c^{in} - c^{out}}{\delta}\right) x + c^{out}$$

has the correct behavior at the surfaces of the membrane.
(b). Assume Fick's Second Law holds for diffusion within the membrane. Show that this linear concentration profile is a valid solution to Fick's Second Law at steady state.
(c). Find the relationship for the flux across the membrane.

6. A very simple model for active transport of Na^+ ions across a membrane is shown below, where the driving force for the transfer results from a H^+ gradient.[1] The key is the membrane-soluble fatty acid that shuttles Na^+ and H^+ ions across the membrane in opposite directions. The fatty acid is only soluble in the membrane. The reactions at the membrane surfaces are shown at right.





The two forms of the fatty acid are HR and NaR. The reactions at the surfaces of the membrane are:

$$\text{Left:} \quad HR + Na^+(\text{left}) + OH^-(\text{left}) \xrightarrow{k_L} NaR + H_2O$$

$$\text{Right:} \quad NaR + H^+(\text{right}) \xrightarrow{k_R} HR + Na^+(\text{right})$$

$$\text{Net:} \quad Na^+(\text{left}) + OH^-(\text{left}) + H^+(\text{right}) \rightarrow Na^+(\text{right}) + H_2O$$

The reactions don't occur within the membrane, so Eq. 6.1.26 applies just at each interface as a surface reaction. For the purposes of this problem, you can assume that the reactions are unidirectional. Assume that the solutions on the left and right are well mixed. Use Fick's Second Law to write the differential equations for the transport within the membrane. Indicate how you

would find the steady state for the fluxes. You don't need to solve the differential equations, but linear concentration gradients would be applicable at steady state if you did.

7. Find the eigenvalue-eigenvector solution to the set of linear equations:

$$\begin{aligned} x + y &= 0 \\ x + y + z &= 0 \\ y + z &= 0 \end{aligned} \qquad \text{which give the coefficient matrix } \underset{\approx}{M} = \begin{pmatrix} 1 & 1 & 0 \\ 1 & 1 & 1 \\ 0 & 1 & 1 \end{pmatrix}$$

Calculate the eigenvalues by hand and the eigenvectors using *MatLab*, *MathCad*, *Maple*, or *Mathematica*. (For symmetric matrices, you can also use the "Matrix Diagonalization" applet on the textbook Web site and on the companion CD.) The *MatLab* command to use is [X,L] = eig(M), where X is the matrix of eigenvectors and L is the diagonal matrix of eigenvalues of the input matrix M.

8. A bi-exponential process is given by the form:

$$[A] = c_1 e^{-k_1 t} + c_2 e^{-k_2 t}$$

The logarithmic plot of a bi-exponential process produces two straight line segments and a transition region between. Bi-exponential decay curves are fit in two segments. First the long time behavior of the logarithmic plot is fit to a straight line to determine the slope, k_2, and intercept $\ln(c_2)$. The non-linear transition region is avoided when points are selected for this plot. Then, the long time behavior is "stripped" from the time course:

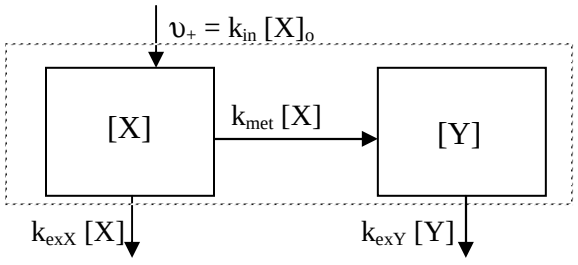
$$\ln[A]_{short} = \ln([A] - c_2 e^{-k_2 t})$$

and a second logarithmic plot of the stripped data produces the short time k_1 and $\ln(c_1)$. These estimated constants are then used as guesses for non-linear curve fitting. Fit the following data to a bi-exponential function. For the non-linear fit, use the four-parameter version of the "Nonlinear Least Squares Curve Fit" applet on the textbook Web site and on the companion CD.

time	0	5	10	20	30	40	60	80	100	120	140
[A]	1	0.727	0.564	0.401	0.328	0.288	0.235	0.196	0.163	0.136	0.114

9. Draw the Chapman ozone mechanism as a box model.

10. Would the residence time in the body for X be altered if an excretion pathway for Y was added to the model in Section 6.2, Figure 6.2.2? The added pathway is shown below.



11. Use *Maple* or *Mathematica* to solve for $X_1$and X_2 for the reversible two-box problem starting from the rate matrix, Eq. 6.3.3. Find the concentrations symbolically first. Then

substitute in the specific constants: $k_1 = 0.3\ s^{-1}$, $k_{-1} = 0.15\ s^{-1}$, and $k_{ex} = 0.1\ s^{-1}$, with initial conditions $[X_1]_o = 1.0$ M and $[X_2]_o = 0$. Solve for the concentrations at t = 1 s. Note that in general Eqs. 6.3.8, 6.3.9, and 6.3.28 can be combined into:

$$[\underset{\sim}{X}] = \underset{\sim}{C}\ (\exp\ \underset{\sim}{\Lambda} t)\ \underset{\sim}{C}^{-1}[\underset{\sim}{X}]_o$$

where $\exp\ \underset{\sim}{\Lambda} t$ is the matrix with the exponential terms along the diagonal:

$$\exp\ \underset{\sim}{\Lambda} t = \begin{bmatrix} e^{\lambda_1 t} & 0 & 0 & \ldots \\ 0 & e^{\lambda_2 t} & 0 & \ldots \\ 0 & 0 & e^{\lambda_3 t} & \ldots \\ \ldots & \ldots & \ldots & \end{bmatrix}$$

