

Biophysics and Physiological Modeling

Chapter 3: Finite difference method and O₂



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Introduction: Dion's passage

In **CHAPTERS 1** and **2** we spent a lot of time talking about single molecules jumping around inside the body, but maybe the puzzle posed in **CHAPTER 1** has been bugging you. Imagine...

You've been talking with Barbara (Barb - a friend in an American medical college) about the oxygen uptake conundrum posed by the improbability of Dion's passage from the air into blood plasma. She says that medical physiology textbooks explain that oxygen simply diffuses from the alveolus into the capillary. Normally there's about 100 mmHg of oxygen in the alveolus and 40 mmHg in the blood plasma entering the lung. O₂ diffuses from high to low until it reaches 100 mmHg in the plasma before it leaves the lung. Simple really!

Barb's explanation seems straightforward, but she's talking a different language from **CHAPTERS 1** and **2**. You've probably heard about diffusion in your biology classes and how molecules move (on average) from high to low concentration because of diffusion. In **CHAPTER 1** we discovered that the marble game realistically **simulates** this behavior. We discovered that random Brownian motion of the molecules tends to spread the marbles out evenly between the two boxes (on average). That is, if you start with more in box 2, the marbles will tend to move to box 1 until they are spread out evenly (on average). Physiological examples that we discussed in **CHAPTER 1** were O₂ delivery to muscle from plasma, and carbon dioxide removal from muscle to plasma.

Barb gave numbers for the amount of oxygen in the alveolus and capillary – but wait – the units she gave are just weird! mmHg stands for “millimeters of mercury” (also called Torr), which is a unit of *pressure* and not a unit of *concentration* as you might have originally thought. In addition, her explanation doesn't address the fact that Dion's jump from plasma back into the air is 40 times more likely than the reverse jump.

To make the connection between standard medical terminology and what we've learned about diffusion from the marble game, we'll need to learn other ways of describing the number of molecules in each box. This is going to be a multistep process. In **SECTIONS 3.1-3.3** we're going to learn about the “finite difference method.” This “FD method” provides a way to talk about what happens in a kMC sim *on average*. Based on a simple “FD diagram” of the system, the FD method predicts how an “ensemble average” of the system will change during a short time. By adding up these finite differences the FD method then **predicts** what will happen in a kMC sim on average.

At the end of **SECTION 3.3**, there is an optional section for readers with calculus. That **optional calculus section** makes the connection between the FD approach and traditional calculus.

However, the main text is written so that you can skip that section. (But if you have taken calculus, you should work through it to discover how the FD method leads directly to a calculus formulation.) In **SECTION 3.4** we'll compare the predictions of the FD method and calculus equation and discover that the FD timestep is a **free parameter** that needs to be “small” to make the FD method work properly.

In **SECTION 3.5** we'll modify the FD method to use concentrations (rather than numbers of molecules). This will allow us to talk about O₂ uptake using the language of biochemists. In **SECTION 3.6** we'll discuss equilibrium for this system and how the concentration of O₂ dissolved in the plasma box is predicted by the partial pressure of O₂ in the gas box. This **equilibrium solubility** is the basis for the use of pressure units in physiology textbooks. It will take us a little while, but at the end of the chapter we should be able to reconcile Barb's description of O₂ uptake with Dion's passage through the alveolar wall.

Simulations are special

In the simulations we've developed so far, the basic event is the jump of an individual molecule. These **molecular-level simulations** are quite different from traditional approaches such as **chemical kinetics** that treat the amount of stuff as a **continuous variable** (i.e. a real-valued number). In our kMC simulations, the amount of stuff is **discrete** and we always have a *whole number* of molecules... breaking marbles in half is against the rules!

In current research, molecular-level simulations are often the best way to model single-molecule experiments in which discrete transitions occur. We'll return to this fascinating topic in later chapters... In this chapter, we'll discover how our molecular simulations relate to more traditional quantitative techniques that can be used to **model** how molecules behave at many levels in physiology ranging from the molecular to the organismal.

Terminology: simulation vs. method etc...

In this book, we're going to reserve the word **simulation (sim)** for algorithms that recreate the model system as realistically as possible at the level of whole (discrete) molecules and ions. In contrast, we'll use terms like **method, technique, or solution** for numerical methods (or recipes) for theories that only account for the *average* behavior of the model system. These numerical approaches use continuous (real number) values for the number of molecules (fractions of a molecule are allowed). FYI, this distinction is *not* always made in bio-related literature, and you will sometimes find numerical solutions to mathematical models of average behavior referred to as “simulations.” We won't do that as we'll often want to compare the (more realistic) simulation data with theoretical predictions for the average behavior obtained using a numerical method or an analytical solution.

In this chapter, we'll discover how to apply “finite difference (FD)” methods to our two-box model systems. These FD techniques are actually *very powerful* and can be used in a similar manner for *much more complicated systems*...

3.1 Finite difference method

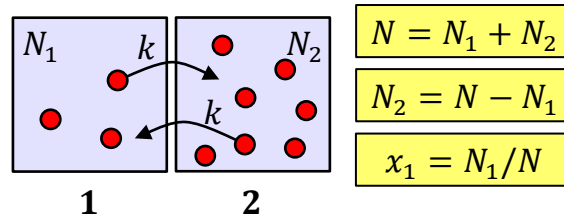


Figure 3.1 Marble game representation of the two-box marble game. The jump rate constant k is the same in both directions.

After completing **CHAPTERS 1** and **2** we have a fairly good idea of what our two-box model actually does, let's see if we can develop a way to **quantitatively predict** what the molecular simulation will do (on average). As you know, there are only two kinds of things that can happen in the simulation: a marble can jump from box 1 \rightarrow 2; or a marble can jump from box 2 \rightarrow 1. The first thing we need to do is convert Figure 3.1 into a **finite difference diagram** of the system, see Figure 3.2. This **FD diagram** includes all the places of interest in the system – in this case box 1 and box 2. The FD diagram in Figure 3.2 includes arrows indicating all the possible ways that the marbles can move from place to place within the system. Each arrow should be labeled with the **rate** at which marbles move in the indicated direction. For example, as each marble in box 1 can jump to box 2 with rate k and there are N_1 marbles in box 1, the total rate of jumps is just N_1 times k marbles per second (left-to-right arrow labeled with N_1k). Similarly the right-to-left arrow is labeled with N_2k – the rate of jumps from box 2 \rightarrow 1.

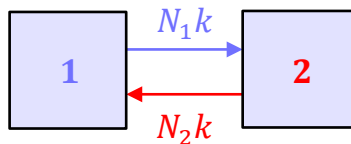


Figure 3.2 Finite difference (FD) diagram of the two-box marble game.

As we're interested in the number of marbles in box 1, let's see how the two rates affect the value of N_1 (on **average**). The way we're going to do this is to imagine what happens during a **short time interval** δt . In this book, we'll usually use the lowercase Greek letter delta δ for a **small difference** and the uppercase Greek letter delta Δ for a change that isn't necessarily small. As we'll see, the idea of what "small" means depends on the situation. For elimination of lead from bone, a month would be considered a short time, whereas for water permeation through aquaporins, a microsecond would be a long time! The time scale depends on the mean residence time τ (introduced in **CHAPTER 2**) which is inversely proportional to the jump rate k (i.e. $\tau = 1/k$). (Watch the video "[Greek letters go green!](#)" [Nelson 2013] for a review of the Greek alphabet.)

By carefully considering the FD diagram above, we can write out the following equation for the small change in the number of molecules in box 1 δN_1 during a short time δt

$$\delta N_1 = -N_1 k \delta t + N_2 k \delta t \quad (3.1)$$

The first term of the right-hand side of equation (3.1) $-N_1 k \delta t$ is the (average) change in the average number of marbles in box 1 *caused by marbles jumping from box 1 → 2*. This term is the product of the **rate** $N_1 k$ (marbles per second) and the **short amount of time** δt (in seconds) that we're considering. We've included the *minus* sign because the arrow is exiting box 1 and N_1 decreases when marbles *leave* box 1 and jump to box 2.

Similarly, the second term on the right-hand side of equation (3.1) $+N_2 k \delta t$ is the change in the average number of marbles entering box 1 *caused by marbles jumping from box 2 → 1*. This term is the product of the rate $N_2 k$ at which marbles enter box 1 from box 2 (on average) and the short time interval δt that we're considering. The plus sign means that these jumps *increase* the number of marbles in box 1. Equation (3.1) has two terms, one for each arrow (entering or leaving box 1) in the FD diagram. Whenever you're writing out an equation like (3.1) there should always be one term for each arrow that starts or ends on the place of interest (in this case box 1).

By doing some algebra, equation (3.1) can be rearranged to give

$$\delta N_1 = (N_2 - N_1) k \delta t \quad (3.2)$$

Equation (3.2) is a **finite difference equation (FD equation)** that tells us how much N_1 changes (on average) during a short but **finite** amount of time δt . This equation tells us a *great deal* about the system. We can get Excel to use this equation to calculate how N_1 changes after a timestep δt using the **FD update instruction**

$$N_1^{\text{new}} = N_1^{\text{old}} + \delta N_1^{\text{new}} \quad (3.3)$$

it says that the new average number of marbles N_1^{new} is the old value N_1^{old} plus the small change δN_1^{new} *predicted* by equation (3.2).

In this **FD method**, δt is a **freely adjustable parameter**. We can change δt to any small value we choose. While this FD approach seems fairly simple, we can use it to model (almost) *all physiological systems!*

Q.3.1 DISCUSSION QUESTION (a) Using equations (3.2) and (3.3) *write out* a complete **finite difference algorithm**, including unit check(s), to calculate how x_1 changes (on average) with time t in our two-box model with $N = 10$, $k = 0.05 \text{ s}^{-1}$, $\delta t = 0.5 \text{ s}$ and $x_0 = 0.3$. **Hint:** Step 1 of your algorithm should look something like Table 3.1. (The “comment or explanation” is not required in your answer.)

Table 3.1 Step 1 of the FD algorithm for the two-box marble game

Instruction	Comment or explanation
$Step^{new} = Step^{old} + 1$	new <i>Step</i> is the previous value plus 1
$t^{new} = t^{old} + \delta t$	increment clock using timestep δt
$\delta N_1^{new} = (N_2^{old} - N_1^{old}) * k * \delta t$	calculate change in N_1 using equation (3.2)
$N_1^{new} = N_1^{old} + \delta N_1^{new}$	calculate the new N_1 from the previous N_1 using (3.3)
$N_2^{new} = N - N_1^{new}$	calculate the new N_2 from the new N_1
$x_1^{new} = N_1^{new}/N$	calculate new fraction in box 1

Note: We've used the "*" symbol for multiplication to remind us that we must use it in Excel.

(b) Using your algorithm, *calculate by hand* what happens for steps 0, 1, 2 and 3 and write your answer in the form of an output table.

Hint: As usual, you should do parts (a) and (b) of this question together. It's easier that way.

Q.3.2 (a) *Briefly explain* in words why $N_2^{new} = N - N_1^{new}$.

(b) *Briefly explain* in words what the combination of equations (3.2) and (3.3) allows us to predict.

Q.3.3 *Implement* your algorithm in a *new* Excel workbook (i.e. start with an empty file) and check that it generates exactly the same sequence that you calculated in Q.3.1(b). Then *change* the initial fraction in box 1 to $x_0 = 1$ and include enough steps in your numerical method to show the approach to equilibrium. Plot x_1 versus time and *record* your graph.

Hint: Your graph should look somewhat similar to the kMC graphs in **CHAPTER 2**.

About what you discovered: broken marbles

One of the things you should have noticed is that x_1 is now a smooth-looking function of time in the FD method. It's *not* random at all! Unlike the original marble game and other kMC sims, fractions of marbles *are allowed* in the FD method. In other words, the FD method is **deterministic** (not random), whereas the kMC sims are **stochastic** (random). □

FD method predicts ensemble average of kMC

The FD method and kMC sim are two ways of modeling the *same* two-box system. However, the FD method is *very different* from kMC sims. In the FD method fractions of a marble are allowed and there isn't any randomness at all! So how can they be compared? Our hypothesis is that the FD method **predicts** the **ensemble average** behavior of the kMC sim. This begs the question: what exactly is an ensemble average?

In musical terminology, a “string ensemble” is a group of musicians all playing the same music. Our use of the term ensemble is similar. Imagine a classroom full of students all playing the marble game using the same rules and the same system parameters at the same time. Each student has their own two boxes, their own ten marbles and their own ten-sided die. The **ensemble average** is the average of all the students’ x_1 values. This average is calculated after all the students have completed the same number of *steps*. In general, an ensemble average is an average over a large number of identical (but independent) systems. In our example, the systems are **statistically independent** because each student rolls their own die and the result in one student’s game can’t affect the outcome in any other student’s game.

