Instructor Guide

Biophysics and Physiological Modeling

Module 1: Introduction – marble game

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This guide focuses on issues relating to **MODULE 1 (V.3.0)**. 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 less than ***three 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!
- BioPhysMod01_IG.pdf – **INSTRUCTOR GUIDE FOR MODULE 1** – this file.
- BioPhysMod01.pdf – **MODULE 1** – handout for students.
- BioPhysMod01_ClassMarbleGame.xls – classroom activity spreadsheet (Excel 2003).
- BioPhysMod01_BrownianMotionDemo.xls – Brownian Motion Demo Spreadsheet (Excel 2003).

Keywords

Biophysics, physiology, diffusion, equilibrium, transport processes, active learning, interactive exercise, kinetic Monte Carlo simulation, kMC sim, random number, RANDBETWEEN, average, probability, graphs, equilibrium, Fick's law of diffusion, enhanced diffusion, hemoglobin, myoglobin, oxygen cascade, glucose, glycolysis.

Educational objectives

1. Learn how to play the ***marble game*** (by hand).
2. Introduce students to using ***Excel*** for science.
3. Review the basics of ***scientific graphs***.
4. Learn how to calculate the ***observed average*** $\langle N_1 \rangle$ and the ***observed probability*** $P(N_1)$ of a particular state of the marble game.
5. Discovering that ***equilibrium*** is a ***dynamic process*** that doesn't depend on the initial state of the system.
6. Discovering that ***diffusion*** of molecules from high to low concentration is the result of ***unbiased*** random ***Brownian motion*** that can be ***simulated*** (and explained) by the marble game.
7. Discover ***Fick's law of diffusion*** by analyzing marble game data.
8. Learn how ***hemoglobin*** and ***myoglobin*** enhance diffusion in the ***oxygen cascade***, and how ***glycolysis*** enhances ***glucose*** transport to tissue.

Challenges to learning

Students generally respond well to these materials, although most students admit that completing a module requires a significant amount of mental effort. Students must carefully follow instructions to be able complete the module. The use of Excel mitigates this somewhat (particularly for students with no prior programing experience) as it provides a familiar (introductory) computational environment. Excel allows students to be immediately involved in ***active learning*** without knowing in advance what the "right answer" should be. As a result, students are expected to evaluate the output of their own work. This type of discovery-based problem solving can be a significant challenge for some students. Group activities and discussions should help.

One impediment to learning is that some students do not read symbolic or mathematical information properly. They tend to skip over the symbols – perhaps with the expectation that the words alone will explain what is going on. Module 1 addresses this issue with an "***About what you discovered***" section that explains how students should read material containing symbolic information. This issue can be quite persistent with some students and occasionally students have not been able to explain what a particular variable is – even though they had been using it for some weeks. In **MODULE 1** the two primary variables are r and N_1. It is important that students think "random number" and "number of marbles in box 1" when they read these. Quizzes and/or tests that ask students to explain what a symbol means may be helpful to focus student attention on this issue.

Diffusion misconceptions

A major goal of **MODULE 1** is to address student misconceptions about diffusion. The marble game is presented as a realistic conceptual model that can be used to understand (and visualize) diffusion. Misconceptions about diffusion such as "molecules go where they are needed.", "molecules do not want to sit next to each other and therefore spread out as evenly as possible", "going from high to low gives the molecules more space" and "there is less force on the molecules when they are less crowded" can be very persistent. It should be emphasized that the marble game is an authentic simulation of diffusion. Molecules do not know where they are going – the process is completely random – it is independent of the state of the system (distance from equilibrium). There is no repulsion between marbles and they do no need "more space". Fick's law results from random movement of ***independent*** particles (that do not interact with each other in any way). Fick's law even applies to a system with only one marble! – see **MODULE R**.

Discussion Questions

Q.1.10 – Random die and RANDBETWEEN(1,10)

This discussion question is intended to get students thinking about how Excel relates to the real world by asking students to compare the graphical output of RANDBETWEEN(1,10) with a real ten-sided die. The simplest answer to part (c) is simply to count how many "1"s, "2"s, etc… are generated. This can lead into a discussion of using a histogram to represent the Excel output. The (optional) challenge problem can motivate the use of (statistical) hypothesis testing.

Q.1.18 – Normal distribution

Technically, the distribution $P(N_1)$ is a binomial distribution, but for $N = 10$ the shape of the distribution can be approximated by a normal distribution. The (optional) challenge problem can motivate the use of (statistical) hypothesis testing. This topic of equilibrium distributions is investigated further in **MODULE E**.

Q.1.21 – Finding equilibrium

The kMC approach used in **MODULE 1** has been very successful in getting students to think about equilibrium as a dynamic process. It is important that students read the "approaching equilibrium" *About what you discovered* before answering question Q.1.21. Some students find it quite challenging to answer Q.1.21(d) to describe the dynamic process of a marble continuing to jump between boxes at equilibrium.

