Instructor Guide
Biophysics and Physiological Modeling
Series Overview

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This guide is an overview of the introductory modules. For a more detailed discussion of the individual modules see http://circle4.com/biophysics/modules

Modeling with the marble game

While the modules contain many traditional biophysics and physiology topics such as diffusion, ion channels and random walks, the primary focus is on ***quantitative scientific modeling***. Every module has modeling as its central theme. The modeling with the "***Marble Game***", which is a ***kinetic Monte Carlo simulation (kMC sim)*** of the classic two-box model system from undergraduate statistical physics. It provides a conceptual framework for the modeling molecular transport in physiology and develops a conceptual, computational and mathematical framework that spans all of science, technology, engineering and math (STEM) [Nelson 2012].

The student modules are written in the style of self-study guides that engage students in discovery-based modeling activities using Excel. The motivation for this approach is that educational research (and personal experience) has shown that students learn more in an ***active-learning environment***. Excel is used as the modeling software because it is ubiquitous, non-threatening to students and it enables them to immediately engage in modeling stochastic systems. While conducting these activities, students ***discover*** for themselves the consequences of the model assumptions and compare the model predictions with experimental data. This active-learning approach also extends to the traditional algebraic derivation of equations. "***Show that…***" questions are used so that students complete key steps in algebraic derivations for themselves. Well-prepared physics students learn to do this as they read traditional texts. However, many life-science students seem to have the idea that if they see math – they should just skip it – and then continue reading when the math is over.

The use of inline activities and questions is designed to make students active participants in the process. This encourages students to critically consider the content while they are working on it. Sometimes after these activities there are ***About what you discovered*** sections. These offer additional explanations of features of the modeling that students might not have considered on their own. These discussions usually make sense only ***after*** the student has completed the preceding activity. Hence, it is important that students be encouraged to attempt the activities ***before*** they read the following ***About what you discovered***. The modules are PDF documents that have been developed as standalone student handouts for biophysics or physiological modeling courses. The core text of the modules can be used by students with ***no calculus background***. However, the modules also include ***optional*** **CALCULUS QUESTIONS** (and sections) aimed at students with university-level calculus. These sections contain connections between the finite difference approach developed in the modules, and more traditional calculus approaches.

In addition to the regular questions and optional **CALCULUS QUESTIONS**, the modules include **DISCUSSION QUESTIONS** that can be used to initiate classroom discussions. **CHALLENGE QUESTIONS** are optional (perhaps for extra credit) and the **RESEARCH QUESTIONS** can be used for open-ended student projects.

Module 1-4 summaries

1. Introduction – marble game

In **MODULE 1**, students are introduced to a simple kMC sim that is presented in the form of a simple children's game. In the game, the student keeps track of the number of marbles N_1 in one of two boxes. This marble game has just one repeated rule

> **Rule:** Roll the ten-sided die. If you rolled a number ***less than or equal to*** N_1, then move a marble from box $1 \rightarrow 2$, otherwise move a marble from box $2 \rightarrow 1$.

That's it! This kinetic model accurately simulates Brownian motion and forms the foundation for the rest of the modules. If students understand the marble game, they can translate their understanding to an amazingly wide variety of physiological situations including:

- membrane transport
- distribution of O_2, CO_2 and glucose
- drug delivery and elimination
- osmosis and osmotic pressure
- bioelectricity & membrane potentials
- diffusion and random walks
- molecular signaling & calcium
- synapses & neurotransmitters
- ion channel permeation
- ion channel gating & action potential
- kinetics of motor proteins
- fluid dynamics and blood flow

In **MODULE 1**, students are guided through how to implement the marble game in an Excel spreadsheet and are then asked leading questions – designed for them to ***discover*** for themselves what the marble game can tell them about how molecules behave in physiological systems. In particular, students discover that equilibrium is a dynamic process and that random Brownian motion is responsible for Fick's law of diffusion. Fick's law is then used to explain the enhancing roles of hemoglobin and myoglobin in the O_2 cascade, and why glycolysis enhances glucose transport into cells.

2. Algorithms and pain relief

In **MODULE 2**, the marble game is generalized and students are introduced to the concept of ***algorithm development***. Students discover what is required to use Excel for quantitative modeling. These skills are essential for the rest of the modules. Students are guided through how to produce graphs in Excel and how to interpret them – vital skills for both physical and life science majors. Drug elimination is introduced as a first quantitative application of this approach. This system was chosen because most pre-med and life science majors find it fascinating and it also provides vital insights into later models.

