

# Physics 280: Physical Models of Biological Systems

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“We all know that Art is not truth. Art is a lie that makes us realize the truth.” — Pablo Picasso

“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

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?” We also hear a lot of pundits announcing the era of “Integrated Systems Biology,” but never defining that phrase.

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 MATLAB. Whatever you may do in science after this course, the skills you get with MATLAB will be useful to you.

**Announcements:** <http://courseweb.library.upenn.edu/> Please log into BlackBoard now and check that you have access, and that it's using your preferred e-mail address, as this is the address I'll use to contact you.

**Grading:** Will be based primarily on roughly 10 problem sets (25%), short reading summaries (10%) two midterms (2×15%), and a comprehensive final exam (35%).

**Time:** We meet MWF 2-3pm in DRL room A7.

**Computer lab sessions:** Dates TBA. Location: Multi-Media Services, DRL (Basement), PC lab. Time: during regular lecture hours. These are short sessions, so be extra prompt and think about the assignment sheet in advance.

**General policies:** see separate handout.

**Prerequisites:**

PHYS 101 (or higher), MATH 104 and [114 or 115]. Recommended: previous or concurrent PHYS 102; basic background in chemistry and biology. We will use the computer-math package MATLAB; no prior experience is assumed.

**Books:**

*Required:*

Many short required readings, including lecture notes, etc. will be posted on BlackBoard. If you find any errors in the main text, please bring them to my attention so I can distribute to the class. Earn bragging rights!

*Recommended* (on reserve in the library in DRL):

M. Denny and S. Gaines, *Chance in biology* (Princeton, 2000).

R. P. Feynman, *QED* (Princeton Univ. Press, 1985).

**MATLAB**

Penn has a site license for this software, and there are many places on campus where you can use it, including: SAS Computing Multi-Media Services (basement DRL), Undergraduate Data Analysis Lab (104/108 McNeil Building), The Weigle Information Commons (Van Pelt Library). In addition, there is the SEAS-supported virtual PC lab. See:

<http://www.seas.upenn.edu/cets/answers/virtualLab.html>

## Tentative Outline

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

### Prolog

"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 MATLAB**

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. **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.

### Some applications

“If you read trendy intellectual magazines, you may have noticed that ‘reductionism’ is one of those things, like sin, that is only mentioned by people who are against it. To call oneself a reductionist will sound, in some circles, a bit like admitting to eating babies.” — Richard Dawkins

### 7. **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.

### 8. **Poisson processes**

*Biological question:* How do you detect an invisible step in a molecular motor cycle?

*Physical idea:* The waiting-time distribution tells us about the mechanism.

### 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.

## Switches in cellular control networks

“Whenever I’m faced with a choice between two evils, I like to choose the one I haven’t tried yet.” — Mae West

### 10. **Bacteria have feelings, too**

*Biological question:* How well can bacteria smell?

*Physical idea:* The Berg–Purcell limit.

### 11. **Gene expression and genetic switching in bacteria**

*Biological question:* How can you make decisions without a brain?

*Physical idea:* Cellular elements can implement logic circuitry.

### 12. **Noise in gene-regulatory circuits**

*Biological question:* How does *B. subtilis* hedge against a wrong decision?

*Physical idea:* A trigger circuit can be driven by noise.

## Light and life

“Query 30: Are not gross Bodies and Light convertible into one another, and may not Bodies receive much of their Activity from the Particles of Light which enter their Composition?” — Isaac Newton

### 13. **Light is lumpy**

*Biological question:* What sets the absolute limit to night vision?

*Physical idea:* The spooky truth about photons.

14. **Devices that manipulate light**

*Biological question:* If light really consists of particles, then how is focusing possible?

*Physical idea:* Intensity as the probability of photon arrival; interference of probability amplitudes.

15. **Applications to microscopy**

*Biological question:* If diffraction limits us to about two hundred nanometers, how can we see individual molecular motor steps?

*Physical idea:* The *location* of a single spot can be measured to great accuracy, if we get enough photons.

16. **Vista: X-ray crystallography**17. **Vista: From photons to electrons****Vision**

“The sages of Chelm began to argue about which was more important: the Moon or the Sun. The reigning wise man ruled: ‘The Moon *must* be more important, because without it, nights would be so dark we could not see anything. The Sun, however, shines only by day—which is when we don’t need it!’” — Leo Rosten

18. **Animal eyes**

*Biological question:* How can we sort out the many objects in our visual world?

*Physical idea:* Limited depth of focus as a data-rejection tool.

19. **Image compression**

*Biological question:* We have  $10^8$  photoreceptors, but only  $10^6$  neurons in our optic nerve. How can all the needed information reach our brains?

*Physical idea:* The redundancy removal hypothesis.

20. **Color vision**

*Biological question:* Why does a mixture of red+green light appear yellow?

*Physical idea:* Color as a 3-dimensional linear vector space.

21. **Vision in dim light**

*Biological question:* Why can’t you see the stars during the day? They’re still there!

*Physical idea:* The contrast threshold can be predicted from experiments done in the dark.

22. **Primary molecular events in vision**

*Biological question:* How are vision, olfaction, and taste the same?

*Physical idea:* The G-protein cascade.

23. **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.