Physics 280: Physical Models of Biological Systems

P. Nelson

Fall 2008

> "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 physical 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: Sep 12, 19. Location: Multi-Media Services, DRL (Basement), room BS3. Time: during regular lecture hours. These are short sessions, so be extra prompt and think about the task 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;* the labs will introduce this useful tool.

Books (more are listed in a separate Book List):

Required:
M. Denny and S. Gaines, *Chance in biology* (Princeton, 2000).
If you find any errors in the text, please bring them to my attention so I can distribute to the class (and to the authors).
Many other short required readings, including lecture notes, etc. will be posted on BlackBoard.

Supplemental (on reserve in the library in DRL):
H. Berg, *Random walks in biology* 2d ed. (Princeton UP, 1993).
R. P. Feynman, *QED.*
P. Nelson, *Biological Physics: Energy, Information, Life,* updated first edition (W. H. Freeman, 2008).

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).

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. "D+G" refers to the main text.

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.

A physical model can help us by clearing away irrelevant details, letting us focus on key features of a problem. It can also help by mobilizing intuitions, and bringing to bear analysis, that we've already gained elsewhere. Finally, some strongly-held intuitions are just wrong, in ways that matter for biology; physics can substitute the unintuitive but correct models that we need.

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***

2a **How to do better on exams, impress interviewers, and discover new physical laws**

Dimensional analysis as a way of looking at everything.

3. **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.

Bayes's formula and false positives. Updating our estimates in the light of new evidence. The likelihood function; maximum likelihood analysis.

4. **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.

    Bernoulli trials; binomial distribution; how to decide if a coin is fair. Geometric distribution. Two-state systems; RNA unfolding example. Poisson distribution; Katz and Miledi's analysis of ion channel conductance.

5. **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.

    How to get a computer to draw from a specified discrete distribution. Luria–Delbrück experiment and its simulation. Why HIV can evade single-drug therapy but not triple-drug therapy.

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

    Gaussian and exponential distributions as limits of binomial and geometric respectively. How to get a computer to draw from a specified continuous distribution. Power-law distributions. The Poisson process (shot noise) and its exponential distribution of wait times.

7. **Poisson processes**
Biological question: How do you detect an invisible step in a molecular motor cycle?
Physical idea: The signature of multiple steps in the waiting-time distribution.

    Convolution of two distributions. The randomness parameter.

8. **Representing experimental data**
Biological question: Do your data reflect a 1-step or multi-step process?
Physical idea: Maximum likelihood analysis as the basis for curve fitting.

    How, why, and when curve-fitting works. Maximum-likelihood includes and extends the usual chi-square procedure. Examples: Poisson-distributed data (counts); power-law distributions.

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

9. **Light is lumpy**
Biological question: What sets the absolute limit to night vision?
Physical idea: The spooky truth about photons.

 Evidence for the particulate character of light, and its importance in vision. A desperate gambit to resolve the intolerable contradiction with the wave model, which unavoidably introduces randomness.

10. **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.

 Reflection. Diffraction. Refraction. Focusing. Imaging. The diffraction limit.

11. **Applications to microscopy**
Biological question: If diffraction limits us to about a 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.

 Fluorescence Imaging at One Nanometer Accuracy. PALM, STED, STORM imaging. 2-photon microscopy.

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

12. **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.

Variable focus in humans, and fish. Diffraction limited pixel array; eagle eyes. How cat eyes deal with low light. When a compund eye is better, and how to design it optimally.

13. **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.

    Blurring and unsharp masks as convolution transforms. Edges are important, and edge enhancement lets us use a smaller dynamic range, achieving compression.

14. **Color vision**
Biological question: Why does a mixture of red and green light appear yellow?
Physical idea: Color as a 3-dimensional linear vector space.

    Resolution of color into primaries is like resolution of a force vector along various axis systems.

15. **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.

    Hecht and Sakitt experiments on the threshold of vision imply that a rod cell can respond to a single photon. Barlow's experiment on contrast threshold obeys a prediction made from Hecht's data.

16. **Primary molecular events in vision**
Biological question: How are vision, olfaction, and taste the same?
Physical idea: The G-protein cascade.

    G-protein cascades, a heavily recycled theme (smell, taste, hormone response, memory, vision. . .).

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

17. **Bacteria have feelings, too**
Biological question: How well can bacteria smell?
Physical idea: The Berg–Purcell limit.