3. Finite difference method and O_2

Finite difference (FD) methods are introduced using the marble game sim as an example. Students test the hypothesis that the FD solution predicts the ***ensemble average*** behavior of the kMC sims. An order parameter u is defined for the marble game system and the ***analytical solution*** for u is presented for its exponential decay to equilibrium (an ***optional*** calculus derivation of $u(t)$ is also included). The analytical solution is compared with FD solutions with various timesteps to investigate the accuracy and stability of the FD numerical method. The FD method is then applied to O_2 uptake in the lungs. Equilibrium O_2 partitioning between gas and blood plasma is related to P_{O_2} – the partial pressure of oxygen (used in physiology and medicine as a measure of O_2 plasma concentration).

4. Model validation and penicillin

In this module, students apply kinetic models to physiological data. Students discover the consequences of the following **ADME** assumptions for a one-compartment drug elimination model. In this model the drug is:

A. absorbed immediately
D. distributed throughout the body rapidly
M. *not* **metabolized** (passes through the body without chemical modification)
E. excreted by a single mechanism (so that we only need one rate constant k_e)

Students analyze **clinical data** and discover that the simple model of drug elimination works ***amazingly*** well! Students do simple curve fitting in Excel and are introduced to data analysis techniques including ***residuals***. As they say at NIST, "R^2 $Is\ Not\ Enough!$" Students learn how quantitative modeling can provide unexpected insights into how things work.

Readership and level

The topics in the modules have been selected to appeal to a wide audience, including biology and pre-med students. The audience for these modules is wider than traditional Biophysics or Mathematical Biology texts as it is **not** limited to students with substantial math backgrounds. The core text can be used by students with ***no calculus background at all***. However, the text also includes ***optional*** sections aimed at students with integral calculus at the university level. These sections contain connections between the finite difference approach developed in the modules and more traditional calculus approaches.

The modules are aimed ***primarily*** at undergraduates in both the physical and life sciences. The prerequisites for the non-calculus materials are an introductory knowledge of chemistry and algebra. The calculus-based sections are aimed at students that have also completed a year of university-level calculus. The introductory modules are also suitable for well-prepared high school students.

Notwithstanding that the materials are accessible to well-prepared high school students; they are also be useful as a resource on scientific modeling for students without strong quantitative backgrounds entering interdisciplinary programs such as biochemistry and molecular biology (BMB), biophysics, biomedical engineering or MD/PhD programs etc…

The primary focus of the modules is ***quantitative scientific modeling with physiological applications***.

Instructional approaches

Because the materials in the modules are nontraditional, it is strongly recommend that the Instructor/teaching assistant ***actually do the module*** before they are assigned. Good students can work through **MODULE 1** in less than ***three hours*** without any prior exposure to the material.

As the modules are self-directed computer labs, they can be used either as in-lab exercises or as outside class homework assignments. The modules can also be used in a flipped classroom environment where students learn the material from the modules and class time is used for "homework" or class discussions.

The approach is new, so any feedback (comments, corrections, evaluations etc.) that you might wish to share would be very helpful. Email: pete@circle4.com

About the marble game

In the past decade there has been a growing movement calling for more quantitative content in the life sciences curriculum. The *Bio2010* report called for more mathematics, physical and information sciences to be taught to new biology students (NRC, 2003). The *Vision and Change* report (AAAS, 2011) identified 6 core competencies required for all students, including the abilities to: 1) apply the process of science; 2) use quantitative reasoning; 3) use modeling and simulation; 4) tap into the interdisciplinary nature of science; 5) communicate and collaborate with other disciplines; and 6) to understand the relationship between science and society. The recent report by the President's Council of Advisors on Science and Technology (PCAST) goes further and calls for widespread curricular reform to develop new pathways to the science, technology, engineering and math (STEM) disciplines (PCAST, 2012). This call has been reinforced by a call for a "learning progression" for life science majors through the curriculum (Klymkowsky and Cooper, 2012).

In addition to changing what we teach, education research has conclusively shown that we need to transform undergraduate education from a (sometimes boring) passive lecture-based process into an active-learning process based on educational research (DiCarlo, 2009). Basically the recommendation is that "we should teach the way we learn". Students should realize that science produces evidence-based knowledge and understanding – not just a list of declarations by some authority that need to be accepted and memorized without any evidence. A recent promo for the Science Channel sums up this idea in two words – "**question everything**" http://youtube.com/watch?v=IH5SQEKIGhA. The modules are designed to engage students in active learning, where they can discover for themselves the consequences of model assumptions in a manner that addresses all of the goals outlined in recent National Research Council (NRC) reports on discipline-based education research (NRC, 2011; NRC, 2012):

- master a few major concepts well and in-depth;
- retain what is learned over the long-term;
- build a mental framework that serves as a foundation for future learning;
- develop visualization competence including ability to critique, interpret, construct, and connect with physical systems;
- develop skills (analytic and critical judgment) needed to use scientific information to make informed decisions;
- understand the nature of science; and
- find satisfaction in engaging in real-world issues that require knowledge of science.

