Instructor Guide
Biophysics and Physiological Modeling
Module 2: Algorithms and pain relief
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This guide focuses on issues relating to **MODULE 2 (V.3.3)**. 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 ***two to 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!
- BioPhysMod02_IG.pdf – **INSTRUCTOR GUIDE FOR MODULE 2** – this file.
- BioPhysMod02.pdf – **MODULE 2** – handout for students.

Keywords

Biophysics, physiology, active learning, interactive exercise, marble game, Excel, kinetic Monte Carlo simulation, kMC sim, chemical master equation, CME, random number, RANDBETWEEN, algorithm development and testing, mean residence time, equilibrium, drug elimination, pharmacokinetics, one-compartment model, drug half-life, semi-log plot.

Dependency

MODULE 2 follows on from **MODULE 1**.

Educational objectives

1. Learn how to ***write*** and ***test algorithms***, including the difference between ***parameters*** and ***variables***.
2. Discover the difference between ***relative*** and ***absolute addressing*** in Excel and how they are used for variables and parameters (respectively).
3. Learn how to plot ***any function*** or ***shape*** in Excel.
4. Discover how the approach to equilibrium depends on the ***jump rate constant*** k but not ***system size*** N.
5. Learn the basics of the one-component model of pharmacokinetics (PK).
6. Discover that the PK model predicts an ***exponential decay***.
7. Learn about ***semi-log plots*** and discover that exponential functions appear ***linear*** in them.
8. Observe that the two-box model of drug elimination ***correctly predicts*** the long-time behavior (of Tylenol) including a ***half-life*** that does not change with time.

Challenges to learning

The biggest pedagogical challenge in this module is getting students to carefully follow the procedure for writing and testing algorithms. Writing an algorithm is much easier if students ***test*** the resulting algorithm ***while they***

are writing it. This makes the algorithm less abstract (more concrete) for students and allows them to identify parameters or variables that they might have missed in their original list. It is important for students to make a clear distinction between variables in the current step (row) labeled with a $\star^{\text{new}}$ superscript whereas variables in the previous step (row) are labeled with a $\star^{\text{old}}$ superscript. This rather complex notation is required to make sure that students pay attention to which version of the variable they need. Because of this complex notation I encourage students to write out algorithms ***by hand***. An alternate notation that is more Word-friendly would be to use inline formatting such as **N_1^old** for N_1^{old}. This choice is really a matter of instructor preference. The inline notation would be advantageous for online instruction, because the whole student answer can be entered as plain text.

Other ongoing pedagogical challenges include getting students to read the material carefully enough. As mentioned in the module, Excel instructions must be read carefully and students must translate mathematical symbols into the system properties that they stand for. It is also important that students realize that they are responsible for ***always including units*** with any numerical quantities. The non-SI units commonly used in physiology make it ***essential*** that students always keep track of them.

