Physics 2280: Physical Models of Biological Systems

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Fall 2024

> "Nature uses only the longest threads to weave her patterns, so each small piece of her fabric reveals the organization of the entire tapestry." — Richard Feynman
>
> "Seek simplicity, and distrust it." — Alfred North Whitehead

Most students in this class are 2nd year or higher.

Every week we hear some highly-placed pundit announcing the end of the qualitative era in life science, and the need to train future scientists in mathematical modeling methods. Normally missing from such pronouncements are issues like "What is a model, anyway?" and "How do we know when a simple, reductionistic modeling approach is appropriate/inappropriate?"

Our goal in this course is to study some classic case studies of successful reductionistic models of complex phenomena, emphasizing the key steps of (1) making estimates, often based on dimensional analysis, (2) using them to figure out which physical variables and phenomena will be most relevant to a given system, and which may be disregarded, and (3) finding analogies to purely physical systems whose behavior is already known. The cases we'll study involve basic biological processes, in the light of ideas from physics.

A model is a distillation of the known relevant behavior of a system into just a few rules. A good model can help us see the forest for the trees; in Picasso's phrase, it is "the lie that makes us realize the truth." But as scientists, we want to take our existing models and poke them, looking for soft spots. We want to look for biologically relevant, incompletely tested aspects of the model. We want to find its falsifiable predictions, then devise uncluttered experiments that bear as directly as possible on those predictions. Quantitative predictions are often the sharpest tool for poking a model.

This course will develop many ideas involving probability. But it's not a course on descriptive statistics, the design of clinical trials, and so on. Rather we'll look at case studies where important insights into biological systems emerged from an appreciation of the intrinsically random nature of the interactions in complex systems. Along the way we introduce some of the key ideas of biological physics, for example the concept of random walks.

Long ago, in a course like this we'd have to be content with me telling you what faraway people had done; you couldn't roll up your sleeves and do the actual science yourself, because it was too difficult to make computers do anything. Luckily all that has changed. We will be learning and using a general purpose computer-math package called Python. Whatever you may do in science after this course, the skills you get with Python will be useful to you.

Prerequisites:
PHYS 0101 (or higher), MATH1400 and [1410 or 1610]. Recommended: previous or concurrent PHYS0102 or 0151; basic background in chemistry and biology. We will use the computer-math package Python; no prior experience is assumed.
Class meetings:
MW 1:45–3:15pm. Attendance in class is essential. If you must miss a class, get notes from another student. Class time will present different approaches to the material than is in the reading; we may uncover and address confusing points in the reading; we may discuss how to get started on the written problems.
Office hours:
These are for you. We'll arrange the times to suit the class. In office hours you can ask for clarification on reading or lecture, fill in background you may need, get help debugging your computer code, and so on. If you have course conflicts with all the announced office hours, alert me and we will change one or more to accommodate you.
Reading:
Reading will be assigned. Doing the reading before the corresponding class will help you to follow the class discussion, answer questions I may ask of you, and so on.
Announcements:
`http://canvas.upenn.edu/` Please log into Canvas now and check that you have access. Instead of the Canvas message system, I will send you e-mail to the address that the registrar has on file for you, or to any other address you like (but you'll have to tell me).
Computer lab sessions:
Time: during regular class hours.
Assessment:
See "course policies" document at the end of this one.

Books:
Paperback editions will be available at the Penn bookstore; e-book editions are also available.
Nelson, *Physical Models of Living Systems* second edition (2021). The e-book edition is just $10. If you find a free bootleg PDF on line, be aware that it is a draft and different in many ways from the actual book.
We will also use *A Student's Guide to Python for Physical Modeling* second edition (2021), by JM Kinder and P Nelson (Princeton U Press).
Other required readings will be posted on Canvas.
Computing
I recommend the free computing environment "Anaconda" from `anaconda.com/` which runs on your own computer. See installation instructions available on Canvas or Appendix A of the *Student's Guide*. You may, however, prefer Anaconda's cloud facility or Google Collaboratory (`https://colab.research.google.com`).

Tentative Outline

We generally only cover about 2/3 of this material each year. See Canvas for each week's reading and homework assignments, and for online documents.

Prologue

"The objective of physics is to establish new relationships between seemingly unrelated, remote phenomena." — L. D. Landau

1. **A breakthrough on HIV**
   Biological question: Why did the first antiretroviral drugs succeed briefly, then fail?
   Physical idea: Steady state is not the same as equilibrium.

Tools and concepts

"The generation of random numbers is too important to be left to chance." — Robert R. Coveyou, Oak Ridge National Laboratory

2. **Hello Python**

3. **How to do better on exams, impress interviewers, and discover new physical laws**

4. **Rules of disorder**
   Biological question: How can we make definite statements about *random* processes?
   Physical idea: The distribution can be definite even if individual samples are unpredictable.