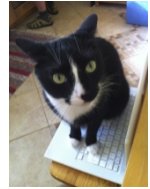
In **CHAPTER 2** you developed a spreadsheet that plotted a graph of how x_1 approached equilibrium for a single system. When you press DELETE in a blank cell, Excel generates a *statistically independent* copy of the sim. When you press DELETE it’s like seeing a different student’s marble game. By pressing DELETE repeatedly, you can get a good feel for what happens on average just like an instructor walking around the classroom observing multiple student marble games. Thus, if we have a spreadsheet, that shows a kMC sim and the corresponding FD prediction on the same graph we can test our hypothesis that the FD method predicts the ensemble average behavior of the system by pressing DELETE in a blank cell and visually checking that the ensemble average behavior (of many kMC sims) matches the FD prediction for x_1 for each value of t . At each value of time t you expect to see roughly the same number of kMC sims with higher and lower than expected values of x_1 .

Save and close your spreadsheet answer to Q.3.3. Then open the preformatted spreadsheet [BPM.Ch03_FD_Method.xlsx](#), which is based on the kMC spreadsheet you saved in Q.2.7. Make sure that the parameters are set to $N = 500$, $k = 0.05 \text{ s}^{-1}$, $x_0 = 1$ (and $N_{\text{steps}} = 2000$). **Hint:** As always, don’t forget to rescale the axes so that you can see everything properly, then save your spreadsheet with a new file name, e.g. BPM.Q.3.4.xlsx. We’re now going to add the FD method to this spreadsheet. Rather than trying to copy from one spreadsheet to another, we’re going to *type* new FD stuff into the kMC spreadsheet in an **FD method table**.

Using your FD algorithm from Q.3.1, fill out the FD method table in the spreadsheet to implement the FD method. As you’ll see, the FD method table contains new columns for the FD variables t , δN_1 , N_1 , N_2 and x_1 . **Note:** You should share the **system parameters** N , k , and x_0 between the kMC simulation and the FD method, but the timestep parameters should be different: Δt is a **calculated parameter** for the kMC sim (see equation (2.1)); and $\delta t = 0.2 \text{ s}$ (added in column **A** of the spreadsheet) is a **free parameter** in the FD method. Make sure that δt is used to calculate t in the FD method table (see cell **L4** in the preformatted spreadsheet).

About what you discovered: one spreadsheet at a time

As mentioned in CHAPTER 2, working with spreadsheets is *not* like working with text documents. When you try to copy cells from one sheet to another (or from one Excel file to another) Excel makes a *guess* for how the links to other cells should change. However, once the algorithm is written, it's easy for us to write the spreadsheet from scratch and get the inter-cell links correct. To avoid the confusion I've seen with some students, my advice is to “*take it one spreadsheet at a time.*” Use only a single sheet in a single spreadsheet file and remember to save a new copy of the spreadsheet to a new filename whenever you get something working correctly. That way if you or your cat messes up, the solution is easy: simply open the version you last saved, which was working correctly! So, don't forget to save your work early and often! ☐



Q.3.4 When your spreadsheet is working correctly, there should be a new series in the graph that shows the FD prediction for x_1 . Set the time axis to have a fixed maximum of $t = 80$ s and the x_1 -axis to a fixed maximum of $x_1 = 1$. The smooth FD curve and the wiggly kMC curve should appear fairly similar (with $N = 500$, $k = 0.05 \text{ s}^{-1}$, $x_0 = 1$). In your graph, look at a particular time e.g. $t = 10$ s and press DELETE about ten times while comparing the kMC value to the FD value at that time. The kMC value at $t = 10$ s should be higher sometimes and lower other times.

(a) Does the FD method appear to successfully predict the ensemble average value of the kMC sim at $t = 10$ s? I.e. *briefly describe* how the kMC values are distributed about the FD prediction.

(b) How about at $t = 20$ s? Does the ensemble average of the kMC sim appear to match the FD prediction? *Briefly describe* what you observed.

(c) How about at $t = 40$ s and $t = 80$ s?

Q.3.5 DISCUSSION QUESTION *Repeat* the procedure of Q.3.4 for $N = 1000, 100, 50, 10$ marble games.

(a) Does the ensemble average of the kMC sim appear to match the FD predictions? *Briefly summarize* what you saw.

Hint: This question is not asking about an individual kMC sim, it's asking about what happens if you average a bunch of them. If you think you see a trend, hit DELETE a bunch more times and see if it persists.

(b) Does the FD curve depend on the number of marbles N ?

(c) For a given value of N , each individual sim will have random deviations away from the FD curve. *Summarize* how the average sizes of these fluctuations vary as N is changed.

(d) *Record* a graph showing the kMC, FD and equilibrium values for $N = 500$.

About what you discovered: theory vs. sim

The FD model and the kMC sim are both of the same physical system. Your graph should look something like [Figure A3.1](#). Hopefully, by carefully comparing the FD prediction with a number of **independent** kMC sims, you've convinced yourself that if you averaged a large number of

sims, the **ensemble average** (average of many independent systems) would look similar to the FD prediction (which doesn't depend on N). Your spreadsheet should have helped you discover this fact... for yourself.

But why do systems with a small number of particles N have the same ensemble average behavior as large systems? Well, from a kinetic point of view, each particle in the simulation is **independent** of the others and does *exactly the same thing* no matter how many other particles there are in the system – each particle *always* jumps to the other box with rate k per second (and hence has the same mean residence time τ). This means that the approach to equilibrium (on **average**) does not depend on the number of marbles N . In **SECTION 3.2**, we'll discover that the FD formulation of the problem provides a quantitative explanation for why the **ensemble average** of systems of *any* number of marbles N approaches equilibrium at the *same rate*.

Another characteristic of the sims that you should have noticed is that the sim fluctuations (away from the FD curve) get larger for small systems. This increase in variability (for small systems) means that they are sometimes able to reach the equilibrium value of $x_1 = 0.5$ significantly earlier than the FD prediction (as in [Figure A3.1](#)) and other times they reach equilibrium later than predicted. □

Predicting equilibrium and steady state

FD equation (3.2) is a general equation that tells us how the system changes during a short time. It applies at any time, including if we wait long enough that the system has reached equilibrium and the ensemble average properties of the system are **steady** and don't change with time. This **steady state** is described mathematically by

$$\delta N_1 = 0 \quad (3.4)$$

because the **state variable** N_1 is constant and doesn't change from step to step. However, because equation (3.2) is also true at steady state, we can set δN_1 in equation (3.4) equal to δN_1 in equation (3.2), to obtain

$$\delta N_1 = 0 = (N_2 - N_1)k\delta t \quad (3.5)$$

Dividing equation (3.5) by $k\delta t$ yields $0 = N_2 - N_1$ (yes, it's legal to say $0/k\delta t = 0$). The equation $0 = N_2 - N_1$ rearranges to give the condition for **steady state**

$$N_1 = N_2 \quad (3.6)$$

Equation (3.6) confirms something that we've already discovered: at steady state, there are an equal number of particles in each box on average. However, the method that we just used to **prove** equation (3.6) is extremely powerful! This approach can be used for any system that can be modeled by FD equations – and that's just about *everything*!

About what you discovered: finding your level...

What we just did was to find the answer to the bonus part of Q.2.9 in CHAPTER 2 using our FD model of the marble game. The FD method provides a simple explanation for the equilibrium values of N_1 and N_2 in the original marble game. At equilibrium, the *ensemble average* number of marbles in each box does not change with time (i.e. $\delta N_1 = 0$). This implies that the rate at which marbles enter box 1 is equal to the rate at which they leave. Entrance ($2 \rightarrow 1$) occurs at rate $N_2 k$ and exit ($1 \rightarrow 2$) occurs at rate $N_1 k$. At equilibrium these two rates are the same $N_1 k = N_2 k$, which means that the number in each box is the same $N_1 = N_2$ (because the jump rate constants are the same for each box).

Most physiological systems “try” to find their own levels in a similar way. In this book, we’ll derive FD equations that completely describe how the state variables of model physiological systems (e.g. N_1 and N_2) change with time. We can then find the steady-state values of the state variables by finding when the differences (e.g. δN_1 and δN_2) are zero. For example, in SECTION 3.4, we’ll derive FD equations for blood plasma oxygenation in the lungs. In SECTION 3.5, we’ll discover the maximum O₂ concentration in blood plasma leaving the lungs – just by setting the change in blood plasma concentration to zero ($\delta c_p = 0$). □

Technicality – steady state vs. equilibrium

At this point, it’s worthwhile identifying an important technicality. When we set all the differences in the state variables to zero, we always calculate a steady-state solution. This is the **definition of steady state** – the system ensemble average is *steady* and so *does not change with time* (or an individual system does not change **on average**, if you watch it for a long time). However, steady state *does not always imply equilibrium*. A mature living organism reaches a steady state when its average properties do not change (significantly) over time. However, a living organism is *not* in a state of **thermodynamic equilibrium**. It’s constantly consuming resources and producing waste products. While the organism does not change with time, its environment does. The word equilibrium is reserved for a system at steady state that produces no net change in its environment. At **equilibrium**, both the system and its environment are at steady state.

About what you discovered: fluctuations at equilibrium...

The finite difference model (equation (3.2)) predicts that box 1 and box 2 will have exactly the same number of molecules (on average) at equilibrium. However, as we’ve already discovered, equilibrium is a dynamic process with particles being randomly exchanged between the two boxes. As a result, state variables such as x_1 fluctuate at equilibrium in the sims and small systems have larger fractional fluctuations than large systems. This is a significant difference between the sim and FD approaches. The molecular simulations are more realistic. Fluctuations, such as those seen in the $N = 10$ system can have significant effects in some circumstances – e.g. spontaneous action potential generation by a small number of ion channels randomly opening at the same time. □

3.2 – FD solution is independent of N

In Q.3.5 you should have noticed that the FD prediction for the ensemble average behavior of the system does not depend on the number of marbles N . But why not? In other words, why doesn't the FD solution depend on N , when the kMC sim behavior clearly does? To answer that question, let's rewrite FD equation (3.2) using only x_1 (instead of using N_1 , N_2 and N). Figure 3.1 includes all the equations that we'll need. Let's take it one step at a time.

Q.3.6 *Show that* equation (3.2) can be combined with equation (1.1) to calculate δN_1 without needing to keep track of N_2 explicitly.

Hint: A good answer is... Solving equation (1.1) for N_2 gives $N_2 = N - N_1$, which can be substituted into equation (3.2) to give $\delta N_1 = [(N - N_1) - N_1]k\delta t$, which can then be rearranged to give

$$\delta N_1 = (N - 2N_1)k\delta t \quad (3.7)$$

Q.3.7 Using the definition of the finite difference of the fraction x_1 in box 1: $\delta x_1 \triangleq x_1^{\text{new}} - x_1^{\text{old}}$ and the definition of the fraction in box 1: $x_1^{\text{new}} \triangleq N_1^{\text{new}}/N$ (for both the old and new values of x_1), *show that*

$$\delta x_1 = \frac{\delta N_1}{N} \quad (3.8)$$

Hint: You will also need to recognize that $\delta N_1 \triangleq N_1^{\text{new}} - N_1^{\text{old}}$ (also by definition).

Q.3.8 Using equations (3.7) and (3.8) and the definition (2.6) that $x_1 \triangleq N_1/N$, *show that*

$$\delta x_1 = (1 - 2x_1)k\delta t \quad (3.9)$$

Equation (3.9) is the finite difference equation for x_1 that we were looking for. You should notice that equation (3.9) does not contain N . This means that the value of x_1 predicted by the FD method does *not* depend on the number of marbles N . This equation shows us that the change in the fraction in box 1 δx_1 only depends on the current fraction in box 1 (i.e. x_1) and not on how many marbles are in the system (i.e. N).

Q.3.9 Using equation (3.9), *derive* an expression for the equilibrium value of x_1 .

Hint: As always, equilibrium implies that the **ensemble average** properties of the system don't change from step to step, implying that the ensemble average equilibrium value of x_1 does not change. This means that $\delta x_1 = 0$ in equation (3.9). To derive the answer, replace δx_1 with 0 and then *solve* the resulting equation for the equilibrium fraction in box 1.

Q.3.10 (a) Using equation (3.9) *write out* a complete finite difference algorithm, including unit check(s), to calculate how x_1 changes (on average) with time in our two-box model with $k = 0.05 \text{ s}^{-1}$, $\delta t = 2 \text{ s}$ and $x_0 = 1$.

(b) By hand, *calculate* steps 0, 1, 2 and 3 of your finite difference algorithm and write your answer in the form of an output table.

1st Hint: Your new algorithm should *not* include N_1 , N_2 or N (anywhere!).

2nd Hint: As usual, you should do parts (a) and (b) of this question together. It's easier that way. This is your last reminder.