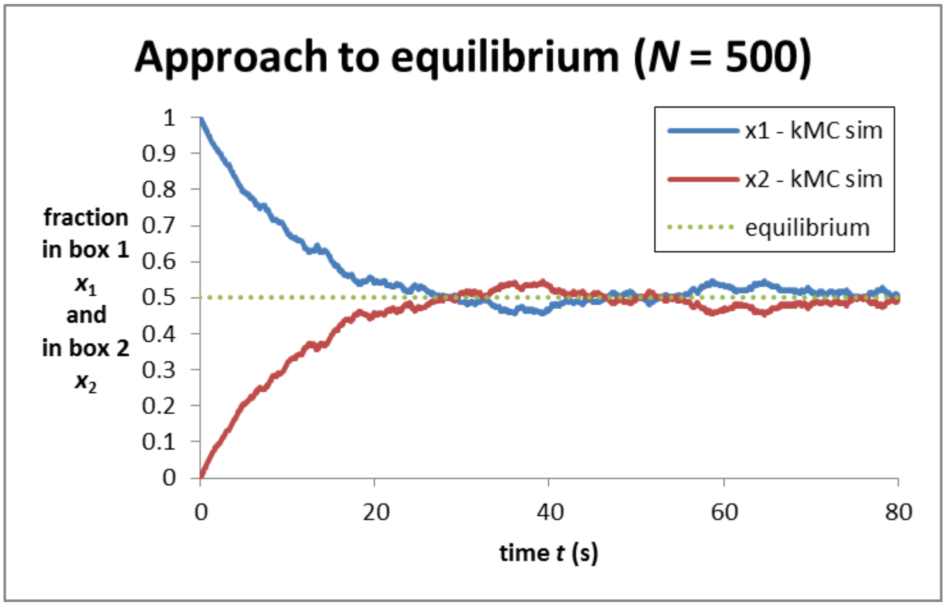
Discussion Questions

Q.2.1 – Omelet recipe

Q.2.1 asks students to write out a recipe for an omelet. A good introductory class activity is to discuss the utility of student recipes. The objective is to get students to describe a detailed list of all ingredients (and cooking apparatus – e.g. gas burner) that are needed to make the omelet. Asking students to come up with a list of ingredients and a separate list of instructions successfully motivates the process of writing an algorithm – before writing a spreadsheet. As students usually forget some of the ingredients (or apparatus) it also successfully illustrates the idea that a list of ingredients is tentative until the recipe has been tested.

An alternate (simpler) activity for high school students, that doesn't require experience with cooking, could be to write out instructions for making peanut butter and jelly sandwiches.

Q.2.9 – Why $\langle x_1 \rangle = 0.5$



Q.2.9 asks students to explain why the marble game has an equilibrium fraction in box 1 of $\langle x_1 \rangle = 0.5$. There are many ways of explaining why the marbles are evenly distributed on average at equilibrium. If you add a column to the spreadsheet for $x_2 = 1 - x_1$ and add x_2 to the chart, students can graphically see the symmetry of the marble game.

A related explanation can be obtained by considering the motion of a single marble at equilibrium. It jumps randomly between the boxes (with equal probability per step). Hence, after a long period of time, you would expect that each marble would spend an even amount of time in each box (on average).

In **MODULE 3** the general method for finding equilibrium values is presented. In the **INSTRUCTOR GUIDE** to **MODULE 3**, there is an additional discussion of the fact that the marble game is isomorphic with a reversible first-order chemical reaction. Most students do not realize that the marble game is related to the kinetics that they studied in general chemistry. Hence, the discussion of this question can provide motivation for the mathematical (FD) approach introduced in **MODULE 3**.

Q.2.10 – Marble independence

This question allows students to discuss the effect of the number of marbles N on the kinetics of the marble game – see following the ***About what you discovered***. During this discussion is is useful to remind students of equation (2.3) and that the mean residence time τ and the rate constant k provide the same information (for this system).

$$\tau = \frac{1}{k}$$

Q.2.16&17 – Effects on system and simulation

Q.2.16 and Q.2.17 are intended to get students to think critically about quantitative details of the ***simulation*** and the ***system*** that it is simulating. It may be useful to start by asking students what each of the symbols actually represents. This is a good opportunity to remind students to think "physical duration of the simulation" when they read t_{sim}.

A common conceptual difficulty for students is that they confuse the length of the simulation in steps N_{steps} with the physical duration (physical amount of time) t_{sim} that elapses during the simulation. The relationship between these summarized in equation (2.11).

$$t_{\text{sim}} = N_{\text{steps}}\Delta t = \frac{N_{\text{steps}}}{kN}$$

Q.2.18 – Applications of the marble game

Q.2.17 stimulates students to think about how the marble game can be used to model transport processes in physiology. This discussion can be used to make the distinction between passive diffusive processes (no external energy source) and active processes that require external energy (e.g. from ATP). Students should be specific about what the boxes and marbles represent.

Q.2.28 – Stochastic kMC sim of drug elimination

The simulation in Q.2.27 uses a fixed timestep of $\Delta t = 1/(k_e N)$ and the sim starts out with $N_0 = x_0 N$ molecules in box 1. During each timestep, each molecule has a constant chance of $1/N$ of leaving the system. Students should see an exponential decay (on average) because the half-life (elimination kinetics) depend only on k_e and not on the starting amount x_0 or N_0.

Other classroom ideas

Half-life and semi-log plots

An important diagnostic feature of semi-log (time) graphs is that they only appear linear ***only if*** the data exhibit an exponential time dependence. Hence, the fact that the clinical data for TYLENOL Liquid and TYLENOL Caplets appear linear on a semi-log plot (after about an hour) shows that they exhibit the same exponential decay predicted by the marble game model (and the one-compartment PK model) of drug elimination. The diagnostic aspect of this graphical representation can be demonstrated by showing what other functional forms look like on a semi-log plot.

