BIO 126/226 // APPHYS 205
Introduction to Biophysics

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Mon, Wed 12:35 PM - 2:05 PM at McCullough 122

Office hours: After class

PART I: 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 nervous activity.

PART II: How do we quantitatively understand fundamental biological processes occurring at a sub-cellular level (i.e. nanometer scale) through the application of basic physics? i.e. how does an understanding of nanometer scale physics elucidate the structural and function organization of biochemical networks, and how do they compute reliably in the presence of thermal fluctuations, which dominate at this scale?

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
- Two exercise sets

- Class presentation
    - Emphasize oral and presentation skills
    - Ability to distill essence of multiple papers in the literature
- Computational final project involving in depth exploration of a current research question using simulation and numerical techniques.

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. The first set will generally be chosen from the classic literature (*e.g.* the Hodgkin-Huxley classics), with the aim of helping students understand the original basis for discovery. The second set will be chosen from the modern literature, with the aim of helping students learn how fundamental concepts are understood and applied today. Students will be expected to perform background reading to fill in missing aspects of their knowledge.

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 – 20%
Analytical exercise set – 20%
Class presentation – 20%
Final Project – 40%

Supplementary Texts:
- ***Physiology of Excitable Cells*, by David Aidley, Cambridge Univ. Press**
- ***Introduction to Biophysics* by William Bialek**
- *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.

Course Themes:

M Jan 7 **Overview of course, Parts I and II**
- **Part 2:** SG on molecular biophysics, statistical mechanics and chemical physics.
- **Part 1:** MJS on neuronal biophysics, intro to neural computation
- In class reading on Cole/Curtis action potential

PART I: ELECTRICAL EXCITABILITY AND NEURONAL BIOPHYSICS (MJS)

1. **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).

2. **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.

3. **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

4. **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.

5. **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.

PART II: MOLECULAR BIOPHYSICS (SG)

6. **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?

7. **Statistical mechanics in biology I: the basics** – thermodynamic potentials, Free energy minimization, Boltzmann distribution, detailed balance in equilibrium, and non-equilibrium steady states in biology

   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.

8. **Statistical mechanics in biology II: chemical kinetics** – 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?

9. **Putting it all together: photon counting in the retina** – statistics of photon arrivals in the retina, and the transformation of light signals first into chemical and then electrical signals in the outer retina

   Goal: Understand the remarkable ability of photoreceptor, or rod cells in the retina to detect *single* photons in the dark and to reliably convert information about a single photon arrival first into chemical signals and then into electrical signals. We will put together all the information learned so far in the course to understand the design principles that allow the final electrical response of rod cells, and subsequent bipolar cells, to signal light intensity almost as reliably as possible, given fundamental limits imposed by Poisson noise in photon arrival counts.

10. **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

11. **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.