BIO 126/226 // APPPHYS 205
Introduction to Biophysics

Winter 2025

Professor Benjamin H. Good & Professor Mark J. Schnitzer

Course Meeting Schedule: TTh 1:30pm – 2:50pm
Course Meeting Location: Hewlett Teaching Center 102
Office Hours: After class.

Motivating Questions: How do we quantitatively understand fundamental biological processes occurring at a cellular and sub- cellular level (i.e. from tens of microns to nanometers in size) through the application of basic physics? For instance, how does physics elucidate the structural and function organization of biochemical networks, and how do these networks compute reliably in the presence of thermal fluctuations, which dominate at this scale? How should we understand the electrical function of nerves? How do we describe the electrical activity of the neural networks that perform spectacular tasks in our everyday lives? This course seeks to address such fundamental questions about both neuronal and biochemical computation.

Course Goals: The overarching goal of the course is to teach students the biophysical basis for biological phenomena and to allow students to use computational methods and physical principles as predictive tools. A few fundamental physical principles will be seen to give rise to a rich set of dynamical activities. Quantitative approaches will be used to describe these physical principles and to create analytical and numerical models of neuronal dynamics.

Another important goal is to convey the flavor and excitement of interdisciplinary biological science. The student audience is expected to be diverse, with representation from the Biology, Neuroscience, Biophysics, Bioengineering, Applied Physics, and other Biological Sciences programs. Students will be strongly encouraged to work together with class members from outside their home program, and to learn from others with complementary scientific backgrounds. Course structure and assignments will be designed to promote student-student interactions as well as experience with research literature readings and both computational and analytical analysis. Thus, both biological science students and physics/engineering students should find the course challenging, but for different reasons.

Prerequisites: Calculus, some undergraduate physics, biology

Teaching Plan and Assignments:

- Mix of lectures
- Class discussions
    - Classic and modern papers in the research literature emphasizing:
        - Mode of discovery
        - Current application of ideas
- Final Project
    - Emphasize oral and presentation skills
    - Ability to distill essence of multiple papers in the literature

Given the expected diverse range of scientific backgrounds in the student body, the lectures will be designed to provide the necessary biological and theoretical background to understand subsequent readings in the original literature. Research literature readings will be organized thematically, and within each theme there will generally be two reading sets. We will focus on the biophysics of cellular and neural computation, starting with the classic literature (*e.g.* the Hodgkin-Huxley classics; Berg & Purcell on chemoreception), with the aim of helping students understand the original basis for discovery. In parallel we will analyze the mathematics of the Hodgkin-Huxley equations for single neurons, as well as emergent properties arising from connecting multiple neurons. We will emphasize learning generalizable mathematical skills to understand and simplify complex biological dynamics.

Readings: Most of the readings will be original research articles in the classic and modern literature. Textbooks will also provide background and supplementary material pertaining to each literature theme.

Grading:
Class participation – 50%
Final Project – 50%

Participation: This course is under continuous development, so your participation and feedback will be critical for improving the material for future generations of students. It will also allow the instructors to better tailor the material to the specific needs of this year's class. We will formalize this process through weekly reflection assignments on Canvas which will count toward your final grade. Each assignment will be due by the end of the day on Saturday (11:59pm). Your comments can include anything from questions about the previous week's lectures or readings, portions of the lectures or reading that you thought were particularly confusing (or particularly interesting), background knowledge you felt you were missing, comments about pacing, etc. Questions about next week's material are also encouraged if you prefer to read the lecture notes before class. Your email can be brief, but please try to aim for about 2-3 comments per week. Don't worry if you feel like your comments aren't particularly insightful – everyone's feedback is extremely valuable in an interdisciplinary course like this one.

Practice problems (optional): Since some students prefer to learn through hands-on examples, we will also be posting several practice problems that review some of the concepts introduced in the course. These practice problems are strictly optional and will not count towards your final grade, though they can be used to make up late reflection assignments as described below. The practice problems will not be graded, but solutions will be made available on Canvas for those who wish to check their work.