Writing algorithms

A good class activity is to go through the procedure for writing an algorithm with the class or as a group activity using questions 2.2 or 2.19 or the algorithm examples below.

Algorithms – Coin toss

Another class activity is to develop an algorithm to simulate tossing a coin using Excel's **RAND** function and then calculate the observed cumulative probability $P(N)$ of the coin landing heads-up after N coin tosses. It is not possible to (easily) use Excel's function **AVERAGE** to do this, so students need to figure out what is required to calculate a running average using a formula like

$$P(N) = \frac{\sum_{i=1}^{N} h_i}{N}$$

where h_i is a variable that has a value of 1 when the coin lands heads and a value of 0 (zero) if the coin lands tails. i is an index for $Step$. It sometimes takes students a while to figure out that they need a separate variable for the running count total of the number of heads (Sum) to use this formula.

While it is possible to use the Excel function **RANDBETWEEN(0,1)** to generate h_i, I prefer having students use the following instructions using the Excel function **RAND()** that generates a real-valued random number between zero and one using something like

$$r = \mathrm{RAND}()$$

$$h = \mathrm{IF}(r < p, 1,0)$$

where the ***parameter*** p is the probability that the coin lands heads-up. If $p \neq 0.5$ then the coin is ***biased***. As will be discussed in a later module, this biased coin can be used as a simple model of a motor protein.

The output of this simulation should be a plot of $P(N)$ versus N, providing a graphical illustration of the ***law of large numbers***.

Potential test questions

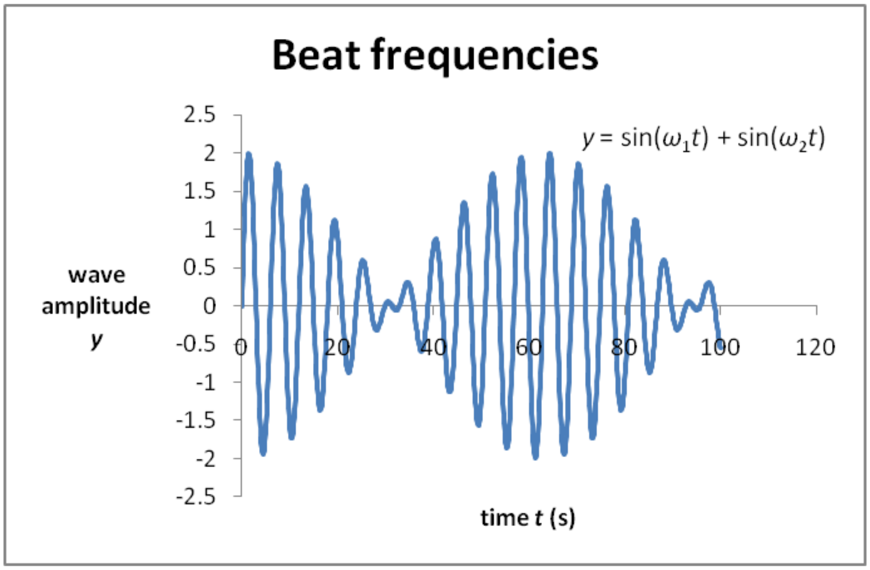
As mentioned in the module, questions like Q.2.2-Q.2.4 and Q.2.19 make good test questions, because they test student's ability to write and understand algorithms. In addition, they can be answered under standard test conditions – no PC required!