5. **Discrete distributions**
   Biological question: If you are your parents' genomes, then why does inheritance seem random?
   Physical idea: Meiosis and fertilization generate draws from two diploid sets of particulate traits.

6. **Bacterial genetics**
   Biological question: How do bacteria become resistant to a drug or virus that they've never encountered?
   Physical idea: Models can be tested via their statistical predictions.

7. **Continuous distributions**
   Biological question: Why does the Gaussian distribution fit so many phenomena?
   Physical idea: Any distribution looks like a Gaussian, if you add many independent measurements.

8. **Random walks on an energy landscape**
Biological question: How can pulling two things apart strengthen their bond?
Physical idea: Bond breaking is a first passage process, controlled by the lowest energy barrier, which can increase upon moderate loading.

9. **Representing experimental data**
Biological question: How can an experiment measure a parameter that you don't directly observe?
Physical idea: Maximum likelihood analysis as the basis for curve fitting.

Vistas

10. **Negative feedback control and homeostasis**
Biological question: How can we maintain a fixed population in a colony of constantly reproducing bacteria?
Physical idea: Negative feedback can stabilize a desired setpoint in a dynamical system by creating a stable fixed point..

11. **Positive feedback control and switching**
Biological question: How can you make decisions without a brain?
Physical idea: Cellular elements can implement logic circuitry and remember the answers by using bistability to create a separatrix (watershed)..

12. **Cellular clocks**
Biological question: How do the cells in a frog embryo know when it's time to divide?
Physical idea: Interlocking positive and negative feedback loops can generate stable, precise oscillation via a limit cycle..

13. **The role of superspreaders in pandemics**
Biological question: Why do some outbreaks of a communicable illness spread explosively, while others, in similar communities, fizzle after the first few cases?
Physical idea: A tiny subpopulation of superspreader individuals can introduce giant variations in the course of an epidemic..

14. **Bet hedging via phenotypic diversity**
Biological question: How does *B. subtilis* hedge against a wrong decision?
Physical idea: A trigger circuit can be driven by noise.

15. **Valedictory**
Physical/biological question: Why did we spend our time studying mere specifics?
Physical/biological idea: There's no truth without the details. But if you look in the right places, you do see universality.

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Course Information and Policies

The reason we have fixed policies is so that we can focus all our attention on learning science, not on wrangling over ad-hoc policies.

ANNOUNCEMENTS, ASSIGNMENTS, AND HANDOUTS

See our pages on Penn's Canvas system (`canvas.upenn.edu`). Weekly reading assignments can be found starting from the Syllabus page on Canvas. Written assignments with due dates will appear on the course Calendar as they are set. Merely interesting events begin with "FYI."

CONTACTING ME

My office is DRL room 2N8. You can leave things under my office door. If you send e-mail, please put `"PHYS2280"` in the subject line.

GRADING

In addition to the regular assigned homework (25%), there will be an in-class midterm (15%), two projects ($2 \times 15\%$), and an in-class final (20%). The remaining 10% is reading responses.

DATES

See the course calendar on Canvas.

CLASSES

Attendance is important. Some things I will say may not be in the assigned reading, and vice versa. I will assume that you have attended all the regular classes or obtained notes from a fellow student, unless you make some other arrangement with me in advance.

OFFICE HOURS

I will try to arrange these to suit the class's schedules. The office hours are for you, so please come. Besides, personal contact is always the most effective way to learn things. And often with computers you can waste unlimited time trying to figure out a simple point by yourself, when in a group setting someone could clear it up rapidly. Even if you don't have any questions, when you come to office hours someone else may have a question whose answer will help you, or which will jog your memory for a question you wished to ask.

READING AND READING RESPONSES

Assigned reading will be listed on the weekly assignment sheets (Canvas) before the class when it is to be discussed. It's important to do it.

Each Monday (unless stated otherwise) you will jointly turn in an ultrashort, free-form Reading Response to that week's reading. This can be online before start of class, or hard copy at start of class. The purpose is to encourage you to do the reading, and to let me know what aspects of the material are confusing so that I can address them. The reading response should contain 3 *short* items, each of which can be a main point of the reading, a question you had about the reading, or an observation about the reading. I don't return these, but ask me in office hours if you are unsure at first what this is about.

DISCUSSIONS

Our Wikis appear in Canvas, linked from the `"Syllabus"` page. These are your community to help each other learn things. The class—that's *you*—will maintain a vocabulary wiki, including all the terms from many disciplines that crop up in the lectures and readings. If you don't know a term, look it up and then enter it here to help other students; if there's already an entry, you may wish to improve it, add a source, etc. There are even some entries with no text; I will occasionally put those there as hints that these terms should be defined.

