

## *Instructor Guide*

### **Biophysics and Physiological Modeling**

#### ***Module 3: Finite difference method and $O_2$***

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This guide focuses on issues relating to **MODULE 3 (v.3.5)**. The series guide [BioPhys\\_Series\\_IG.pdf](#) discusses of the series as a whole. As the material in this module is nontraditional, it is *strongly recommended* that the Instructor/teaching assistant actually do the module ahead of assigning it to students. Good students have told me that they can work through the entire module in about *four hours*.

### **List of resource files**

- [BioPhys\\_Series\\_IG.pdf](#) – **INSTRUCTOR GUIDE FOR THIS SERIES OF MODULES** – common guide introducing this series of Modules – Read me first!
- [BioPhysMod03\\_IG.pdf](#) – **INSTRUCTOR GUIDE FOR MODULE 3** – this file.
- [BioPhysMod03.pdf](#) – **MODULE 3** – handout for students.

### **Keywords**

Biophysics, physiology, interactive exercise, marble game, quantitative modeling, Excel, kinetic Monte Carlo simulation, kMC sim, finite difference method, FD method, numerical method, approaching equilibrium, thermodynamic equilibrium, steady state, two-compartment model, calculus, testable hypothesis, ensemble average, fluctuations at equilibrium, order parameter, blood plasma oxygenation, oxygen uptake, CPR, oxygen tension, oxygen partial pressure.

### **Dependencies**

**MODULES 1 & 2** – Module 3 follows on from **MODULE 2**, which in turn depends on **MODULE 1**. These first three modules are the *common core* modules for this series.

### **Educational objectives**

1. Learn how to use the *finite difference method* for solving *kinetic problems* using the marble game as an example.
2. *Test* the *hypothesis* that the FD method *predicts* the *ensemble average behavior* of kMC sims of the same system.
3. Compare the FD method with the *analytical solution* for the *order parameter* of the same system.
4. Discover that the *stability of the FD numerical method* depends on the timestep and that the FD method agrees with the analytical solution, if the timestep  $\delta t$  is sufficiently small.
5. Learn how to use the FD formulation to *predict* steady-state (*equilibrium*) properties.
6. Model *plasma oxygenation* using the marble game.
7. Predict equilibrium *dissolved oxygen* using the model.
8. Understand the origin of *oxygen tension*  $P_{O_2}$  as a measure of *oxygen concentration* in blood plasma.

## Challenges to learning

The FD approach introduced in this module is *very powerful*. While it's applied to two simple situations in the module, it can be applied to much more complicated physiological systems (and networks) and to basically any problem that can be written in differential form. However, many students tend to compartmentalize knowledge and understanding. As **BIOPHYSICS AND PHYSIOLOGICAL MODELING** is an intrinsically *interdisciplinary* endeavor, students need to be encouraged to think across traditional subject boundaries. Many of the kinetic and thermodynamic concepts illustrated by the marble game are fundamental biophysical chemistry concepts. However, many students have difficulty making connections between this new approach and concepts that they are already familiar with from general chemistry and biology. In the classroom ideas section (below) I discuss how the marble game can be related to traditional chemical kinetics.

Another challenge to learning that often arises at this point is that some students do not make a distinction between kMC, FD and analytical approaches. It is important that students realize that while system parameters are shared, variables and modeling methods need not be.

## Discussion Questions

### Q.3.5 – FD is independent of $N$

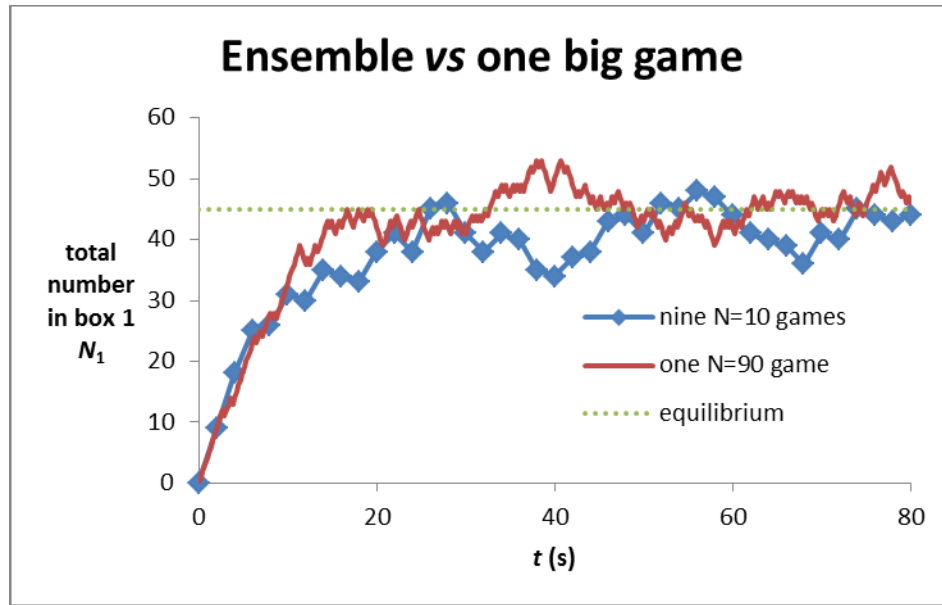
Q.3.5 (a) Asks students whether the ensemble average of the kMC sim matches the FD prediction. Sometimes students get distracted by the fluctuations in simulations with a small number of marbles. It is important that these observations be discussed. Using a demonstration spreadsheet can be helpful in this circumstance.