18. **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.

    Monod's discovery of diauxie. Specificity plus allostery yields the operon hypothesis. Bistable devices: the transistor flip-flop. Hyperbolic and cooperative binding; the gene regulation function. The genetic flip-flop. Single-cell measurement of the gene regulation function and its noise. Binomial statistics used to normalize data. The birth of synthetic biology.

19. **A developmental genetic switch**
Biological question: How does *Xenopus* know when it's time for a change?
Physical idea: Bifurcations in a control system.

Random walks and their successors

"In the future, the revolutionary effect of Mendelism will be seen to flow from the particulate character of the hereditary elements. – R. A. Fisher, 1930

20. **Everything is dancing**
Biological question: Why can cold-water fish see fainter light flashes than warm-blooded animals?
Physical idea: The distribution of thermal speeds has a tail controlling chemical reactions, such as spontaneous isomerization of rhodopsin.

    Decoding the Ideal Gas Law. The full distribution of molecular velocities. From gases to condensed matter (e.g. liquid water).

21. **Random walks**
Biological question: Why do eukaryotic cells have elaborate internal transport apparatus, but bacteria don't?
Physical idea: The scaling properties of diffusive transport.

    Bernoulli trials with a cumulative memory yield random walks. Universality of diffusion law. Fundamental point-diffusion solution. Origin of friction and Einstein relation.

22. **More random walks**
Biological question: Why do most cells have roughly the same electrical potential drop across their membranes?
Physical idea: Diffusion to equilibrium sets a fundamental scale of potential.

Fick laws and diffusion equation. Basic solutions in 1D and 3D. Diffusion erases order, leads to increase in entropy. Time reversal noninvariance of the diffusion equation signals dissipative dynamics. Diffusion with drift leads to the Boltzmann distribution: Nernst equilibrium relation.

23. **Diffusion to capture**
Biological question: How can a cell carry dozens of different receptors on its surface? There isn't enough room for them all!
Physical idea: If a diffusing particle hits a sphere once, it's likely to hit it many times.

    Diffusion to capture. Flux to an absorbing sphere. Flux to an absorbing disk. The flux to a sphere with absorbing patches can be large even at low coverage fraction.

24. **Why sex is a good idea**
Biological question: How can a population maintain its genetic diversity, and how does selective pressure act on it?
Physical idea: Genetic drift, too, is a random walk problem.

    Hardy–Weinberg equilibrium. Moran model for genetic drift. Wright–Fisher model: Genetic drift as a diffusion problem with position-dependent diffusion constant. Kimura's result on the fixation rate; the genetic clock.

25. **Macromolecular conformations and tethered particle motion**
Biological question: How can we see single molecules in action? They're too small to see!
Physical idea: Thermal motion allows indirect readout of conformational changes.

    Biopolymers for elastic energy storage. Conformation of a polymer as another random walk problem. Force versus extension of a chain molecule. Motion in an external potential as a diffusion problem with a position-dependent drift term.

26. **Random walks on graphs: The PageRank algorithm**
Biological question: How can you guess the function of a gene whose protein you've never even seen?
Physical idea: Sequence similarity gives clues to function, but it's hard to perceive.

    A technology that literally transformed human civilization, based on a simple idea. From Web surfing to bioinformatics.

Neural coding

"The Analytical Engine *weaves algebraical patterns,* just as the Jacquard loom weaves flowers and leaves." — Ada, countess of Lovelace, 1815–1853

27. **Spike world**
Biological question: What is the internal language of the brain?
Physical idea: The action potential idea.

    It's not analog. It's not quite digital either. The Astonishing Hypothesis. A very brief outline of nerve signaling.

28. **Dynamic visual coding**
Biological question: Why does lateral inhibition turn off at low illumination?
Physical idea: The best choice of coding depends on the nature of the typical signals to be encoded.

    Optimal coding strategies depend on the expected statistics of typical scenes, and on the level of noise. Why green and red receptors are very similar in primates, but not in fish.

29. **The *Limulus* eye**
Biological question: How do you implement lateral encoding in hardware?
Physical idea: The reciprocal, recurrent, lateral inhibition network.

30. **Decoding**
Biological question: How can the eye say so much with so few spikes?
Physical idea: Beyond rate coding.

31. **Valedictory**
Physical/biological question: Why did we spend our time studying putzy specifics?
Physical/biological idea: If you look in the right places, you see universality.