The marble game includes many of the features identified by multiple inter- and multi-disciplinary reports as being desirable (AAAS, 2011; Henderson and Dancy, 2009; HHMI-AAMC, 2009; NRC, 2003; NRC, 2011; NRC, 2012). From a disciplinary point of view, the marble game ***directly*** illustrates at least five of the seven general physiological models applicable from the molecular to organismal level (Modell, 2000). It also provides a prototypical model for molecular kinetic processes in biology, chemistry and physics that can be immediately applied to most biomedical engineering problems (Truskey et al., 2009). This stochastic framework is useful for modeling a vast array of processes including: nuclear decay, single-molecule dynamics, chemical kinetics, Brownian motion and diffusion, membrane transport for organelles, cells, organs, entire organisms and even evolution of populations and ecosystems. The marble game is a prototypical kinetic Monte Carlo (kMC) method that can be used to solve the master equations for stochastic processes (Markov chains). The marble game is based on kMC simulation methods that were developed independently for molecular transport processes (Nelson et al., 1991), but are isomorphic with methods developed earlier for solving the chemical master equation (CME) (Gillespie, 1977). These methods are gaining widespread adoption as a computational research technique for solving the CME. According to Beard and Qian "*We suggest that the importance of the CME to* *small biochemical reaction systems is on a par with the Boltzmann equation for gases and the Navier-Stokes equation for fluids. This is a big claim…"* (Beard and Qian, 2008). The marble game allows this technique to be introduced at the beginning of the STEM curriculum.

After students have learned how to play the marble game and apply it to realistic situations such as drug elimination in **MODULE 2**, they then learn in **MODULE 3** how to predict the "ensemble average" behavior of kMC sims using finite difference (FD) methods. These computational methods can be used in an introductory pedagogical setting instead of calculus. The marble game thus provides a mathematical and computational framework that can be applied to problems throughout the STEM disciplines (PCAST, 2012). Students gain in-depth knowledge of a few important systems by deliberately practicing the scientific method (Deslauriers et al., 2011). The pedagogical approach relies heavily on interpretation and critical evaluation of student-generated graphs. The connection with the physical system is reinforced with questions and follow-up comments in the ***About what you discovered*** sections. By developing quantitative models and then critically comparing them with experimental data, students gain in-depth experience with applying the scientific method to real world problems (circle4.com/biophysics/modules). Student evaluations of these materials consistently indicate that they have learned both metacognitive and procedural skills after working with the modules, gaining a realistic understanding of what is possible with quantitative scientific modeling. They assessed this approach as producing "great gains" in their understanding of real world problems and scientific research. As one anonymous student noted:

> *"I never knew models could apply to virtually any process given the right algorithm. This is crazy!!!"*

The marble game provides a new pathway to understanding molecular-level biological systems. Students are also introduced to the basics of computer programming. Finite difference methods are used instead of traditional calculus. This approach more accurately reflects the quantitative and computational methods that are actually used by most practicing engineers and scientists. Students without calculus have been able to successfully complete **MODULE D** even though the transient diffusion problems they were able to solve (from scratch) are traditionally introduced in advanced calculus-based courses using partial differential equations.

In this approach, students write and then implement their own algorithms, starting with a blank Excel spreadsheet. The pedagogical method does not use any computational black boxes. This provides students with an introduction to programming and computer science in an engaging manner that is able to provide an alternate pathway to computational STEM disciplines (PCAST, 2012).

It is my hope that these methods will form the basis for a new interdisciplinary course that introduces students to quantitative scientific modeling.

About the author

Dr. Pete Nelson received a master's degree in Physics from Victoria University of Wellington in New Zealand in 1990 where he initially developed kinetic Monte Carlo simulation techniques. As a PhD student at MIT he further developed these techniques while studying the traditional chemical engineering approach to modeling transport phenomena. After graduating from MIT in 1998 with a PhD in Chemical Engineering, Nelson held a post-doctoral *position in the Chemistry Department at the University of Massachusetts in physical chemistry. In 2000 he was* awarded an NIH Postdoctoral Fellowship in Quantitative Biology. In 2002 Nelson began teaching Biophysics, Physics and Physiological Modeling and since then he has been developing modular teaching materials for biophysics and physiological modeling with support from the NIH, HHMI, Title III and NSF. In 2009 Nelson received a $2000 uScience award from the Association of American Medical Colleges (AAMC) for **MODULE 4**.

Nelson has a continuing interest in curricular reform for the quantitative life sciences. See http://circle4.com/biophysics

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