About what you discovered: on average the number of marbles doesn't matter

What we just discovered is a quantitative explanation for why the **ensemble-average** behavior of the system (as described by x_1) does not depend on the number of marbles. One implication of this is that we can use the FD method to describe the ensemble-average behavior of systems as small as $N = 1$. We'll return to this topic of modeling ensemble-average single-molecule behavior in later chapters. □

Q.3.11 DISCUSSION QUESTION (a) Using the fraction of marbles in box 1, x_1 , *briefly describe* the (i) similarities and (ii) differences between an ensemble of nine $N = 10$ marble games (think 9 students playing the marble game as a group and averaging) and one $N = 90$ marble game (each with the same jump rate constant k).

(b) *Briefly explain* why the (physical) time t_{eq} required to reach equilibrium does not depend on the number of marbles N , but

(c) the number of steps N_{steps} does depend on N .

About what you discovered: do you speak math?

An excellent answer to Q.3.11(b)&(c) uses the language of math. As we noted in the caption of Figure A3.1, the marble game is close to equilibrium after about two jumps per marble. The average time it takes a marble to jump is $\tau = 1/k = 20$ s. Using this information, we can write out a math answer for Q.3.11(b)

$$t_{\text{eq}} = 2\tau \quad (3.10)$$

which does not depend on N . However, we also know that the time t_{eq} is the kMC timestep Δt times the number of steps N_{steps} , i.e. $t_{\text{eq}} = 2\tau = N_{\text{steps}}\Delta t$. Solving for N_{steps} (and noting from equation (2.2) that $\Delta t = 1/Nk$) gives

$$N_{\text{steps}} = \frac{2\tau}{\Delta t} = \frac{2\left(\frac{1}{k}\right)}{\left(\frac{1}{Nk}\right)} = 2N \quad (3.11)$$

Hence in answer to Q.3.11(c), the number of kMC steps required reach equilibrium is approximately twice the number of marbles. □

3.3 Approach to equilibrium – a new state variable u

The right-hand side of equation (3.9) (yes, you should go back and look at it now) has a factor in parentheses that tells us how far the system is away from equilibrium. Using this factor, we can define a new state variable

$$u = 2x_1 - 1 \quad (3.12)$$

This is just the negative of the factor in parentheses. Why the negative? Well, when defined this way, u has some properties that turn out to be quite convenient:

- $u = 0$ at equilibrium.
- $u = 1$ when $x_1 = 1$.
- $u = -1$ when $x_1 = 0$.

Q.3.12 You might have noticed that equation (3.12) isn't very intuitive. By substituting the definition of x_1 into equation (3.12) and then substituting the definition $N = N_1 + N_2$ *show that* u can be rewritten as

$$u = \frac{2N_1 - N}{N} = \frac{N_1 - N_2}{N} \quad (3.13)$$

Hint: To do that you should start by writing equation (3.12), then substitute in the definition of x_1 (i.e. $x_1 \triangleq N_1/N$). After some algebra you should be able to get to the middle expression. You can then substitute the definition $N = N_1 + N_2$ into the middle expression. Remember, the purpose of a **show that** question is not to get to the answer (it's given to you already) the purpose is to communicate your *understanding* of how to get to the answer – so carefully write out your answer like an argument and *don't skip steps*.

The numerator in equation (3.13) is the difference between the numbers in each box and N is the total number. Hence, according to this equation, we have just figured out that u is the fractional distance away from equilibrium. Positive values of u mean that there are more particles in box 1 and negative values of u mean that there are more particles in box 2. u is a simple example of an **order parameter**.

The order parameter u

Many everyday English words take on special technical meanings in physics (e.g. for mechanical systems, “work” is defined as “force times distance”). The “order” in **order parameter** is also a technical term that needs to be carefully discussed. Most people would agree that clothes neatly folded and packed into a suitcase are more *ordered* than the same clothes crumpled up and randomly jammed into the same suitcase. A deck of playing cards, fresh out of the wrapper, is *ordered* in a particular manner, but shuffling the cards randomizes the deck making it *disordered*. The meaning of order for the marble game is similar, but the marbles in our game have only one property – location, which is specified by N_1 the number of marbles in box 1 (or by x_1 or now by

u). For the marble game, **order** is defined by how well we know where the marbles are. When $u = 1$ we know the location of each and every marble – they are all in box 1. As a result, the marble game is **ordered** like a fresh deck of playing cards. However, when $u = 0$, the marbles are as mixed up as possible and the marble game is as **disordered** as it possibly can be – because any marble has an even chance of being in either box.

Q.3.13 DISCUSSION QUESTION What can be said about the location of a marble in an $N = 100$ marble game when

- (a) $u = 1$
- (b) $u = -1$
- (c) $u = 0$
- (d) $u = 0.7$
- (e) $u = -0.3$

About what you discovered: normalized order

In statistical physics, the words **order** and **disorder** are technical terms that apply to molecular systems. In our marble game we always know that the marbles are in one of two boxes. $u = 1$ (**maximum order**) is similar to a fresh deck of playing cards because we have the most information about where an individual marble is located (we are 100% sure that each marble is located in box 1). $u = 0$ (**completely disordered**) is similar to a well-shuffled deck of cards because we have the least information about where an individual marble is located (every marble has a 50/50 chance of being in box 1).

According to the IUPAC Compendium of Chemical Terminology Gold Book (Version 2.3.2 2012-08-19) <http://goldbook.iupac.org/PDF/goldbook.pdf> definition (p.1037):

order parameter

A normalized parameter that indicates the degree of order of a system. An order parameter of 0 indicates disorder; the absolute value in the ordered state is 1.

Note: When all the marbles are in box 2, $u = -1$ and the absolute value is $|u| = 1$ (completely ordered). □

FD solution for the order parameter u

Our task in this section is to rewrite the finite difference equation (3.9) in terms of u . To do this we need an equation for x_1 in terms of u and an equation for δx_1 in terms of δu .

Q.3.14 By definition, $\delta u \triangleq u^{\text{new}} - u^{\text{old}}$. Using equation (3.12) for both u^{new} and u^{old} show that:

$$\delta u = 2\delta x_1 \quad (3.14)$$

Hint: the definition of δx_1 is $\delta x_1 \triangleq x_1^{\text{new}} - x_1^{\text{old}}$.

Q.3.15 By substituting equation (3.9) into equation (3.14) *show that*

$$\delta u = -2k(2x_1 - 1)\delta t \quad (3.15)$$

Q.3.16 Using equation (3.15) and the definition of u (3.12) *show that*

$$\delta u = -2ku\delta t \quad (3.16)$$

...which is the **finite difference equation** for u that we were looking for.

About what you discovered: proportional change

Equation (3.16) is a finite difference equation for a quantity u that changes by an amount δu that is proportional to itself (i.e. the change δu in u is proportional how big u is). If u is twice as big – the change is also twice as big, or conversely, if u is twice as small – the change is twice as small. This type of situation occurs in an amazingly wide range of situations ranging from unconstrained population growth to drug elimination and radioactive decay, and (as we have just seen) it also applies to the marble game if we consider the order parameter u that tells us how far away we are from equilibrium.

The minus sign in equation (3.16) means that the change always makes u smaller. This means that as time goes by, the system will (on average) tend towards a state in which u is zero. As we'll see next, this produces an **exponential decay** in u that is characteristic of many processes that have a stable equilibrium value corresponding to $u = 0$. If the minus sign was missing from equation (3.16) then the change would always make the quantity bigger – and the bigger the quantity – the bigger the change. This occurs during unconstrained population growth where the growth rate of bacteria is proportional to the number already present. This results in an unstable **exponential growth**. □

If we make δt **infinitesimally small** (i.e. extremely small), the solution to equation (3.16) can be found using **calculus** to give the following formula for u as a function of time.

$$u = u_0 e^{-2kt} \quad (3.17)$$

where u_0 is the value of u at time $t = 0$. We can use this **theory equation** (3.17) to calculate u (and hence x_1 and N_1) using a calculator at any time we like... no need to write an FD spreadsheet. Obviously, if we can find an **analytical solution** like equation (3.17) then it is *definitely* preferable to an FD solution (but not kMC). However, analytical solutions are only available for very simple problems. As we'll see later, more complex problems (like diffusion and models of the spread of COVID-19) can be solved in Excel using FD methods even though no *simple* analytical solution *has ever been found!*

About what you discovered: calculus solution for $u(t)$

This section is included for students who have taken a year of calculus at the university level. If you haven't taken calculus you can skip this derivation... its main purpose is to show how the analytical solution (3.17) can be derived from the FD equation (3.16) using basic calculus. This is actually a very cool and useful mathematical trick that *shows* why calculus is definitely worth taking if you have the time and the inclination.

If you have taken calculus, the following section shows one of the few problems in biophysics and physiology that can be solved exactly using calculus. Luckily it's one that is both important and ubiquitous (common) – first-order kinetics – as seen in drug elimination, radioactive decay, etc. ...

In the traditional chemistry approach, calculus is used to model chemical kinetics. We can get to the calculus formulation of our two-box simulation by starting with the finite difference equation we derived above

$$\delta u = -2ku\delta t \quad (3.16)$$

Dividing both sides of equation (3.16) by δt gives

$$\frac{\delta u}{\delta t} = -2ku \quad (3.18)$$

Taking the limit $\delta t \rightarrow 0$ results in the **derivative** of u with respect to time t

$$\lim_{\delta t \rightarrow 0} \frac{\delta u}{\delta t} = \frac{du}{dt} \quad (3.19)$$

Substituting this limit into equation (3.18) produces the **differential equation**,

$$\frac{du}{dt} = -2ku \quad (3.20)$$

Multiplying both sides of equation (3.20) by dt and dividing by u collects all the “ u ”s on the left and all the “ t ”s on the right. This method is known as **separation of variables**.

$$\frac{du}{u} = -2kdt \quad (3.21)$$

Integrating from $t' = 0$ (and $u' = u_0$) to up to $t' = t$ (and $u' = u$), gives

$$\int_{u_0}^u \frac{du'}{u'} = \int_0^t -2kdt' \quad (3.22)$$

where u' and t' are dummy variable versions of u and t . Evaluating the integrals yields

$$[\ln u']_{u_0}^u = [-2kt']_0^t \quad (3.23)$$

Substituting in the limits,

$$\ln u - \ln u_0 = -2kt - (-2k \cdot 0) \quad (3.24)$$

and the dummy variables disappear. Using the property of logs that $\ln u - \ln u_0 = \ln \frac{u}{u_0}$, we get

$$\ln \frac{u}{u_0} = -2kt \quad (3.25)$$

Taking e^x of both sides gives

$$\frac{u}{u_0} = e^{-2kt} \quad (3.26)$$

Rearranging gives

$$u = u_0 e^{-2kt} \quad (3.17)$$

which is the equation we were trying to derive... and we're done! Phew... that took a while, but we successfully derived an **analytical solution** (an algebraic equation) for the ensemble average value of u as a function of time for the two-box system. This analytical solution is a **predetermined function** of time. \square

About what you discovered: connection with Calculus I

Equation (3.19) is exactly the same as the derivative you learned about in Calculus I. However, students sometimes have trouble seeing that because the notation in their calculus textbook is different. In calculus textbooks the **derivative** of a function $f(x)$ is often written as

$$f'(x) = \lim_{h \rightarrow 0} \frac{f(x+h) - f(x)}{h} \quad (3.27)$$

This equation really doesn't look much like equation (3.19), so let's go over how they match up.

h is a small step in x , so we would change $h \mapsto \delta x$

$$f'(x) = \lim_{\delta x \rightarrow 0} \frac{f(x + \delta x) - f(x)}{\delta x} \quad (3.28)$$

Changing to Leibniz notation: $f'(x) \mapsto \frac{dy}{dx}$; $f(x) \mapsto y(x)$; and $f(x + \delta x) \mapsto y(x + \delta x)$

$$\frac{dy}{dx} = \lim_{\delta x \rightarrow 0} \frac{y(x + \delta x) - y(x)}{\delta x} \quad (3.29)$$

Finally, $y(x + \delta x) - y(x)$ is a small change in y corresponding to a small change in x . Hence, $y(x + \delta x) - y(x) = \delta y$, and equation (3.29) becomes

$$\frac{dy}{dx} = \lim_{\delta x \rightarrow 0} \frac{\delta y}{\delta x} \quad (3.30)$$

which is exactly the same form as equation (3.19). As you know from Calculus I, the derivative $\frac{dy}{dx}$ is the slope of a graph of y versus x . As we'll see below, if we make δt small enough in our FD method, we'll approach the calculus answer as $\delta t \rightarrow 0$. Hence, the FD method should give the same answer as the analytical solution (3.17) that we derived using the derivative in equation (3.19).

Note: We are using δy for a change in y that *must be small* and we're reserving Δy for a big change or difference. However, you should note that most math and physics textbooks use uppercase Δx and Δy in equations (3.28), (3.29) and (3.30) because they don't make that distinction. \square

About what you discovered: three "d"s

We now have three "d"s for a change or difference in y (or x or t etc.). Δy is a change or difference in y that does not need to be small, e.g. the difference in height between sea level and the top of Mt. Everest. δy is a change or difference in y that must be small, e.g. the height increase for your first step up the mountain (think a small piece of Δy). dy is the infinitesimal piece of y that we get if we take the limit $\delta y \rightarrow 0$. It is useful to think of each of them as a step in y . Δy is a big step, δy is a small step, and dy is an infinitesimal increment. \square

3.4 Comparison of FD method with theory

Now that we have an analytical solution for the marble game, let's use it to investigate the accuracy of the FD solution for u .