Make-up policy for late reflection assignments: Each week's reflection assignment will close at 11:59pm on Saturday, and late submissions will generally not be counted. However, we will allow you to recover the participation points for individual assignments according to the following process: For each missed reflection assignment, please send an email Prof. Good (bhgood@stanford.edu) that includes (i) your reflections for the content covered in that week and (ii) a scanned or typed copy of an attempt at one of the optional practice problems posted on Canvas (it doesn't have to be linked to that week's content). Problems will be graded for effort rather than correctness, so please describe your thinking if you get stuck; you may consult the posted solutions, but your submitted write-up must be in your own words. **All make-up assignments must be received by the last day of classes (11:59pm, March 14, 2024).**

Final Project: The final project will be a written report that will require you to explore a topic in the modern biophysics literature; to use PubMed database search, Google Scholar and other search methods to identify seminal and impactful papers; to digest the content and significance of research papers; and to present clearly the key background, ideas and advances to a broad scientific audience. The goal is for you to work and discuss together within a group of 3-4 students, but every group member will write up and be graded on their own final report. Detailed instructions about the content of the report and the rules for choosing topics will be posted on Canvas later in the quarter. **Final projects will be due at the end of the final examination period (11:59pm on Friday March 21).**

Supplementary Texts:

- ***Physiology of Excitable Cells*, by David Aidley, Cambridge Univ. Press**

- ***Molecular Biology of the Cell,* by Rob Phillips, Jané Kondev, Julie Theriot, & Hernan Garcia, Garland Science, 2012.**
  An excellent (but lengthy) introduction to many of the concepts we will cover in this course. Written for both biologists and physicists.
- ***Biophysics: Searching for Principles* by William Bialek**
  A more advanced treatment that may be of interest to upper level physics students.

- *The Neuron,* by I.B. Levitan and L.K. Kaczmarek, Oxford Univ. Press, 2002
- *Ionic Channels of Excitable Membranes,* by Bertil Hille, Sinauer.
- Biophysics of Computation: Information Processing in Single Neurons, by Christof Koch, Oxford University Press, 1999.
- Dynamical Systems in Neuroscience by Eugene Izikevich, MIT Press, 2007.

Course Themes:

Statistical mechanics in biology: the basics – thermodynamic potentials, free energy minimization, Boltzmann distribution, detailed balance in equilibrium

Goal: Understand (A) What are thermodynamic potentials (i.e. mechanical energy, Gibbs free energy, chemical potentials, *etc*.) and how and why can many biological processes be described through the minimization of these potentials? (B) Understand the notion of detailed balance as a characterization of chemical processes occurring at equilibrium, and how and why life must violate detailed balance and operate far from equilibrium in order to generate characteristics like order, growth and motion, that separate life from non-life.

Physics and biology of diffusion – random walks, Fick's law, Stokes-Einstein's relations, diffusion to capture, diffusion limited reaction rates

Goal: To understand the physics of diffusion and the role this physics plays in biological processes, both as a source of stochasticity that cells must eventually deal with, and as a fundamental bottleneck in the rates at which the chemical transformations underlying life can occur. For example, understand: (A) What is a

diffusion constant? (B) How is it related to temperature and viscosity? (C) How does diffusion connect the spatial scales and temporal scales over which biological processes like transport and reactions occur?

Rate equations and dynamics in the cell – reaction rates, Kramer's escape problem, Michelis-Menten kinetics, cooperativity and nonlinear thresholds

Goal: To derive from statistical mechanics, basic results in chemical reaction rate theory. For example: (A) How can one define reaction coordinates, and calculate rates of reactions along these coordinates (B) How do reaction rates depend on temperature (C) How can one derive Michelis-Menten type enzyme kinetics from statistical mechanics? (D) What is cooperativity and what role does it play in generating nonlinear, threshold like response properties in biological systems?