Q.1.23 – Alternate simulation – tracking individual marbles

The simulation described in this question produces an equivalent (random) sequence of N_1 values, although the actual changes for each value of r are not identical. This is a useful conceptual model for students to retain because it reinforces the idea that each marble is treated identically by the roll of the random die. If this simulation is implemented then a detailed history (of box locations) can be generated for each one of the marbles. Technically, the jumps of each marble approximate a Poisson process – see **MODULE K**.

Q.1.27 – Discovering Fick's Law

Student answers to this question should look something like Figure A1.2 (in appendix of **MODULE 1**). They have to follow the directions carefully to get the correct graph. The first purpose of this question is for students to discover that the marble game predicts Fick's First Law. Topics that can be discussed are:

(i) Why choose $\Delta N(0)$ as the independent variable and $N(2 \rightarrow 1)$ as the dependent variable?

(ii) Using a scientific method to ***discover*** an empirical relationship (Fick's law).

(iii) The technical meaning of the phrase "y is proportional to x" – meaning $y = mx$ (with zero intercept).

Q.1.28 – The cause of diffusion

The discussion question is intended to allow students to discuss how the marble game illustrates that random Brownian motion is the ultimate cause for Fick's law. This question provides an opportunity for metacognitive discussion of (prior) student misconceptions about diffusion.

Q.1.32 – Diffusion enhancement by reaction

Glucose transport across membranes is quite slow and is facilitated by "glucose transporters". The process is entirely passive and reversible. Glycolysis reduces N_c and increases the net transport of glucose given sufficient glucose transporters. This can lead to a discussion of glucose transport and diabetes.

Q.1.33 – Fetal hemoglobin (Hb)

The marble game provides a simple explanation for the O_2 transport enhancement provided by fetal Hb binding O_2 more strongly than adult Hb. As an extension, students could discuss the consequences if fetal Hb was identical to adult Hb.

Other classroom ideas

The marble game

The marble game can be introduced by having students actually play the game using ten marbles, a ten-sided die and two boxes made from two taped-together weigh boats.

These materials are relatively inexpensive and were obtained from the following sources (in 2010).

Panacea Products Corp. Marbles 100ct Bag Teal
From www.amazon.com Sold by: Seacorals ~ US$ 2 per bag

Chessex Dice Sets: Teal/White Translucent d10 Set (10) ~ US$ 6
from www.frpgames.com

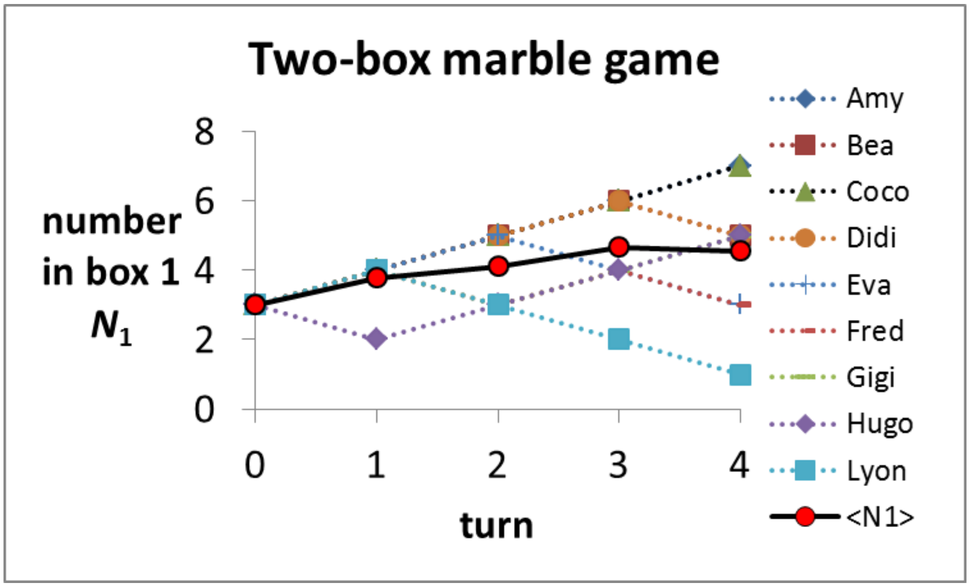
Plastic Square Weigh Boats Medium Dish 100pk
From www.amazon.com Sold by: Scientific Equipment of Houston ~ US$ 9 per 100pk

The file BioPhysMod01_ClassMarbleGame.xls is an Excel 2003 spreadsheet that can be used for a class (group) activity. Each student starts the game with $N_0 = 3$ marbles in box 1. They then roll the die to determine which way to move a marble. Students call out the number they rolled and their new value of N_1 determined using the game rules. The instructor (or a student volunteer) can record the results in a spreadsheet for graphical analysis with the whole class being responsible for checking that the change that was called out complies with the game rules. This activity makes sure that all students understand how to apply the game rules, and it gives each student hands-on experience with the model system. Inevitably there will be some mistakes made and discussion of what the mistake was and how to fix the spreadsheet engages students in a group activity where they learn aspects of the game that they may not have originally recognized.