Q.3.17 (a) Using equation (3.16) *write out* a complete FD algorithm, including unit check(s), to calculate how the order parameter u changes (on average) with time t in our two-box model with $k = 0.05 \text{ s}^{-1}$, $\delta t = 5 \text{ s}$ and $u_0 = 1$.

(b) By hand, *calculate* steps 0, 1, and 2 of your finite difference algorithm and write your answer in the form of an output table.

Hint: Your new algorithm should not include any "x"s or "N"s – only "u"s.

Note: Equation (3.17) is a theory equation that we'll use in Q.3.18, but it's not needed for this question Q.3.17. If you get stuck, try reading the following AWYD.

About what you discovered: making a new u

Your algorithm should include an instruction using the δu calculated from equation (3.16) to calculate u^{new} . This is the standard finite difference approach that results in the following algorithm instruction

$$u^{\text{new}} = u^{\text{old}} + \delta u^{\text{new}} \quad (3.31)$$

My students thought it was amusing when this was recited as “the new you is the old you plus the change in you” – **self-improvement** using the FD method! ☺ ◻

Implement your algorithm in the **FD theory table** of the preformatted spreadsheet [BPM.Ch03_Order_param.xlsx](#) (that doesn't include any mention of “ x ”s or “ N ”s) and check that it generates exactly the same sequence that you calculated in Q.3.17(b). Then *extend* your numerical method to the desired number of steps to show 60 seconds in a graph of u versus t with a timestep of $\delta t = 0.03$ s. Then *complete* the **Theory table** in your spreadsheet – one column for time with increments of 0.5 seconds and a second column with the theoretical prediction for u using equation (3.17). **Hint:** Equation (3.17) can be input into the spreadsheet using an algorithm instruction $u^{\text{new}} = u_0 * \text{EXP}(-2 * k * t^{\text{new}})$ where $\text{EXP}()$ is Excel's exponential function $e^x = \exp(x)$ and where t^{new} is the time in that row of the **Theory table**. The FD method and the theory values for u should be plotted as lines only (with no markers) the **Dash type** of the **Line** of the theory curve should be changed to **Round Dot** – so that you can see both series better (see also Figure 3.3).

About what you discovered: entropy and disorder

As you discovered, the order parameter u approaches its lowest possible value ($u = 0$) as the marble game approaches equilibrium. This tendency towards disorder in the marble game is an example of a much more general scientific observation – the **second law of thermodynamics**, which states that an isolated system, such as our two-box marble game, will always move (on average) towards maximum **entropy**. In our marble game entropy is simply related to the (dis)order of the system as measured by the order parameter u . If you understand why the order parameter tends towards $u = 0$, then you also understand the prediction of the second law of thermodynamics as it applies to the marble game. ◻

Accuracy and stability of the FD method

Q.3.18 DISCUSSION QUESTION Set the **Maximum** of the time axis to a **Fixed** value of 60 s, then *sample* different values of δt to discover how changing δt affects the FD method compared with theory. Starting with a really small value of $\delta t = 0.03$ s, and gradually increasing δt , *find*

(a) the largest value of δt that keeps the FD method looking the same as theory (i.e. you can't see any difference)

(b) the smallest value of δt that makes the FD method look noticeably different from theory (i.e. you can tell it's not exactly the same graph, but it looks almost identical) and

- (c) the smallest value of δt that makes the FD method have the wrong shape.
 (d) *Explain* what happens when $\delta t = 20$ s?
 (e) *Record* the graph for your answer to part (b), but first *insert* a **Text Box** or use the legend to indicate the value of δt that you chose for the graph.
Hint: The following AWYD includes a graph in a format that your answer could take.

About what you discovered: stability of numerical methods

As shown in Figure 3.3, the FD curve with $\delta t = 5$ s is clearly different from the theoretical prediction (and hence is inaccurate), but at least it has the same basic shape (BTW this is *not* the answer to Q.3.18(e)). The FD curve with $\delta t = 15$ s produces behavior that is **qualitatively different** from theory (the shape of the curve is just wrong!).

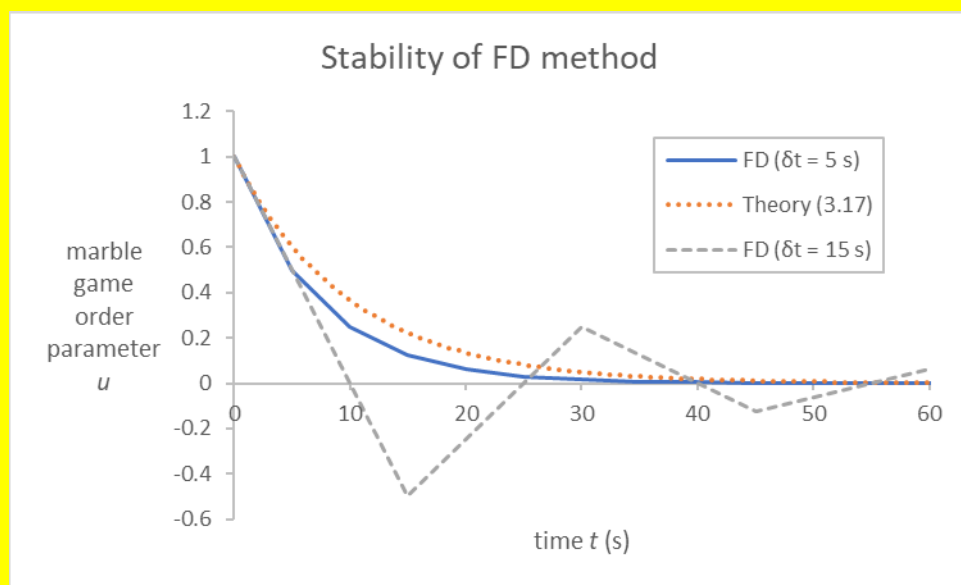


Figure 3.3 Excel 2016 chart of the order parameter for the two-box marble game. Comparing FD methods (with different timesteps δt) with the theoretical prediction of equation (3.17) for $k = 0.05 \text{ s}^{-1}$ and $u_0 = 1$.

What you just discovered turns out to be generally true for all numerical methods. With small timesteps, the algorithm works just fine and produces the “correct” answer. As you increase the timestep of the algorithm, the algorithm slowly moves away from the correct solution. As you increase the timestep further, the algorithm gets less and less accurate until it finally approaches a point where the algorithm breaks down and fails to model the system properly at all! Whenever we use a finite difference method, we’ll need to make sure that the timestep is short enough that we’re getting numbers that reflect the model system to the accuracy that we’re interested in.

Aside – Chaos Theory

For $\delta t = 20$ s our finite difference method is **periodic** and oscillates between $u = 1$ and $u = -1$. For $\delta t > 20$, the algorithm breaks down completely and produces a solution that diverges (gets further and further way from $u = 0$) for long times. Other algorithms can exhibit even more

complex behavior. A classic example is the **logistic map** which exhibits **chaotic behavior**. Using our terminology, the logistic map can be summarized as

$$\delta N = \left(1 - \frac{N}{K}\right) N k \delta t \quad (3.32)$$

and can be investigated in Excel using the techniques we've been developing. Here k is the population growth rate constant and K is the steady-state population. For reasons that are not immediately obvious, we can define $x = Nk\delta t/[K(k\delta t + 1)]$ and $r = (k\delta t + 1)/4$. Using these variables, the logistic map can be written in its traditional form as

$$x^{\text{new}} = 4rx^{\text{old}}(1 - x^{\text{old}}) \quad (3.33)$$

Unfortunately, discussion of this topic is beyond the scope of this book. BTW in the late 1940s, a famous computer science guy, John von Neumann, suggested using the logistic map as a random number generator that behaves like the Excel function **RANDBETWEEN()** that we've already used. If you're interested, search online for the "logistic map" or check out Gould *et al.* [2007] or go to http://www.bioquest.org/esteem/esteem_details.php?product_id=197#. We'll talk more about John von Neumann and one of his famous quotes in **CHAPTER 6** and **CHAPTER 12**. □

As discussed in the previous AWYD, the **accuracy** of the FD method depends on the value of δt chosen. We now want to investigate quantitatively (i.e. using numbers) how the value of δt affects the accuracy of the FD method. To do that we'll need to *delete* the two-column theory table that you added for Q.3.18 above. What we want to do now is calculate the theory value of u (u_{theory}) that corresponds to each time considered in the FD method. *Change* the heading of your FD column to u_{FD} then *add* two *new* columns to the FD table in your spreadsheet, one for u_{theory} and one for Δu , which is the difference (observed (FD) minus expected (theory)) for the order parameter u at the *same time* t as the FD method. You should think of Δu as the **error** in the FD method caused by δt not being small enough. **Hint:** The theory value should be calculated using $u_{\text{theory}}^{\text{new}} = u_0 * \text{EXP}(-2 * k * t_{\text{FD}}^{\text{new}})$, where $t_{\text{FD}}^{\text{new}}$ is the time for the corresponding FD step, and the difference can be calculated using $\Delta u^{\text{new}} = u_{\text{FD}}^{\text{new}} - u_{\text{theory}}^{\text{new}}$, where $u_{\text{FD}}^{\text{new}}$ is the order parameter for the corresponding FD step.

Q.3.19 Plot Δu vs. time in a *new* graph (with a time axis maximum of 60 s). Sample different values of δt e.g. 0.01, 0.1, 1, 5, 20 s. *Record* your graph for $\delta t = 2$ s.

About what you discovered: errors are transient

Your graph should look something like [Figure A3.2](#). However, [Figure A3.2](#) is *not* your answer to Q.3.19, as the value of the FD timestep is $\delta t = 0.5$ s. □

Q.3.20 Using your spreadsheet from Q.3.19, *estimate* the maximum value of δt that produces an FD solution for u accurate to at least

- (a) 1 decimal place (± 0.1),
- (b) 2 decimal places (± 0.01) and
- (c) 3 decimal places (± 0.001).

Hint: You can do that by simply looking at your Δu vs. t graph and adjusting the value of the FD timestep δt . E.g. in [Figure A3.2](#), $\delta t = 0.5$ s and the biggest magnitude error ($\Delta u = -0.0094$) occurs at an elapsed time of about $t = 10$ s. This means that the magnitude of the error $|\Delta u|$, is always *less than* 0.01. However, when you change the timestep to $\delta t = 0.6$ s the biggest magnitude error changes to $\Delta u = -0.0113$ and $|\Delta u|$ is *not* always less than 0.01. Hence, your answer to Q.3.20(b) should be $\delta t = 0.5$ s as that is the (maximum) value of δt that produces an FD solution for u accurate to at least 2 decimal places (you only need one significant figure in your answer).

(d) *Summarize* the trend you observed.

Hint: If δt is decreased by a factor of ten, by what factor does the accuracy of the FD method increase?

About what you discovered: accuracy of numerical methods

As you just discovered, the accuracy of the finite difference method depends on the timestep δt . With a longer timestep, fewer steps are needed to get to the desired time, but the cost is *reduced accuracy*. If you want better accuracy, you need to decrease the timestep with the cost being that more FD steps are required to reach the time that you're interested in. This means that *every time* you implemented and tested an FD method in a spreadsheet, you'll then need to adjust the timestep and the number of steps to get the desired accuracy in a reasonable number of steps. □

Q.3.21 CALCULUS QUESTION Using the definition of the derivative in equation (3.19), *briefly explain* why you would expect the FD method to approach the analytical solution of equation (3.20) as the timestep gets smaller.

About what you discovered: connecting numerical methods to calculus

In your answer to Q.3.21 you should have explained the idea that if you make δt small enough the FD method produces a numerical answer that approaches the limit that $\delta t \rightarrow 0$ in the FD equation (3.16). That's the same limit that results in the derivative in equation (3.19). Hence, the analytical solution we obtained using calculus should be the same as making δt sufficiently small in our FD method. □

3.5 Blood plasma oxygenation (Dion's passage revisited)

In the introduction to this book we talked about how O₂ molecules get from the air into the blood stream and how the outward jump of an O₂ molecule (like Dion) is actually 40 times more likely than the inward jump. This system can be represented by a two-box system as shown in Figure 3.4. Box 1 contains blood **plasma** in a small blood vessel (capillary) in the lung and box 2 contains breath **gases** in one of the small air sacs (alveoli) of the lung (right next to the blood vessel). As we'll see in a later chapter, the two rate constants are determined by the physical size of the boxes and other factors. For boxes the size (diameter) of a typical capillary, the rate constants are about

$k_d = 0.88 \text{ ms}^{-1}$ for **dissociation** of O₂ from the plasma into the gas and about $k_a = 0.022 \text{ ms}^{-1}$ for **association** of O₂ with the plasma from the gas. **Note:** As discussed in the introduction, the outward jump rate constant k_d is 40 times bigger than the inward jump rate constant k_a (i.e. $k_d = 40k_a$). In the following we're going to use the following subscripts.

p = plasma (in capillary – a small blood vessel in the lung)
 g = gas (in alveolus – a small air sac in the lung)
 d = dissociation (jump from plasma to gas)
 a = association (jump from gas to plasma)

The idea is that when you see N_p you will know to pronounce it “number of O₂ molecules in the plasma.”