Q.3.5 (b) Asks students to confirm that the FD prediction for  $x_1(t)$  does not depend on  $N$ . This can be most easily justified by considering that each marble jumps independent of the others so that dynamics depends only on the mean residence time of a single marble  $\tau = 1/k$ .

Q.3.5 (c) Asks students to summarize how the variability in  $x_1$  varies as  $N$  is changed. This topic is discussed in more detail in Module E.

### Q.3.11 – Ensemble versus one big game

Q.3.11 (a) makes for a good classroom discussion. The figure below shows sample output from a simulation developed during class based on the classroom spreadsheet from **MODULE 1** (with  $k = 0.05 \text{ s}^{-1}$ ). As can be seen the total number of marbles determines the variability so that nine  $N = 10$  games behave in a similar manner to one  $N = 90$  game. The primary difference between them is that the timestep for the ensemble average is nine times longer than the single  $N = 90$  simulation. The single game does one jump at a time whereas the ensemble average has nine jumps per timestep. (**MODULE K** discusses how to properly simulate Poisson processes of small systems with a continuous-time simulation. If this is done then the average of nine  $N = 10$  games will be equivalent to one  $N = 90$  game, as is expected if every marble jumps at rate  $k$  independent of the number of marbles  $N$  in the game.)



### Q.3.18 – Accuracy and stability of FD method

This question asks students to determine values of  $\delta t$  that meet various criteria. Some students are uncomfortable with using their own judgment to answer this question, which makes this a good discussion question.

### Q.3.24 – Criteria for oxygen uptake

Q.3.23 and Q.3.24 ask students to close the loop on the discussion Dion's passage from air into plasma and explain how there can be a net flux even though the rate constant is 40 times larger for passage back from plasma into air. **Note:** A common student misconception is that hemoglobin is the cause of  $O_2$  uptake. {While it is true that hemoglobin is responsible to binding oxygen (and thereby reducing the free  $O_2$  concentration in plasma for a given total  $O_2$  content) it is only the concentration of free oxygen concentration in the plasma that determines the magnitude (and direction) of the net flux (for constant  $O_2$  concentration in the lung).}

### Q.3.29 – Interpreting graphs

The purpose of this question is to have students practice interpreting graphs. Some students are uncomfortable making their own determination. Part (b) leads into the following AWYD discussion of CPR and the idea that the oxygen concentration in the alveolus only decreases slowly because of its 40-times higher concentration at equilibrium.

### Q.3.36 – Physiology versus marble game picture

Q.3.36(a) This question provides an opportunity for students to compare the marble game picture of oxygen uptake with the traditional description in physiology textbooks. It is important that students include the role of the solubility  $\sigma$  in their translation.

Q.3.36(b) In part (b) students should realize that the use of partial pressure (as a measure of concentration (strictly speaking chemical potential)) simplifies the description.

Q.3.36(c) Barb's abbreviated description (reproduced in some physiology textbooks) omits the fact that the transfer from high to low is what happens *on average*. Randomness is implied by the process of *diffusion*, but students sometimes take the simplified description literally leading to one of the common misconceptions that diffusion is directed (deterministic) process.

### Q.3.37 – Henry's law and solubility

Using the notation in **MODULE 3**, Henry's law is

$$P_g = k_H c_p$$

comparing this with equation (3.42)  $c_p = \sigma P_g$  gives

$$\sigma = \frac{1}{k_H}$$

which shows that the solubility  $\sigma$  and the Henry's law constant  $k_H$  give the same information (but in different form).

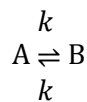
### Q.3.39 – Plasma doesn't store significant oxygen

This question is intended to have students discover that blood plasma (by itself) does not store a significant amount of  $O_2$ . The question also introduces them to an alternate measure of oxygen content in whole blood (including hemoglobin).

## Other classroom ideas

### Isomerization

As mentioned in the instructor guide to **MODULE 2**, the original marble game is isomorphic with a reversible first-order chemical reaction.