Plotting functions in Excel

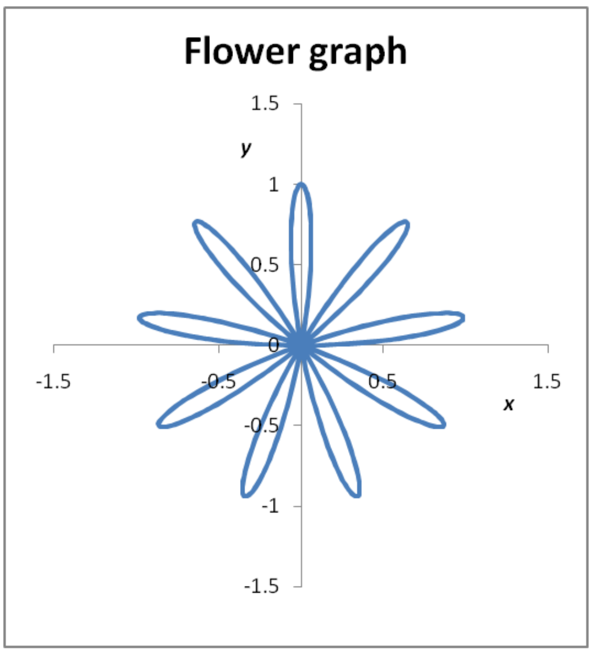
Many students do not realize that Excel can be used to plot any arbitrary function and that such a plot can be added to any **XY scatter** chart by adding a new table to the spreadsheet for both the **X** and **Y** data. You might like to choose a visually appealing graph that students may not have seen before e.g. the following graph plots the function

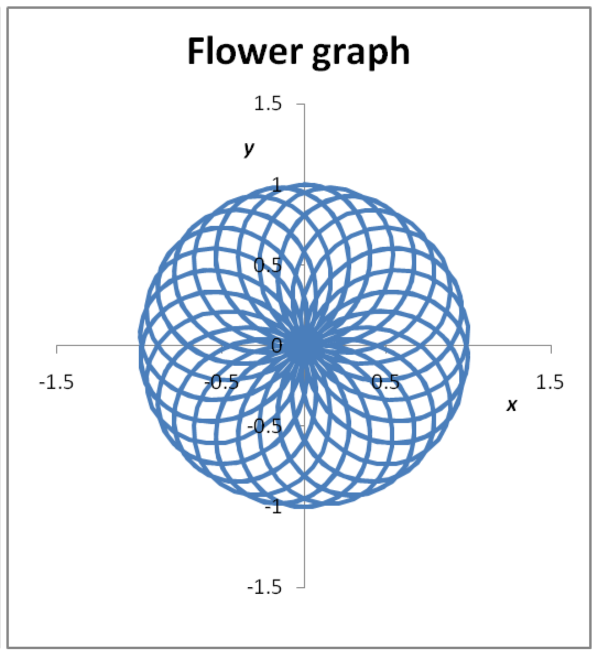
$$y = \sin(\omega_1 t) + \sin(\omega_2 t)$$

with using parameters $\omega_1 = 1.0\ \mathrm{s}^{-1}$ and $\omega_2 = 1.1\ \mathrm{s}^{-1}$. The ***timestep*** parameter for the plot was $\Delta t = 0.1$ s.



Writing an algorithm for this plot reinforces the idea of what an algorithm is about – and that any function can be plotted in Excel. You can (of course) replace the function with any that you like.





You can also ***parametric equations*** in Excel. E.g. the preceding can be plotted using $A = \cos(\omega_2 t)$, $x = A\sin(\omega_1 t)$ and $y = A\cos(\omega_1 t)$. The following graphs both have $\omega_1 = 1\ \mathrm{s}^{-1}$. The first graph has $\omega_2 = 7\ \mathrm{s}^{-1}$ and the second has $\omega_2 = 1.3\ \mathrm{s}^{-1}$.

Half-life step graph

As a more advanced exercise, students can develop an algorithm to plot a theoretical half-life step graph similar to the one shown in the "exponential decay and half-lives" ***About what you discovered***, which is also discussed in the “using Excel to plot functions” ***About what you discovered***. This algorithm has one ***parameter*** $t_{1/2}$ and two ***variables*** t and N_1. The tricky part about this algorithm is that it has *two* steps that must be repeated e.g.

Step 1

$$t^{\text{new}} = t^{\text{old}}$$

$$N_1^{\text{new}} = \frac{N_1^{\text{old}}}{2}$$

Step 2

$$t^{\text{new}} = t^{\text{old}} + t_{1/2}$$

$$N_1^{\text{new}} = N_1^{\text{old}}$$

…to produce the step graph. This type of step graph is useful in later modules where histograms of random data are plotted using an **XY Scatter** graph. BTW in Excel if you highlight two rows and then **click-drag copy** the two-step algorithm it will successfully replicate itself for the desired number of steps.

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