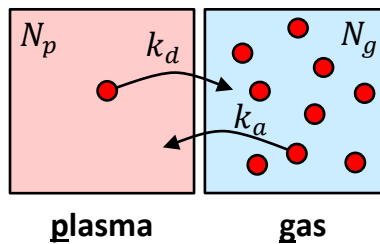


Figure 3.4 Marble game representation of a two-box system for blood plasma oxygenation. O₂ associates with the plasma with rate constant k_a and dissociates with rate constant k_d .

During the plasma's time in the capillary, O₂ molecules can jump from the gas to the plasma and become dissolved in the plasma and vice versa, just like in our marble game – but with an important difference – the jump rate constants in each direction now differ by a factor of 40 because the boxes are different. The plasma in box 1 is a salty solution similar to diluted seawater and box 2 contains breath gases – an ideal gas mixture. O₂ is not very soluble in aqueous solution, which is why the rate constants are so different. For the moment, we're going to *completely ignore* other important blood components such as red blood cells and just consider the O₂ dissolved in pure plasma. From a physiological point of view, it's important that we understand this first – before the effects of hemoglobin and myoglobin are considered (**CHAPTER 6**).

Q.3.22 (a) *Draw* an FD diagram for the two box system shown in Figure 3.4. (Don't forget to include the rates in your diagram, e.g. see Figure 3.2.)

(b) By carefully considering your FD diagram, *show that* the finite difference equation for the change in the number of O₂ molecules in the plasma box (that occurs during a short time δt) is given by:

$$\delta N_p = (k_a N_g - k_d N_p) \delta t \quad (3.34)$$

Q.3.23 At equilibrium the number of O₂ molecules in the plasma does not change. This means that $\delta N_p = 0$ in equation (3.34).

(a) In equation (3.34), replace δN_p with 0 and then *solve* the resulting equation for the equilibrium number in the plasma box.

Hint: Your answer should be an equation including N_g .

(b) Using this equation *calculate* how many molecules are located (on average) in the plasma box – at equilibrium – if there are a fixed (average) number of $N_g = 40$ molecules in the gas box with $k_a = 0.022 \text{ ms}^{-1}$ and $k_d = 0.88 \text{ ms}^{-1}$.

Hint: Your answer should be an actual number.

(c) Using the same equation, *calculate* the equilibrium number in the plasma box if there are $N_g = 100$ molecules in the gas box.

Your answer to the previous question should have included the following equation

$$N_p = \frac{k_a}{k_d} N_g = K_a N_g \quad (\text{only at equilibrium}) \quad (3.35)$$

where we have also *defined* the **equilibrium association constant** as

$$K_a \triangleq \frac{k_a}{k_d} \quad (\text{even when } \textit{not} \text{ at equilibrium}) \quad (3.36)$$

The value of this equilibrium constant is determined solely by the values of the rate constants $k_a = 0.022 \text{ ms}^{-1}$ and $k_d = 0.88 \text{ ms}^{-1}$ so that $K_a \triangleq k_a/k_d = 1/40 = 0.025$ at *any time* including during transient conditions. Equation (3.35) can be rearranged to show that it *predicts* the ratio of the number of molecules in the two boxes *at equilibrium*

$$\frac{N_p}{N_g} = K_a \quad (\text{only at equilibrium}) \quad (3.37)$$

About what you discovered: k_a , K_a , K!

Just like in general chemistry, you have to be very careful about the *case* of k in variables. In this book lower-case k is used for rate constants e.g. k_a (the association **rate constant**). Big K is used for equilibrium constants e.g. K_a (the association **equilibrium constant**) and big K (no italics) is the unit of temperature (**kelvins**). If you didn't notice the difference in the preceding paragraph in the main text – go back and re-read it – it should now make much more sense. Forget about “p”s and “q”s... *...mind your K's!* **Hint:** To make the distinction clear, you might like to write your handwritten lowercase “ k ”s with a loop like this one – k . □

Q.3.24 If blood plasma reaching the lung has $N_p = 1$ O₂ molecule (on average) and the gas has $N_g = 100$ molecules (on average), *briefly explain* (in words) how N_p will change (on average) as the system approaches equilibrium.

About what you discovered: boundary conditions

The hypothetical situation posed in Q.3.24 with N_g fixed at $N_g = 100$ is an example of where the property of the system is specified at an edge or boundary of the system. In Q.3.24 the stated **boundary condition** is that the number of O₂ molecules is held (approximately) constant at $N_g = 100$ molecules in box g as a result of normal **respiration** (the breathing process). This type of **boundary condition** is common when considering a normal **steady state** in physiology – where the body keeps the amount approximately constant. The numerical example has the average number of O₂ molecules increasing from $N_p = 1 \rightarrow 2.5$ as the system approaches equilibrium, which is a 150% increase (a $2.5 \times$) increase in the amount of O₂ dissolved in the plasma. As we'll discover in the next section, these numbers correspond to the normal (resting) physiological situation where the O₂ content of the plasma does indeed increase by this amount as it passes by an alveolus. However, you should keep in mind that this type of boundary condition may not be appropriate for more extreme situations (such as holding your breath while swimming under water). □

Q.3.25 DISCUSSION QUESTION Consider the ratio N_g/N_p . If this ratio is 40, the system starts at equilibrium and there is no net transfer (on average).

(a) What happens (on average) if $N_g/N_p > 40$?

(b) What happens (on average) if $N_g/N_p < 40$? (This could happen if the air you were breathing contained little or no oxygen – e.g. in a house fire.)

(c) In light of your answers in (a) and (b), briefly explain what is required for O₂ to move from the gas into the plasma (on average) even though an individual O₂ molecule is 40 times more likely to jump from the plasma back into the gas.

Note: This is the answer to the conundrum posed in **CHAPTER 1** concerning Dion's passage.

So far, we've been talking about the number of O₂ molecules in two small boxes (that must be of the same physical size). However, this is not how scientists or medical practitioners talk about the amount of O₂; they don't count the number of molecules directly (it's usually a number that's way too big to count!). Chemists typically use O₂ **concentration** measured in mol/L and medical practitioners use O₂ **partial pressure** (or **tension**) measured in mmHg (Torr) in the USA (or kPa (SI units) in the rest of the (metric) world). We'll start by talking about how concentration can be used instead of number of molecules. In **SECTION 3.6** we'll see how (and why) a **partial pressure** is usually used for the same information by the medical profession.

When blood plasma enters the pulmonary (lung) capillary it is deoxygenated with a low concentration of dissolved O₂ of about $c_p = 5.2 \times 10^{-5}$ mol/L. The O₂ concentration of the gas in the alveolus is about 100 times higher at $c_g = 5.2 \times 10^{-3}$ mol/L. This system is shown in Figure 3.5 where we've specified the number of O₂ molecules in each box using concentration in moles per liter mol/L. As indicated in Figure 3.5, the concentration in each box is just the number in moles divided by the volume of the box in liters. To get the actual number of molecules from

this you need to multiply the number in moles by **Avogadro's constant** $N_A = 6.022 \times 10^{23} \text{ mol}^{-1}$, i.e. $N_p = N_A n_p$, where we've used the usual chemistry convention that upper case N stands for the number of **molecules** and lowercase n stands for the number of **moles**.

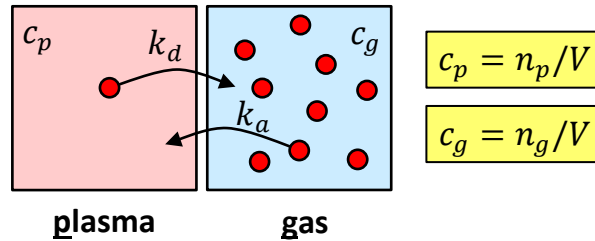


Figure 3.5 Marble game representation of a two-box system for blood plasma oxygenation. Amount of O₂ is now represented by concentrations c_p and c_g [=] mol/L.

Finite difference model of oxygen uptake

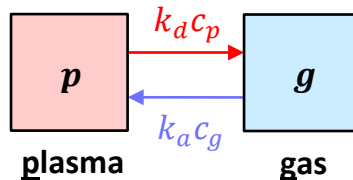


Figure 3.6 FD diagram for blood plasma oxygenation.

Using the notation discussed above, the FD diagram for this system is shown in Figure 3.6. The rate at which O₂ molecules leave the plasma box is $k_d c_p$ (in moles per liter per second) and the rate at which O₂ molecules enter the plasma from the gas is $k_a c_g$. By carefully considering Figure 3.6, we can write out the following equation for the change in the concentration in box 1 δc_p during a short time δt

$$\delta c_p = -k_d c_p \delta t + k_a c_g \delta t \quad (3.38)$$

Note: The negative for the arrow leaving box p and the positive sign for the entering arrow. This equation simplifies to

$$\delta c_p = (k_a c_g - k_d c_p) \delta t \quad (3.39)$$

... just like the original two-box model, except that jumps from box $p \rightarrow g$ occur with rate constant k_d and jumps from box $g \rightarrow p$ occur with rate constant k_a , and we have used the concentrations c_p and c_g instead of the numbers N_p and N_g .

We now want to check that equation (3.39) is the same as equation (3.34) – your answer to Q.3.22(b) (that used “ N ”s instead of “ c ”s).

Q.3.26 (a) Using the definition of concentration (3.57) ($c_p \triangleq n_p/V$), *show that* $c_p = N_p/(N_A V)$ and $c_g = N_g/(N_A V)$.

Hint: by definition $n_p \triangleq N_p/N_A$.

(b) Using the definition of a finite change in x , $\delta x \triangleq x^{\text{new}} - x^{\text{old}}$ (for any x . e.g. $\delta c_p \triangleq c_p^{\text{new}} - c_p^{\text{old}}$), *show that* $\delta c_p = \delta N_p/(N_A V)$ and $\delta c_g = \delta N_g/(N_A V)$.

(c) By plugging your answers to Q.3.26(a)&(b) into equation (3.39), i.e. by replacing the “ c ”s in equation (3.39) with the equivalent “ N ”s, *show that* equation (3.39) is equivalent to equation (3.34), which is what you derived using the “ N ”s in Q.3.22(b).

Hint: Your answer should start with equation (3.39) and end with equation (3.34) (showing all your work).

About what you discovered: using concentrations in the FD method

What you just discovered means that it’s okay for us to use concentrations “ c ”s instead of number of molecules “ N ”s in FD methods from now on. BTW you should note that the rate constants (the “ k ”s) have units of *per second* and hence don’t depend on what units we use for the amount of O₂ in each box. Note also that boxes 1 and 2 *must have the same volume V* to make equation (3.39) equivalent to $\delta N_p = (k_a N_g - k_d N_p)\delta t$. \square

Q.3.27 (a) Using the approach outlined in SECTION 3.1, carefully consider the FD diagram 3.6, write out an equation for δc_g and *show that* it can be rearranged as

$$\delta c_g = (k_d c_p - k_a c_g)\delta t \quad (3.40)$$

(b) Using equations (3.39) and (3.40) *show that* $\delta c_g = -\delta c_p$ so that c_g^{new} can be calculated using

$$c_g^{\text{new}} = c_g^{\text{old}} - \delta c_p^{\text{new}} \quad (3.41)$$

Q.3.28 (a) Using equations (3.39) and (3.41) *write out* a complete FD algorithm, including unit check(s), to calculate how the plasma and gas concentrations change with time using: the initial concentrations $c_{p_0} = 5.2 \times 10^{-5}$ mol/L and $c_{g_0} = 5.2 \times 10^{-3}$ mol/L; rate constants $k_d = 0.88 \text{ ms}^{-1}$ and $k_a = 0.022 \text{ ms}^{-1}$; and a timestep of $\delta t = 1 \text{ ms}$.

Hint: Using equation (3.39) to calculate δc_p^{new} we can then calculate c_p^{new} using the usual FD update equation $c_p^{\text{new}} = c_p^{\text{old}} + \delta c_p^{\text{new}}$ and c_g^{new} using equation (3.41).

(b) By hand, *calculate* steps 0, 1, and 2 of your finite difference algorithm and write your answer in the form of an output table.

Q.3.29 *Implement* your algorithm in a blank spreadsheet and check that it generates exactly the same sequence that you calculated in Q.3.28(b). Then plot c_p versus time (as usual for FD models, your plot should be a **Scatter with Straight Lines** chart). The graph you get won’t have the correct shape (it looks chunky – like connected straight lines)

because the timestep ($\delta t = 1$ ms) is too big. Fix that by *making* δt *smaller* until you're sure that your graph is accurate. While you're doing that, you should also extend your numerical method to the number of steps required to show the approach to equilibrium properly. From now on, it will be up to you to decide how long the sim needs to run to show what's happening clearly.