Let K be the rate matrix, L be the vector of eigenvalues, C be the matrix of eigenvectors, and E be the diagonal matrix, $\exp\ \underset{\sim}{\Lambda} t$. The set of initial conditions is given by the vector X_o. After defining the rate matrix, K, and initial values vector, X_o, the Maple commands to do these calculations symbolically are:

(L,C) := Eigenvectors(K) ;
*E := DiagonalMatrix(Map(exp,L*t)) ;*
X := C.E.MatrixInverse(C).X_o ;

12. Use *MatLab* to solve the two-box model in Figure 6.3.1 and Eq. 6.3.3. Plot $[X_1]$ and $[X_2]$ for t = 0 – 30 s. See Problem 11 for a hint on how to compactly write the solution. The corresponding *MatLab* commands are in the form:

```
[C,L] = eig(K) ;
```

to determine the eigenvalues, L, and eigenvectors, C. Then at time t, the vector of concentrations is given by:

```
E = diag(exp(diag(L)*t)) ;
X = C*E*inv(C)*X0 ;
```

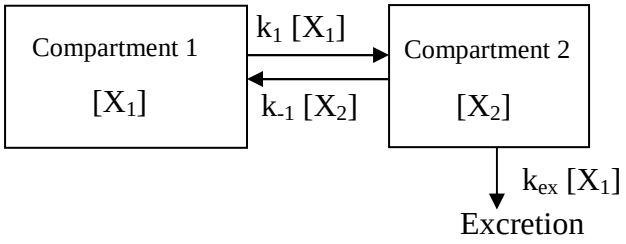
[Note: You can create a matrix with concentrations as the rows and the time points indexed along the columns by using:

```
X(:,t+1) = C*E*inv(C)*X0 ;
```

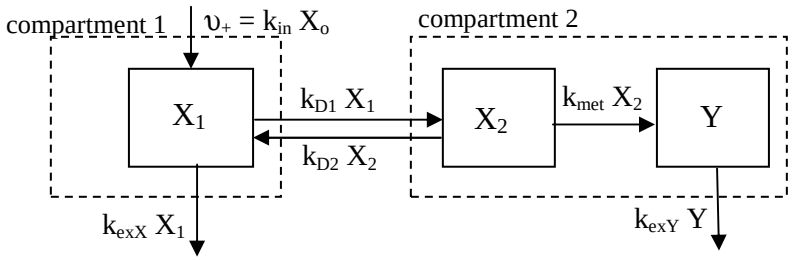
which makes plotting easier. The t values would be successive integers, so they can be used as array indices. The t+1 is necessary because we want to evaluate the concentrations at t = 0, but *MatLab* indexes vectors and matrices starting at 1.]

13. Use *Maple* or *Mathematica* to symbolically verify the solution to the reversible two-box problem, Eq. 6.3.24-6.3.26, and also find the time course for X_2.

14. The box model below corresponds to a reversible first-step mechanism, as in Section 4.1, with all first-order processes. Determine the eigenvalues and time constants. Compare the results with the model in Figure 6.3.1 and Eq. 6.3.3.

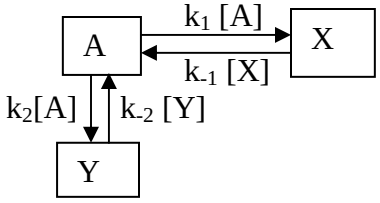


15. The model in Section 6.2, Figure 6.2.2, considers the metabolic elimination of a drug in parallel with excretion. Since the liver is often the site for metabolic processes, this model would be more realistic if the drug is first transported by the blood plasma (bulk flow) to the liver where the drug is metabolized (catabolized) and excreted. (Compounds can be excreted from the liver in the bile.) The added pathways are shown below, including a constant flow input.



(a). Set up the differential equations for this model and write the rate matrix. (b). Find the relationship between k_{D1} and k_{D2}. The typical plasma volume of a 70 kg person is 3 L, and the volume of extracellular fluids, excluding plasma, is 12 L. The total body water is about 42 L, so most of the water volume is in the cellular cytoplasm, which is about 80% water. Assume compartment 1 is the blood plasma and compartment 2 is the liver. Assume the effective volume for this process in the liver is 0.5 L.

16. Show that the kinetic versus thermodynamic control mechanism in Example 4.1.2 gives two exponential time constants. Calculate the time constants using the rate constants given in Example 4.1.2, namely: $k_1 = 0.020\ s^{-1}$, $k_{-1} = 0.00050\ s^{-1}$, $k_2 = 0.50\ s^{-1}$, and $k_{-2} = 1.50\ s^{-1}$. The corresponding box model is shown below.



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