Bacterial Chemotaxis and Molecule Counting – the principles allowing chemical networks to estimate chemical concentrations by counting molecules, and applications to how bacteria navigate concentration gradients

Goal: Understand the role of diffusion, i.e., molecular shot noise, in limiting the accuracy with which chemical networks can estimate concentration (gradients) of important molecular species, like food or harmful chemicals, and what type of design principles chemical networks can use to estimate such concentrations as reliably as possible given the physical limits

Kinetic proofreading and the transmission of biological information – mechanics of protein synthesis through the ribosomal complex, analysis of error rates in this process, and how kinetic proofreading controls these error rates

Goal: Understand (A) basics of protein synthesis (in particular conversion of RNA sequences into amino acid sequences) and how this process imposes highly stringent constraints on ribosomal machinery in order to achieve the copying of very long sequences with few errors. (B) The principles that allow ribosomal machinery to control error rates (C) General theories governing how well thermodynamic processes can achieve reliable final states with a given free energy budget.

Passive membranes – equivalent circuits, Nernst potentials, ionic pumps and transporters

Goal: Understand (A) physical description of lipid neuronal membrane in terms of resistance and capacitance; (B) Why ion concentration gradients lead to membrane resting potential; (C) How cells actively create the ionic gradients that enable membrane potentials.

Background Reading: Aidley, Ch 1-3; Hille, Ch 1; *The Neuron*, Ch 1 and 2

Please read background materials as needed before research articles:

- Introduction and Course Overview, Cole & Curtis, Nature (1938).

Cable theory - electronic distance and equivalent cylinders,

> **Goal**: Understand how electrical signals propagate and change within neuronal branches as a function of the distance from the cell body and of the shape of the dendritic tree. Learn how to create a compartmental model of a neuron.

Biophysics of the squid giant axon – voltage dependent ionic permeabilities. Voltage clamp studies, driving force, reversal potentials, Hodgin-Huxley formalisms, action potentials (a first look).

> **Goal**: Understand the experimental observation that the permeability of neuronal membrane to specific ionic species depends on both the present membrane voltage and on its the recent history. Learn how to predict the results of voltage clamp experiments. Learn how to predict ionic currents within cells using the concept of electrical driving force. Understand the Hodgkin-Huxley analytical description of excitability and action potentials (spikes) in the squid giant axon

Computing with single neurons – multiplicative (shunting) vs. additive inputs, the utility of dendrites, retinal directional selectivity.

> **Goal**: Understand how neurons can use their physical properties to perform elementary computations. Predict the results of these computations based on the structure of the neuronal tree and on passive and active membrane properties.

Computing with networks – Rate coding, attractor models of associative memory, Hopfield networks, persistent neural activity.

> **Goal**: Understand that the dynamical activity of a neuron can encode information. Understand that a complex network of neurons can collectively encode information. Learn to create simple network model of associate memory.

Approximate Schedule of Lectures: (M = Mark, B = Ben).

M&B	Tu 1/7	Introduction to class structure; tour of length, time, & number scales in biology; basics of bioelectricity
B1	Th 1/9	Intro to Statistical Mechanics: Entropy; Boltzmann factors & thermal energy; chemical potentials & osmotic pressure
M1	Tu 1/14	Cole & Curtis, action potential phenomenology
B2	Th 1/16	Applications of Statistical Mechanics: ligand binding; cooperativity; allostery
M2	Tu 1/21	Active transport through pumps
B3	Th 1/23	Introduction to Diffusion: Brownian motion; Einstein's equation relating drift, diffusion, & temperature; Fick's law & the diffusion equation
M3	Tu 1/28	Start of H&H papers
B4	Th 1/30	Applications of Diffusion: timescales, diffusion-to-capture, limits on cell size
M4	Tu 2/4	Channels, H&H paper 1
B5	Th 2/6	Dynamics in the cell: rate equations, activation energies & enzymes, diffusion-limited reactions, Michaelis-Menten kinetics

M5	Tu 2/11	H&H paper 2
B6	Th 2/13	Rate equations II and Introduction to Chemotaxis.
M6	Tu 2/18	H&H paper 3
M7	Th 2/20	H&H paper 4
B7	Tu 2/25	Chemotaxis: key experiments; Berg-Purcell limit; phenomenological models of adaptation
B8	Th 2/27	Kinetic proofreading & active noise reduction
B9	Tu 3/4	Proofreading II and limits to evolutionary optimization
M8	Th 3/6	Finish H&H papers
M9	Tu 3/11	Null clines, Sompolinsky/Hausser work on Purkinje neuron
TBA	Th 3/13	TBA