Now *add* a series for c_g versus time. You should notice that the gas concentrations are much larger than the plasma concentration. This makes it difficult to see what's happening with c_p . To fix that, we'll plot the gas concentration on a **secondary axis**. *Change* the axis of the c_g series by right clicking on the c_g curve. Select **Format Data Series...** change **Series Options** to **Secondary Axis**. *Change* the scale of the secondary axis by right clicking on it, select **Format Axis > Axis Options > Bounds** and set **Minimum** to 0.0 (to show that the fractional change in c_g is small). *Add* an **Axis Title** to the c_g -axis using **Design > Add Chart Element > Axis titles > Secondary Vertical**. And *add* a suitable **Legend** to your graph. Then *change* the maximum of the c_p -axis so that the two curves don't appear to cross. Lastly, *change* the **Dash type** of the c_g line (to identify it).

Record your graph.

About what you discovered: design your own graph

Before you check your answer by looking at [Figure A3.3](#) – you should review your graph to check that it shows your FD model properly. Your graph should include a smooth curve for c_p like the one in [Figure A3.3](#) – if it looks like connected straight lines then you should make δt smaller – just like in Q.3.18. The graph you just plotted tells us a lot about oxygen uptake into blood plasma. If you've labeled them correctly, the axes and legend combined will tell anyone interested what the curves actually are. The axis scales (with units) are also essential.

Lets' go through the components of [Figure A3.3](#) to make sure it is constructed properly. (You should do this for any graph that you design or read.) In [Figure A3.3](#), time is in milliseconds (ms) and both concentrations are in millimolar (mM) but the c_p and c_g axes have different scales. I added arrows pointing from the curves toward the corresponding concentration axes. These arrows are intended as a visual reminder that there are two different y -axes. The arrows are not *required*, but they do help the reader to recognize which axis goes with which curve.

Note: The scales of each of the two y -axes differ by a factor of about 40 which allows us to conclude that $c_p \ll c_g$ (plasma concentration is *much less* than gas concentration) throughout the whole graph. In this graph we also had to select a range (and units) for the time axis. When you're doing this you should ask yourself the following two questions: 1) Does the shape of the graph make sense? 2) Does the concentration approach the correct equilibrium value? I chose a duration of 8 ms so that roughly the first half of the graph shows the shape of the approach to equilibrium and the second half shows that we really have reached equilibrium. Normally it will be up to you to determine the length of the simulation shown in the graph and the ranges of the axes. □

Q.3.30 DISCUSSION QUESTION

(a) By inspecting the graph in Q.3.29, *estimate* how long it takes the plasma O₂ concentration to reach equilibrium in this model.

(b) *Briefly explain* why c_g appears constant in the graph.

Hint: From the beginning to the end of the graph, the same number of O₂ molecules leave box g as enter box p .

About what you discovered: change in CPR guidelines saves lives

In 2005 the American Heart Association (AHA) announced updated cardiopulmonary resuscitation (CPR) guidelines. The most significant change was to the ratio of chest compressions to rescue breaths – from 15 compressions for every two rescue breaths (in the 2000 guidelines) to 30 compressions for every two rescue breaths (in the 2005 guidelines). Even more recently (2010) the order of the three steps of (CPR) was rearranged. The old way was A-B-C – for airway, breathing and compressions. The new way is **C-A-B** – for compressions, airway, and breathing.

The increased emphasis on compressions can be seen in your graph of blood plasma oxygenation. It only takes a few milliseconds for the blood in the lungs to become oxygenated. The key to saving lives is to get that O₂ to vital organs (e.g. the brain). In the short term, keeping the blood flowing (through chest compressions) is more important than replacing the air in the lungs (through rescue breaths). The O₂ level in the lungs goes down relatively slowly, but if the blood stops flowing, O₂ stops being absorbed in the blood *within milliseconds*. Similarly, at the other end of the circulatory system (middle of the oxygen cascade), O₂ delivery (to brain tissues) also slows down rapidly if the blood flow stops. □

Q.3.31 CALCULUS QUESTION (a) *Convert* FD equation (3.39) into a differential equation and *derive an analytical expression* for $c_p(t)$ assuming the boundary condition that c_g is constant, e.g. $c_g = 5.2 \times 10^{-3}$ mol/L *at all times* and $c_p = c_{p_0} = 5.2 \times 10^{-5}$ mol/L *only at $t = 0$* .

(b) Add a series to your graph in Q.3.29 to show the analytical expression you derived in part (a).

(c) *Briefly explain* why the curve you added in part (b) predicts a higher concentration than the FD model in Q.3.29.

Q.3.32 CHALLENGE CALCULUS QUESTION (a) *Derive an analytical expression* for $c_p(t)$ assuming the boundary condition that $c_p + c_g$ is constant and the initial values of c_p and c_g are those given in Q.3.31.

1st Hint: It is useful to define $c_s = c_p + c_g$, which is the constant (time independent) sum of the two concentrations and $k_s = k_a + k_d$ is the sum of the two rate constants.

2nd Hint: You will also need to substitute $c_g = c_s - c_p$ into equation (3.39) to eliminate c_g from the resulting differential equation.

(b) **EXTRA BONUS POINTS** *Derive* an expression for the order parameter of this system.

Q.3.33 RESEARCH QUESTION *Find* experimental data that correspond to Figure A3.3.

Q.3.34 DISCUSSION QUESTION Using the FD diagram 3.6, *briefly explain* how and why Dion's passage through the alveolar wall really is consistent with O₂ uptake in humans (even though the reverse jump really is 40 times more likely).

About what you discovered: Dion's passage

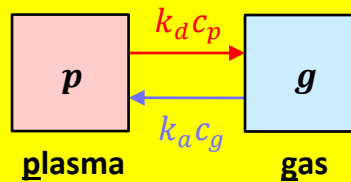


Figure 3.6 (repeated) FD diagram for blood plasma oxygenation.

By inspecting Figure 3.6 we can see that to get a net transfer of oxygen from $g \rightarrow p$ the rate into box p must be greater than the dissociation rate, hence

$$k_a c_g > k_d c_p \quad (3.42)$$

so

$$c_g > \frac{k_d}{k_a} c_p \quad (3.43)$$

or

$$c_g > 40 c_p \quad (3.44)$$

Hence our FD formulation provides a simple explanation: the requirement for oxygen uptake is that the gas concentration must be *more than 40 times* the plasma concentration. BTW it's normally about $100c_p$ for plasma entering the lungs. \square

3.6 Equilibrium and physiological units for c_p

As we've seen, the plasma O₂ concentration rapidly reaches an equilibrium value determined by the O₂ concentration in the gas. This is also true in normal human physiology and the O₂ concentration in blood plasma exiting the capillary is normally in equilibrium with the alveolar gas.

Q.3.35 *Show that* the equilibrium value of the plasma O₂ concentration is given by

$$c_p = \frac{k_a}{k_d} c_g = K_a c_g \quad (3.45)$$

Hint: As usual, the ensemble average system properties don't change at equilibrium, and hence $\delta c_p = 0$ in equation (3.39). In equation (3.45) the equilibrium association constant K_a is the same constant defined in equation (3.36).

By rearranging equation (3.45) it is easy to see that the equilibrium association constant also *predicts* the ratio of the concentrations in the two boxes at equilibrium

$$\frac{c_p}{c_g} = K_a \quad (\text{at equilibrium}) \quad (3.46)$$

Equation (3.45) implies that once we know the concentration of O₂ in the gas, we can *predict* the O₂ plasma concentration of blood leaving the lungs (it will be forty times less than the concentration in the gas). In physiology, the gas concentration is not usually given in mol/L, but it is represented by mmHg (or kPa). Let's see where these units come from... The O₂ in the alveolar gas is basically an ideal gas. Hence, the ideal gas law for O₂ in box g is

$$P_g V = n_g RT \quad (3.47)$$

where P_g is the **partial pressure** of O₂ gas in box g , V is the volume of box g (in m³), n_g is the number of moles of O₂ in box g (in moles), $R = 8.314 \text{ J} \cdot \text{K}^{-1} \cdot \text{mol}^{-1}$ is the molar gas constant and $T = 310 \text{ K}$ is the (absolute) temperature of box g (normal body temperature). We can use equation (3.47) and the definition of concentration (3.57) to give $c_g = n_g/V = P_g/(RT)$. Combining this with equation (3.45) gives

$$c_p = \frac{K_a}{RT} P_g = \sigma P_g \quad (3.48)$$

where $\sigma = K_a/(RT) = 9.6 \times 10^{-6} \text{ mol} \cdot \text{m}^{-3} \cdot \text{Pa}^{-1} = 1.3 \times 10^{-6} \text{ mol} \cdot \text{L}^{-1} \cdot \text{mmHg}^{-1}$ is the **solubility** of O₂ (per mmHg) in blood plasma. If we know the oxygen partial pressure P_g then equation (3.48) tells us the plasma O₂ concentration *in equilibrium with it*. This is worth repeating: equation (3.48) is *only true* when the plasma is in equilibrium with gaseous O₂ at partial pressure P_g .

In physiology textbooks, equation (3.48) is used in *non-equilibrium* situations to relate a plasma O₂ concentration to a (thermodynamically equivalent) “**oxygen partial pressure**” or “**oxygen tension**” P_{O_2}

$$P_{\text{O}_2} = \frac{c_p}{\sigma} \quad (3.49)$$

The P_{O_2} in equation (3.49) tells you the same information as c_p (the O₂ **concentration** in the plasma), even when there is *no* gaseous O₂ actually in equilibrium with it.

Q.3.36 (a) Use equation (3.49) to *calculate* the P_{O_2} of plasma entering the lung (at the beginning of your spreadsheet in Q.3.29). Give your answer in both mmHg and kPa.

(b) Use equation (3.49) to *calculate* the P_{O_2} of plasma leaving the lung (at the end of your spreadsheet in Q.3.29 when it reaches equilibrium). Give your answer in both mmHg and kPa.

(c) As a check on your calculation, *convert* your answers to parts (a) and (b) back into the usual concentration units (mol/L).

Hint: You should write out your answer in the same format as the following AWYD. You should include the units in your written calculations and then make sure that they cancel out correctly. If they don't – then all hope of getting the correct answer ... *is lost!* BTW your answer to part (c) should be the same as the number you started with. This is a check that you did both of the conversions correctly.

About what you discovered: units, Units, UNITS!

A couple of features we've discovered in our model are key observations made in physiology textbooks when they describe plasma oxygenation. The first is that the alveolar O₂ concentration c_g remains essentially constant under normal conditions. This can be included as a boundary condition in our analysis. The second is that the timescale for O₂ uptake is sufficiently rapid that the plasma reaches equilibrium with the gas before the blood leaves the capillary even if we do account for the presence of red blood cells and hemoglobin.

units, Units, UNITS!

In the real estate business, they say that the three most important things are *location, location, location!* When working in science, the three most important things are *units, units, units!* More students have gotten more headaches from mistakes with units than *any other issue*. The SI (metric) system that's used in most general chemistry and physics textbooks is organized so that units usually just work out right... ..meaning that you can just **plug** in the numbers then **chug** through the calculation and *voila!* the correct answer just pops right out. Unfortunately, this is not the case in **BIOPHYSICS AND PHYSIOLOGICAL MODELING**. The medical profession (particularly in the United States) is notorious for using non-SI units! This means that if we are going to analyze physiological quantities in the traditional units, then we'll need to be good with unit conversions. As a concrete example, let's consider the factor σ in equations (3.48) and (3.49). When you calculate it, you should write out the following

$$\sigma = \frac{K_a}{RT} = \frac{(0.025)}{\left(8.314 \frac{\text{J}}{\text{K} \cdot \text{mol}}\right) (310 \text{ K})} = 9.6 \times 10^{-6} \frac{\text{mol}}{\text{J}} \quad (3.50)$$

where we have replaced each letter with a corresponding number-with-units in parentheses. Note that we've written the units in "**over-under format**" to help us see that the units K cancel out, but there's a problem. The units mol · J⁻¹ don't match what we want to use in equation (3.48). A

chemist would want σ in the units of $\text{mol} \cdot \text{L}^{-1} \cdot \text{Pa}^{-1}$ and an American physiologist would want σ in units of $\text{mol} \cdot \text{L}^{-1} \cdot \text{mmHg}^{-1}$. The unit conversions should be written out as

$$\sigma = \left(9.6 \times 10^{-6} \frac{\text{mol}}{\text{J}}\right) \left(\frac{1 \text{ J}}{1 \text{ N} \cdot \text{m}}\right) \left(\frac{1 \frac{\text{N}}{\text{m}^2}}{1 \text{ Pa}}\right) = 9.6 \times 10^{-6} \frac{\text{mol}}{\text{m}^3 \cdot \text{Pa}} \quad (3.51)$$

Each of the new factors in parentheses are simply one thing (1 J) over the same thing (1 N · m) i.e. $1 = (1 \text{ J})/(1 \text{ N} \cdot \text{m})$. The last factor in parentheses is also one as $1 \text{ Pa} \triangleq 1 \text{ N}/\text{m}^2$ by definition. This version of σ is in standard SI units. To convert to chemistry units, you should write out

$$\sigma = \left(9.6 \times 10^{-6} \frac{\text{mol}}{\text{m}^3 \cdot \text{Pa}}\right) \left(\frac{1 \text{ m}^3}{1000 \text{ L}}\right) = 9.6 \times 10^{-9} \frac{\text{mol}}{\text{L} \cdot \text{Pa}} \quad (3.52)$$

as there are 1000 L in 1 m^3 . To convert to physiological units

$$\sigma = \left(9.6 \times 10^{-9} \frac{\text{mol}}{\text{L} \cdot \text{Pa}}\right) \left(\frac{1.013 \times 10^5 \text{ Pa}}{760.0 \text{ mmHg}}\right) = 1.3 \times 10^{-6} \frac{\text{mol}}{\text{L} \cdot \text{mmHg}} \quad (3.53)$$

as one atmosphere at STP is $1.013 \times 10^5 \text{ Pa} = 760.0 \text{ mmHg}$.