The particles are now the molecules in the reaction.  $N_1$  is the number of A isomers;  $N_2$  is the number of B isomers; box 1 is the beaker containing the A molecules; and box 2 is the same beaker! (containing the B molecules). This is actually a one box system with two kinds of particles, but the *exact same* model can be used! We just have to reinterpret the variables.

For this chemical reaction to be modeled correctly, the reaction must be *first order* in both the forward and backwards directions – and – the *equilibrium constant*  $K_{eq}$  must have a specific numerical value. It's an interesting class (or group) activity to ask students to come up with the value of the equilibrium constant and explain why it doesn't depend on the numerical value of  $k$ . It usually takes some time for students to correctly come up with the general chemistry explanation of the equilibrium constant.

$$K_{\text{eq}} = \frac{k}{k} = 1$$

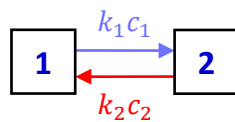
which is a property of the system (whether or not it is at equilibrium). At equilibrium, the ratio of the numbers (or concentrations) in the marble game is predicted by equilibrium constant

$$\frac{N_2}{N_1} = \frac{[B]}{[A]} = K_{\text{eq}} = 1$$

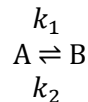
During this class activity it's a good idea to remind students that (just like in general chemistry) when we write equilibrium constants we will always use an uppercase  $K$ , whereas rate constants will always be written as lowercase  $k$ . Students should be reminded that they should make this distinction clear in any notes that they take, e.g. writing lowercase  $k$  with a loop e.g. " $k$ " so that it can be easily distinguished from uppercase  $K$ . Also in the modules (and in textbooks) these variables are usually written in *italics* whereas the unit kelvin  $K$  is not.

### General two-compartment model

The numerical model used for blood oxygenation is applicable to any first-order two-compartment model



or any first-order reversible reaction



The particles are now the molecules in the reaction.  $c_1$  is the concentration of A isomers;  $c_2$  is the concentration of B isomers. And the equilibrium constant is

$$K_{\text{eq}} = \frac{k_1}{k_2} = \frac{c_2}{c_1} = \frac{[B]}{[A]}$$

so that at equilibrium the ratio of the concentrations is predicted by equilibrium constant

$$\frac{c_2}{c_1} = \frac{[B]}{[A]} = K_{\text{eq}} \left( = \frac{k_1}{k_2} \right)$$

In this kinetic model it is important to emphasize that  $K_{\text{eq}} \neq 1$  because  $k_1 \neq k_2$ . One way to characterize this system is to specify the two initial concentrations, the rate constant  $k_1$  and the equilibrium constant  $K_{\text{eq}}$  as adjustable parameters and have  $k_2 = k_1/K_{\text{eq}}$  as a calculated parameter. A class activity could consist of (a) writing an algorithm for an FD method to calculate the approach to equilibrium of this system. (b) Testing the algorithm by calculating the first few steps of the algorithm by hand. (c) Implementing the algorithm in a spreadsheet and plotting  $c_1$  and  $c_2$  as a function of time for  $K_{\text{eq}} = 1$  (the original marble) with  $c_2 = 0$ . (d) Asking the class to predict what will happen as  $K_{\text{eq}}$  changes. E.g. how will the graph change if  $K_{\text{eq}} = 10$  or  $K_{\text{eq}} = 0.1$ ?

The goal is for students to realize that the equilibrium constant is the ratio of the rate constants and that it predicts the ratio of  $c_2/c_1$  at equilibrium.

### Calculus connection

For students and classes with calculus, a connection can be made between the finite differences derived in sections 3.2 and 3.3 and the corresponding derivatives, e.g. equation (3.5) can be written as

$$\frac{dN_1}{dt} = k(N - 2N_1)$$

Because  $x_1 = N_1/N$ , equation (2.6) can be derived by finding the derivative

$$\frac{dx_1}{dN_1} = \frac{1}{N}$$

Hence, equation (3.7) can be derived using the chain rule

$$\frac{dx_1}{dt} = \frac{dx_1}{dN_1} \frac{dN_1}{dt} = \left(\frac{1}{N}\right) k(N - 2N_1) = k(1 - 2x_1)$$

In section 3.3 the order parameter is defined as  $u = 2x_1 - 1$ . By taking the derivative we find equation (3.12)

$$\frac{du}{dx_1} = 2$$

and using the chain rule and  $x_1 = (u + 1)/2$  we can derive equations (3.14) and (3.16).

$$\frac{du}{dt} = \frac{du}{dx_1} \frac{dx_1}{dt} = 2k(1 - 2x_1) = 2k \left( 1 - 2 \left( \frac{u + 1}{2} \right) \right) = -2ku$$

### Exponential decay (and growth)

This module introduces exponential decay and briefly discusses exponential growth. These topics make great classroom discussion topics. – See instructor guide for **MODULE 2**.



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