We have a separate wiki for Python hints that people have found useful, etc., and a third one for discussions that arise over your written questions to me.

REGULAR PROBLEM SETS

There will be regular assigned problem sets roughly biweekly, posted on Canvas. Actually doing the problems is crucial to understanding the material! You can't think the big think without some *fluency* with the math, and practice is the only way to get it. You may need to come to office hours and/or discuss with your classmates to get started on some of the problems, so don't wait till the last minute.

Each of you may turn in any **one** regular homework at or before the start of the next class after the due date, with no penalty, for any reason (or no reason). Write, `"This is my free late"` on the top. Apart from that, late homework will not be accepted (even if Canvas seems to accept it).

Your work will be checked for completeness and selected problems will be graded. Make sure your work is neat and *tells a logical story.* Technical communication is one of your most important job skills, no matter what you do later on, and the only way to get good at it is to practice.

For the computer problems, it can be tempting to turn in reams of output. Please resist this temptation; limit what you turn in to three pages per problem (not counting any graphics). Remember: *It's not communication until it actually gets into another person's brain.*

If you believe a homework paper is incorrectly graded, let me know. I will route your query first to the TA. If you and he can't resolve it, I'll be glad to look then. In any case, requests for changes in homework grades must be made within one week after the homework was returned.

Scientific work is usually done in collaboration. More generally, collaboration is fun, and it really helps you to argue with your friends. Feel free to work together on the problems, but of course the smart way is to take the necessary ideas from each other and then go work out the details yourself—the goal is for you to become an autonomous agent.

COMPUTING

I will ask you to do some computer problems using Python. We'll have a lab session to help you get oriented. Even if you know Python, you have to come anyway—to help your assigned partner(s) to learn it. To make the best use of the time, read and think about the material in advance.

PROJECTS

You'll have a few days for each project. *They will have hard deadlines,* listed on the Canvas calendar (the one-time "Free Late" option does not apply to the projects). You are encouraged to collaborate with anyone you like in the class, but turn in your own work.

You should prepare just as you would for an in-class exam, so that you can hit the ground running when the project is released. Each book chapter ends with a list of useful formulas; make sure you understand where each one came from, what it's good for, what all the symbols mean, and so on.

Projects, regular homework, and reading responses may be turned in electronically over Canvas or in class as hard copy; in either case, it is due at the *start* of class. Do not submit work directly to the TA.

You can hand-write some of your work, but legibility can sometimes be an issue when scanning. So please find a good solution that gives you high-contrast, sharp scans. A "scanner" app for a personal device will give better results than a "camera" app; various free options exist. If a project involves computer coding, be sure to *include your code* and any output such as graphics, as parts of a single combined document.

If you believe a mistake has been made in the grading of your exam, e-mail me a description of the mistake, as you see it, or write on a separate piece of paper and give it to me in person within a week after I return the project.

IN-CLASS EXAMS

In accordance with University policy, cheating will not be tolerated. If you are caught cheating, you will be given a failing grade. See https://next.catalog.upenn.edu/pennbook/code-of-academic-integrity/ .

The in-class exams will be taken with closed books. Bring a calculator. Before the exam, I'll distribute a sheet of useful formulas. I'll distribute the *same* sheet with the exam itself, so you won't need to memorize it; rather, you will want to make sure you understand where each one came from, what it's good for, what all the symbols mean, and so on.

If because of *illness*[1] you cannot be present for an exam, I'll prorate your other work to compute your grade. Certification of the reason for your absence will be required. If you have some other truly exceptional problem preventing you from taking an exam, *you must get me to agree at least 24 hours before the start*. A job interview is not "exceptional," so keep our schedule in mind as you plan, or choose another semester to take PHYS2280.

You should show the steps you took when solving exam, project, and homework problems. But do your scratch work on separate paper, so you can turn in a neat, concise paper. Put a box around numerical results.

If you believe a mistake has been made in the grading of your exam, e-mail me a description of the mistake, as you see it, or write on a separate piece of paper and give it to me in person within a week after I post grades.

The final examination is scheduled by the Registrar and must be taken at the scheduled time, unless you have *another exam* at that same time. After grading, your final exams will be available for you to look at, but not remove.

YOUR SUGGESTIONS

I believe that nobody can teach anybody else physics. My goal is to help you to teach *yourself* this difficult material. With that attitude, we can all learn a lot. If you think I could be doing things in a more effective way, let me know. You can tell me, or if you prefer tell the TA, but please don't wait till the end of the term. (If you do, you'll only be helping future students!)

[1] Your own illness, not someone else's.