Concentration measured as a pressure!?

When physiologists discuss the **oxygen partial pressure (tension)** P_{O_2} in plasma they are *not* using it as a unit of actual physical (hydrostatic) pressure (like in a car tire). As we've seen, it's really being used as a unit of **concentration**. For example, the blood flowing into the lung has a P_{O_2} of about 40 mmHg and the blood leaving the lung has a P_{O_2} of about 100 mmHg. This means that the oxygen concentration in the blood plasma is higher leaving the lung. It does *not* mean that the **hydrostatic pressure** is higher! In fact, the (hydrostatic) blood pressure is *higher entering the lung*... So, don't be fooled, the driving force for O₂ **diffusion** in blood and tissue is not a pressure difference (like when you inflate a balloon or tire), but rather a difference in concentration (number of molecules per unit volume) just like in the marble game. □

Q.3.37 DISCUSSION QUESTION (a) *Briefly translate* Barb's description of oxygen uptake in the lungs (see chapter introduction) into the language we used in the marble game. In particular, you should translate the description using oxygen tensions (40 mmHg and 100 mmHg) into concentrations.

(b) In light of your answer to part (a), *briefly explain* why physiologists prefer to use oxygen tension.

(c) Barb's description of oxygen uptake does not mention randomness. Explain what is missing from her description and how it could be improved so that it does not mislead people into thinking that "diffusion" is a simple non-random directed process.

About what you discovered: Barb's explanation of plasma oxygenation

Barb's (medical physiology textbook) explanation of plasma oxygenation describes O₂ diffusing from high to low oxygen tension P_{O_2} (in units of mmHg – corresponding to O₂ partial pressure). This **oxygen tension** (or **O₂ partial pressure**) is used as a **measure** (indication of the value) of the amount of oxygen. Oxygen partial pressures are directly comparable between different oxygen environments because they refer to an ideal gas reference states *that would be in equilibrium with them*. The advantage of this measure is that the O₂ tensions in the gas and plasma will be the same at equilibrium. This makes direct numerical comparisons (like Barb's) correctly predict the direction of diffusion between different oxygen environments without having to talk about O₂ solubility or the fact that $k_a = 40k_a$. □

Q.3.38 DISCUSSION QUESTION Briefly explain how the solubility (per mmHg) σ is related to the Henry's law constant $K_H = P_{O_2}/c_p$.

Hint: Review what you learned about Henry's law from general chemistry. A mathematical relationship (between σ and K_H) is the *best* way to summarize your answer.

Your friend Barb tells you that most American physiology textbooks state that at a normal arterial P_{O_2} of 100 mmHg there is 3 mL of O₂ at standard temperature and pressure (STP) dissolved per liter of blood plasma *at equilibrium*. This 3 mL of O₂ (at STP) has units of a (gas) volume, but it is really telling you the amount of O₂ (think moles).

Q.3.39 (a) Calculate n the number of moles of O₂ in a volume $V = 3.00$ mL of (at STP).

Hint: To find n you can use the ideal gas equation ($PV = nRT$) and solve for n . In this equation you should use the standard values for temperature and pressure. I.e. $T = 273.15$ K (0°C) and $P = 1.013 \times 10^5$ Pa (1 atm) and $R = 0.082057$ L · atm · K⁻¹ · mol⁻¹.

(b) Using this mole-amount n of O₂ per 100 mmHg per liter of whole blood, equation (3.49) and the definition of concentration (3.57) ($c = n/V$), *calculate* the corresponding solubility $\sigma [=]$ mol · L⁻¹ · mmHg⁻¹.

(c) Compare your answer in part (b) with the value of $\sigma = 1.3 \times 10^{-6}$ mol · L⁻¹ · mmHg⁻¹ given in this chapter.

Hint: (They should be close to each other). A good answer will discuss whether the difference is significant and give a percent comparison (percent change or error, as discussed in the “talking numbers” AWYD in CHAPTER 2).

Plasma is not enough

A final word of warning... In this chapter, we've only considered O₂ dissolved in blood plasma. If plasma was the only thing carrying oxygen around in your blood, the amount of O₂ stored in all your blood plasma (about 5 L) would keep you alive for only *four seconds*! Luckily for us, human **whole blood** has **red blood cells** that include hemoglobin (Hb) molecules that bind O₂ molecules. As a result, red blood cells carry much more O₂ than the plasma in which they float. We'll discuss this topic in more detail in CHAPTER 6, but for now answer the following:

Q.3.40 DISCUSSION QUESTION Your friend Barb tells you that her physiology textbook states that at a normal arterial P_{O_2} of 100 mmHg there is about 200 mL of O₂ dissolved per liter of whole blood (i.e. including red blood cells etc...).

(a) *Quantitatively compare* this number with the amount dissolved just in plasma (3 mL per L).

(b) What would be the percent error in the whole-blood O₂ if the amount of O₂ dissolved in the plasma was ignored (i.e. assumed to be zero?).

(c) Is your answer in (b) a significant difference?

Q.3.41 DISCUSSION QUESTION Like diffusion, there are many misconceptions surrounding oxygen uptake and what causes it to occur. How would you use what you've discovered from the marble game to *explain what's really going on* to a student who had the following misconceptions? –

(a) *“The binding of oxygen to Hb pulls oxygen from the lungs into the blood.”*

1st Hint: Is there really a physical force pulling the molecules?

2nd Hint: Once oxygen molecules are in the blood plasma, many of them are bound to Hb so that they can't participate in the oxygen marble game. This situation is analogous to glycolysis in the cytosol removing glucose molecules from the glucose marble game, as discussed in Q.1.34.

(b) *“The higher oxygen tension in the lungs pushes oxygen into the blood.”*

Hint: Is there really a physical force pushing the molecules?

(c) *Briefly describe* any other misconceptions about oxygen uptake that you've corrected or heard from others?

Q.3.42 RESEARCH QUESTION (a) Using the estimate of 4 seconds in the discussion above calculate the basal amount of O₂ used per second by a typical person.

(b) *Compare* this number with literature values – don't forget to cite references properly.

Q.3.43 RESEARCH QUESTION Find experimental data for plasma O₂ solubility. How does it depend on temperature?

(a) What do the textbooks say?

(b) What do reference books say? (e.g. the **CRC HANDBOOK OF CHEMISTRY AND PHYSICS**.)

(c) Primary research literature?

(d) Which sources are the most authoritative?

Conclusion – about what you discovered

Congratulations! If you made it here, then you've successfully learned how to develop a *predictive* numerical model – just by analyzing a properly labeled FD diagram. This is an incredibly useful technique! If you can draw an FD diagram of the system, then you can develop a FD model and get Excel to crunch the numbers for you. The vast majority of molecular systems of physiological interest can be modeled in this general manner. In the marble game model of plasma oxygenation, the jumping process consists of one reversible step: a jump from box $g \rightarrow p$ (gas \rightarrow plasma), which occurs with rate $k_a c_g$; and the reverse jump from box $p \rightarrow g$ (plasma \rightarrow gas), which occurs with rate $k_d c_p$. By drawing an **FD diagram** with these rates (Figure 3.6), we were able to write an FD equation (3.39) for the small change in the concentration δc_p during a short time δt , allowing us to predict the new value of c_p from the old

$$c_p^{\text{new}} = c_p^{\text{old}} + \delta c_p^{\text{new}} \quad (3.54)$$

The main limitation of this approach is our knowledge of physiology. We have to know (or at least be able to guess) the steps and their rates. Once we've done that, we need to relate what we've done back to the physiological system. In some cases, we'll have to change units or even the way we express the answers – just like we did with P_{O_2} .

If you're interested in a new system (and you're not exactly sure how it works), then you can use this approach to test your guesses *for how it might work*. Personally, I think using numerical (or simulation) models for hypothesis testing is the most fun part of doing science! The challenge problem is this: – Can we figure out the *simplest possible explanation* for how something works? We can then test our hypothesis by comparing its consequences with experiment. Basically, that's what **quantitative scientific modeling** is all about.

In the optional calculus section, we derived an analytical expression for the **order parameter** u in the original two-box system. If you can derive an analytical expression for the solution to a problem, then it's (often) the most useful form of the model. Analytical solutions completely (and very succinctly) describe the ensemble average behavior of the model. If possible, you should always try to find an analytical solution for the model system. Equation (3.17) tells us everything we could ever want to know about the **ensemble average** value of the order parameter u . Once we know u , we can calculate x_1 using equation (3.12) and subsequently $N_1 = x_1 N$ so that we can calculate any of the system state variables, e.g.

$$N_1 = \frac{u + 1}{2} N \quad (3.55)$$

No matter what the initial value of x_0 , N_1 always approaches $N/2$ as $t \rightarrow \infty$. We can tell this from equation (3.55) because $u \rightarrow 0$ as $t \rightarrow \infty$. If a real system does not behave this way, then the model is not applicable.

In our marble game, the order parameter u is a measure of **order**. The order parameter has a minimum magnitude of $u = 0$ at equilibrium (maximum **disorder**). If you understand why the order parameter tends towards $u = 0$, you can also understand the second law of thermodynamics, which states that isolated systems always move (on average) towards maximum disorder (entropy). We'll investigate the connection between entropy, order, the second law of thermodynamics and the marble game in **CHAPTER 8**.

Equation (3.17) **predicts** the precise shape of the u versus t curve for a marble game system of any number of marbles N and jump rate constant k . This is a rather detailed (and profound) **testable hypothesis** of the model (the FD method makes exactly the same prediction). One (perhaps surprising) prediction is that the rate of the approach to equilibrium does not depend on the number of marbles N , but only on the jump rate constant k . If we believe that this model explains the behavior of a real system, then we can use these testable hypotheses to **confirm** that the model is applicable. For example, in this chapter we have shown that this mathematical model successfully predicts the ensemble average behavior of our kMC simulations. In the following chapters, beginning with **CHAPTER 4**, we'll develop models of real systems and then test the hypothesis that the model predicts the behavior of the real system by comparing the model predictions with real experimental (or clinical) data. Even if the model turns out to *not* model the real system accurately, then we still learn something about the system... at least one of the model assumptions is *not* correct. If you can figure out which assumption(s) are incorrect – and how to change them to model the real system better – then you'll discover even more about how the molecules of life actually work.

Barb's medical physiology textbook explanation that O_2 molecules diffuse from high to low values of **oxygen tension** P_{O_2} (or **partial pressure**) is an example of how comparisons with *thermodynamically comparable* reference states can predict how a system will behave when it is *not* at equilibrium. As characterized by its partial pressure P_{O_2} , the **ideal gas reference state** is used as a **measure** (an indication of the value of) the **chemical potential** of the O_2 in the plasma by stating the partial pressure P_{O_2} of a gas phase *that would be in equilibrium with it*. By using this method for specifying the chemical potential, it's possible to directly compare the plasma and the gas using the same **measure** – P_{O_2} . However, this approach obscures the fact that the gas phase is preferred forty-to-one over the gas phase at equilibrium (as summarized in equation (3.45)). As you discovered, the resolution of Dion's oxygen uptake conundrum (from **CHAPTER 1**) is this – the forty-fold difference in the inward and outward jump rates corresponds to a forty-fold difference in the O_2 concentrations at equilibrium, i.e. the O_2 concentration is forty times higher in the gas than in the plasma at equilibrium.

This chapter has been our introduction to finite difference methods. As we've discovered, they are extremely powerful, and we'll be using them extensively in the following chapters. However, you should also remember that FD methods only predict the **ensemble average** behavior. So, don't forget the marble game – a kMC simulation is always a more realistic representation of the random events occurring at the molecular level.