In the spreadsheet, Excel can also automatically calculate the ***ensemble average*** $\langle N_1 \rangle$ of all the games for the class as a whole at each turn. This activity is a fun icebreaker for the first day of class, and any student misconceptions about how the marble game is played, should be resolved. If a projector screen is available, it also makes it possible for the instructor to do a quick demonstration as to how Excel can be used to plot graphic data and calculate averages…

The instructor can take this opportunity to discuss the art and science of designing and reading graphs. As mentioned in **MODULE 1**, the graph shown above should not (strictly speaking) have lines connecting the dots as the data are ***discrete***. However, the dotted lines are added as a "guide to the eye". The instructor can take this opportunity to show the class what the same data would look like as **Scatter with only Markers** (technically correct); **Scatter with Smooth Lines and Markers** (banned in these modules); **Scatter with Straight Lines and Markers** (sometimes okay as a guide to the eye); **Scatter with Smooth Lines** (banned in these modules); and

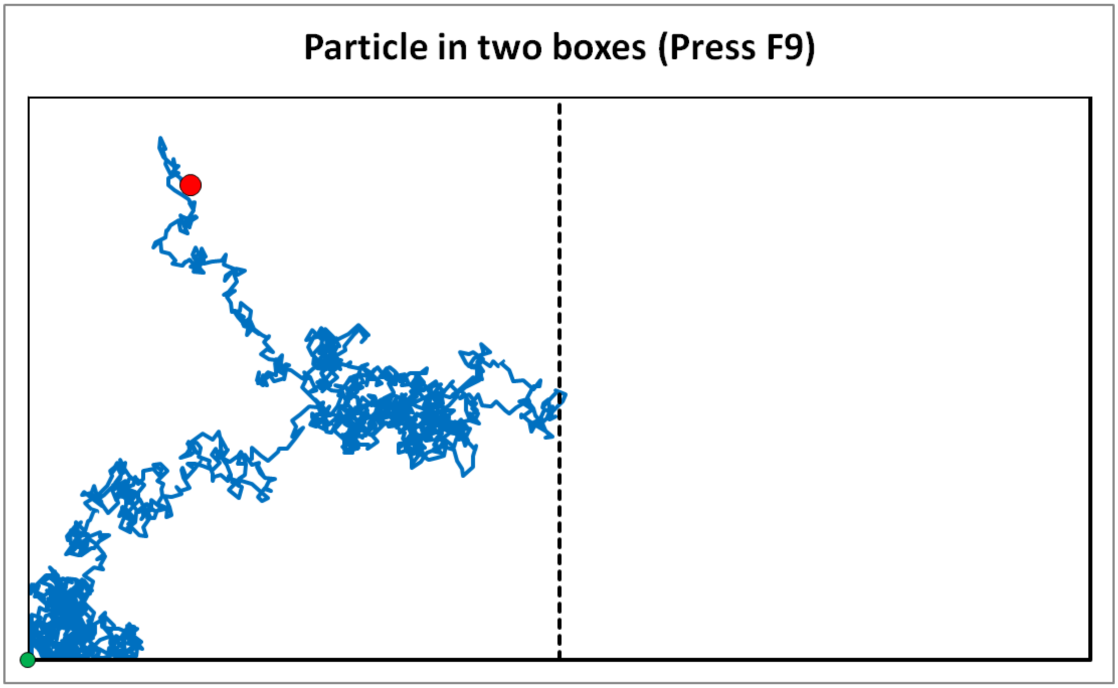
Scatter with Straight Lines (used for continuous functions in these modules). These changes in format can be made by ***right*** clicking on the chart and selecting **Change Chart Type…**



Demonstration – Brownian Motion

Another class demonstration is to use the Excel demonstration spreadsheet (BioPhysMod01_BrownianMotionDemo.xls mentioned in **MODULE 1** and posted on the companion website) to show students what Brownian motion in solution looks like. This provides good motivation for the rules of the marble game where all marbles have an equal chance of jumping to the other box at each turn – just like the Brownian particle.

The Excel 2003 file (see below) shows a ***snail trail graph*** of a 2000 step random walk. The two boxes are physically identical and the dotted line between them has no physical significance. It's just an imaginary dividing line. The green circle is the starting point and the red circle is the ending point (2000 steps later). To make this spreadsheet work, you must "**make a circular reference work by changing the number of times that Excel iterates formulas**" by setting **Maximum Iterations** to 1. In Excel 2010, the following instructions should work. Click the **File** tab, select **Options**, and then select the **Formulas** category. In the **Calculation options** section, select the **Enable iterative calculation** check box. Set value in the **Maximum Iterations** box to **1**. Don't forget to click **[OK]** to return to the spreadsheet. Press F9 to make a new random walk starting out where you left off. This sim represents any molecule (e.g. O_2) executing Brownian motion (e.g. O_2 within cytosol, or within interstitial fluid).



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