Summary: Finite difference method and O₂

Key math and computational science concepts

Finite difference (FD) method

- Concentrations are analyzed at discrete locations (boxes).
- During a small **timestep** δt , the small change in concentration δc_p can be determined from an **FD diagram** (Figure 3.6)

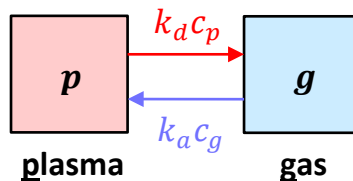


Figure 3.6 FD diagram for blood plasma oxygenation (repeated from main text).

to give an FD equation

$$\delta c_p = (k_a c_g - k_d c_p) \delta t \quad (3.39)$$

and predict that

$$c_p^{\text{new}} = c_p^{\text{old}} + \delta c_p^{\text{new}} \quad (3.54)$$

- It's important to remember that the purpose of an FD equation like (3.39) is to allow us to calculate how a variable (e.g. c_p or u) changes. That change can then be used to calculate the new value using an **FD update equation** (3.54), which is *always* of the form

$$u^{\text{new}} = u^{\text{old}} + \delta u^{\text{new}} \quad (3.31)$$

– the new u is the old u plus the change in u – **self-improvement** ☺ using the FD method!

- When the FD method is implemented in a spreadsheet, the timestep δt is an **adjustable parameter** that should be decreased until it no longer affects the graph of $c_p(t)$ so that you have a smooth accurate curve. You will also need to make sure that you increase the number of FD steps accordingly.
- In the limit that $\delta t \rightarrow 0$, the FD ratio becomes a **derivative**

$$\lim_{\delta t \rightarrow 0} \frac{\delta c_p}{\delta t} = \frac{dc_p}{dt} \quad (3.56)$$

and in some cases, we can obtain an **analytical solution** to the FD equation using calculus.

Key chemistry concepts

Equilibrium constants predict equilibrium ratios

- **Rate constants** – describe how frequently a molecule **jumps** between boxes (in a particular direction) as a result of **random thermal motion** (a **passive process**).
- **Equilibrium constants** – are determined by the ratio of the rate constants.
- For the original marble game, the rate constant is the same (k) in both directions and the equilibrium constant is $K_{\text{eq}} = 1$ so that the prediction is that $N_1 = N_2$ at equilibrium.
- For plasma oxygenation the **equilibrium association constant** is given by

$$K_a \triangleq \frac{k_a}{k_d} \quad (3.36)$$

- **Concentration** c [=] mol/L – number in a box (n [=] mol) divided by the volume of the box (V [=] L).

$$c \triangleq \frac{n}{V} \quad (3.57)$$

- **Steady state** – occurs when state variables, e.g. c_p , are steady and don't change, i.e.

$$\delta c_p = 0 \quad (3.58)$$

- **Equilibrium** – is a special type of **steady state** where there is also no change in the environment. For example, at equilibrium $\delta c_p = 0$ and $\delta c_g = 0$ and the ratio of the concentrations is *predicted* by the equilibrium constant

$$\frac{c_p}{c_g} = K_a \quad (3.37)$$

- **Normalized order parameter** u – the fractional distance that the **marble game** is away from equilibrium. The marble game is most **ordered** ($|u| = 1$) when we know where all the marbles are and most **disordered** ($u = 0$) when we have the maximum uncertainty about where a particular marble is located. According to equation (3.16) $\delta u = -2ku\delta t$ and the change in the order parameter δu is proportional to its current value u . This produces an **exponential decay**

$$u = u_0 e^{-2kt} \quad (3.17)$$

towards equilibrium and maximum disorder ($u = 0$) from any possible initial value u_0 . This exponential behavior (decay or growth) is extremely common in science and occurs whenever the change in a quantity is **proportional** to its current value. We'll see many

examples of this, starting with **CHAPTER 4** and ending with the COVID-19 pandemic in **CHAPTER 12**.

Key physiology concepts

Plasma oxygenation

- The FD model *predicts* that the equilibrium association constant for O₂ in blood plasma is given by

$$K_a \triangleq \frac{k_a}{k_d} = \frac{1}{40} = 0.025 \quad (3.36)$$

so that the equilibrium concentration of oxygen in plasma c_p is given by

$$c_p = K_a c_g = \sigma P_g \quad (3.45) \text{ \& } (3.48)$$

where P_g is the (actual) **partial pressure** of O₂ in the gas and σ is the **plasma O₂ solubility**

$$\sigma = 9.6 \times 10^{-9} \frac{\text{mol}}{\text{L} \cdot \text{Pa}} = 1.3 \times 10^{-6} \frac{\text{mol}}{\text{L} \cdot \text{mmHg}} \quad (3.59)$$

- Rearranging equation (3.48) gives

$$P_{\text{O}_2} = \frac{c_p}{\sigma} \quad (3.49)$$

which defines the **oxygen tension** P_{O_2} – the partial pressure of O₂ *that it would be in equilibrium with* c_p . The oxygen tension P_{O_2} is the standard medical **measure** of plasma O₂ **concentration** that allows direct numerical comparisons between different oxygen environments (but it obscures the effect of limited solubility on the O₂ concentration).

Key scientific concepts

Scientific research

- Quantitative scientific models** make a **network** of **testable hypotheses**.
- We found **graphical evidence** to support the hypothesis that the **FD method predicts** the **ensemble average** of our **kMC sims**.
- Our **conclusion** is that the **FD method** can be used to predict the **ensemble average behavior** of **systems** that can be represented by an **FD diagram**.

Terminology to remember

- Steady-state** – none of the **system** properties (**variables**) change (on average) with time e.g. $\delta c_p = 0$ and $\delta c_g = 0$.

- **Thermodynamic equilibrium** – both the **system** *and* its **environment** must be at steady-state.
- **Timestep** δt – a **freely adjustable parameter** in **FD methods**. You need to make this small enough that your FD model is sufficiently accurate.

Reminder – find your mistakes with units, Units, UNITS!

- Getting the units right in biophysics and physiological modeling is always an ongoing struggle. If you work with quantitative models, you *will* make mistakes! I often tell my students that the following is my favorite question in all of physics and biophysics...

Q. “Do the units matter?”

A. ALWAYS! 😊

- Watch the video “My favorite physics mistake” <http://youtu.be/7lMadULeBXc> for how units saved my life!

Appendix – Answer graphs

Figure A3.1 – Theory vs. sim

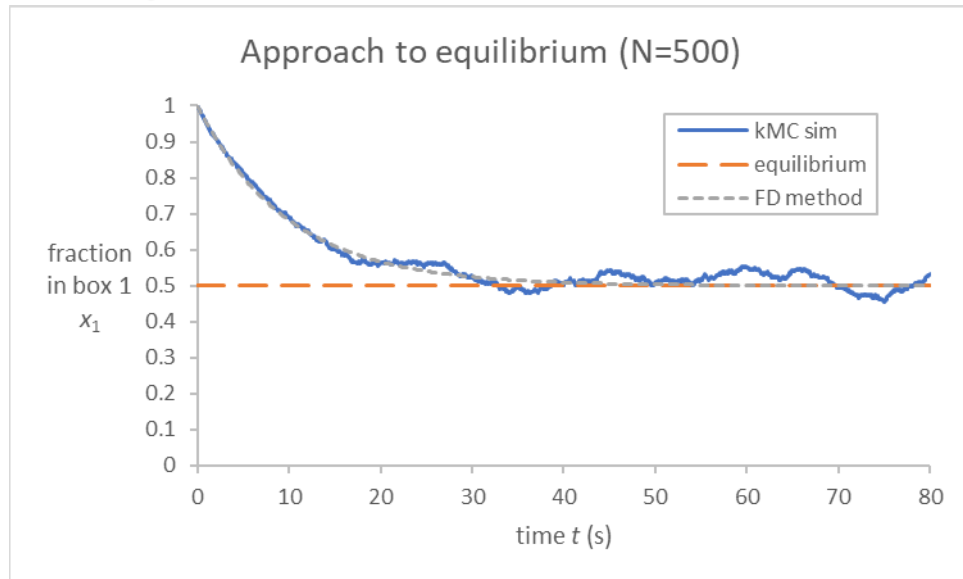


Figure A3.1 Excel 2016 chart of the two-box marble game. Comparing kMC simulation with the FD method for a system with $N = 500$, $k = 0.05 \text{ s}^{-1}$ and $x_0 = 1$. **Note:** The mean residence time is $\tau = 1/k = 20 \text{ s}$ and the system is close to equilibrium at $t = 2\tau = 40 \text{ s}$.

[Return to main text](#)

Figure A3.2 – Errors are transient

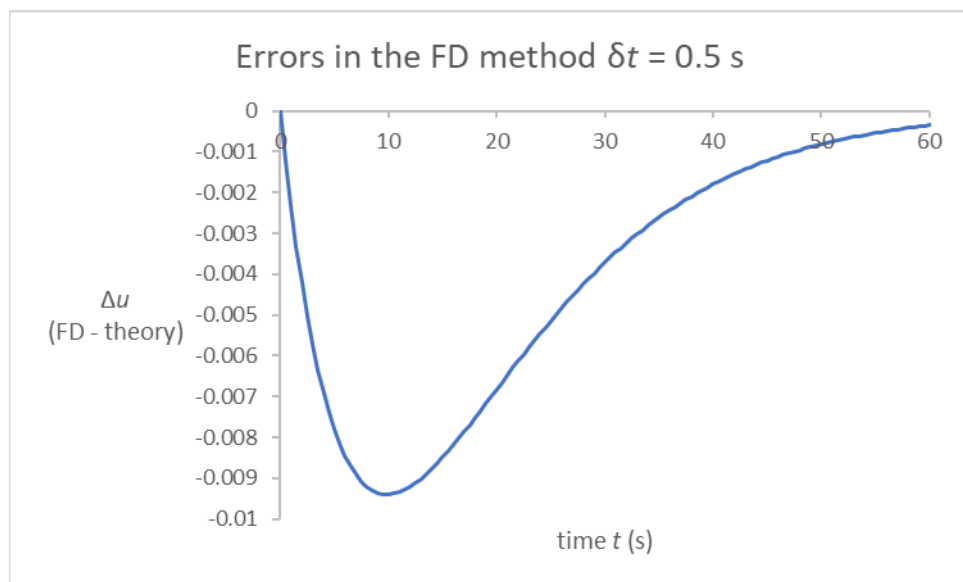


Figure A3.2 Excel 2016 chart of the two-box system. Comparing FD method for the order parameter u with theory (equation (3.17)) with $k = 0.05 \text{ s}^{-1}$ and $\delta t = 0.5 \text{ s}$.

[Return to main text](#)

Figure A3.3 – Design your own graph

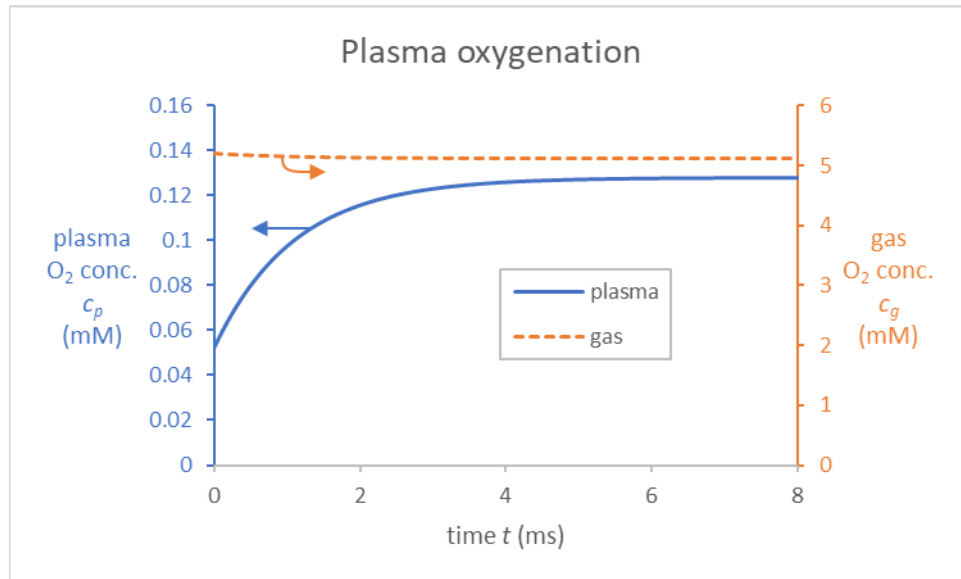


Figure A3.3 Excel 2016 chart of the FD method for blood plasma oxygenation. See the main text for rate constants and initial concentrations.

[Return to main text](#)

References

- Gould, H., J. Tobochnik, and W. Christian. (2007) *An introduction to computer simulation methods: applications to physical systems*. Pearson Addison Wesley, San Francisco, CA.
- Nelson, P. H. (2013) *Greek letters go green!* <http://circle4.com/biophysics/videos/>

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