

# Cellular Biophysics & Modeling — Fall '16

APSC 351 / TR 3:30–4:50 / ISC 1127

*Cellular Biophysics & Modeling* is an introduction to dynamic phenomena of cellular and systems neuroscience, electrophysiology and computational neuroscience. Topics include: the biophysics of excitable membranes, the gating of voltage- and ligand-gated ion channels, neuronal calcium signaling, Hodgkin-Huxley-style mathematical modeling of the neuronal action potential, the ‘geometry’ of electrical bursting, central pattern generation, and the role of inhibition, network connectivity, synaptic dynamics, and synchronization in brain function.

*Cellular Biophysics & Modeling* is a rigorous quantitative course. In particular, students are introduced to dynamic systems modeling—i.e., mathematical modeling using ordinary differential equations. The course includes challenging readings from the primary literature and weekly homework assignments. Some problem sets will be analytical in nature; others will involve calculations using web-based or freely available software.

Prerequisites are MATH 112/132 (Calculus II or Calculus II for Life Sciences) and BIO 225 (Intro to Molecules, Cells, Development); or permission of instructor.

## Exams & Grades

Homework, quizzes, and classroom participation contribute 20% to your overall grade. There will be two equally weighted midterm exams (20% each) and a final exam (40%). Because the course material and exams are cumulative, improved performance on exams will be redemptive. That is, the overall midterm score (midterms) will be the arithmetic average of the two midterms, or the second midterm, whichever is better,

$$\text{midterms} = \max\left(\frac{m_1 + m_2}{2}, m_2\right),$$

provided the student sat for the first midterm ( $m_1 > 0$ ). The overall exam score (exams) will be the average of the midterms and final, or the final, whichever is better,

$$\text{exams} = \max\left(\frac{\text{midterms} + \text{final}}{2}, \text{final}\right),$$

provided the student sat for both midterms ( $m_1 > 0$ ,  $m_2 > 0$ ). The grading scheme is A = 94.0–100, A– = 90.0–93.9, B+ = 87.0–89.9, B = 84.0–86.9, and so on.

All deadlines and exam dates are final (see attached calendar). There will be no make-up exams or assignments without a letter from a Dean providing justification and a specific request (documentation from a medical professional is necessary but not sufficient). Serious schedule conflicts influencing midterms may be resolved by arranging an early exam, but this will occur at the instructor’s discretion.

Students are always evaluated with reference to course objectives, never by relative performance. Any ‘curving’ will be to the advantage of all students and decided upon by the location

(not the scale) of grade distribution. Exam format will be discussed about a week prior to each exam (in-class vs. take home, open vs. closed book). Violations of academic integrity will be aggressively pursued within the W&M Honor System.

## Attendance, Homework, Honor Code

Attendance is required, but will not be monitored. In-class events (e.g., a short quiz) are equivalent to homework assignments and may be unannounced. The two lowest homework and/or in-class-event grades will be dropped (that is, not included in homework score), but late homework will not be collected or graded. There will be no opportunity to make up in-class events, but these may be one of the two dropped scores.

This course is entirely open with respect to materials generated in previous years. Students should deliberately and carefully review past homework assignments, exams, and exam answers. If you have access to helpful materials or links from previous years that are not posted on blackboard, please disclose these with me so that everyone will have access.

Collaboration on homework assignments is strongly encouraged, so long as each student is entirely responsible for preparing the final draft of his/her assignment before scanning and uploading to blackboard. On the top of the first page of your homework indicate the scope of collaborations, people, resources involved, e.g., “Worked with Ed Jones and Eve Marder. Followed answers from 2014 when necessary. Ann Graybiel was consulted on problem 3.”

## Office hours

Smith’s office hours are posted on blackboard. In addition, there are several Teaching Assistants who will hold recitation sessions; see blackboard for schedule and email addresses.

## Readings

There are no required texts for *Cellular Biophysics & Modeling*. Readings from the following texts and the primary literature will be posted on blackboard.

- **Cellular Biophysics and Modeling: An introduction to the computational biology of excitable cells.** Gregory D. Smith. Cambridge University Press. In preparation.
- **Dynamical Systems in Neuroscience: The Geometry of Excitability and Bursting.** Eugene M. Izhikevich. The MIT Press. Cambridge, MA. 2006.
- **Ionic Channels of Excitable Membranes,** Third Edition. Bertil Hille. Sinauer Associates. Sunderland, MA. 2001.

There are numerous links to review materials, online software, videos, located under “Resources” on the course Blackboard page.

# Cellular Biophysics & Modeling — Representative Topics

## Unit 1

- exponential growth, decay, relaxation; exponential time constants; characteristic times
- classification of scalar ODEs; solution of simple ODE IVPs by separating variables and integrating; checking candidate solutions of ODE IVPs
- single compartment models of biochemical kinetics; conservation laws vs. constitutive relations; conservation laws expressed in terms of rate of change of concentration vs. number; physical dimensions and units of variables and parameters
- deriving ODE systems for chemical reactions using mass action kinetics; eliminating equations by identifying conserved quantities; conservation laws expressed in terms of concentration vs. number
- phase diagrams for scalar ODEs; classification of steady-states (stable, unstable) using both graphical and analytical techniques; the concept of bistability
- Nernst equilibrium potential (diffusion potential); relative sizes of conductances of resting membranes; relative sizes of physiological ion concentrations inside vs. outside cells; reversal potentials of physiologically important ions
- equivalent circuit view of the cell plasma membrane; current-voltage relations for membrane currents; effective reversal potentials for multiple passive currents
- vocabulary for describing ionic currents: depolarizing, hyperpolarizing, inward, outward, passive, voltage-gated, depolarization activated, hyperpolarization activated, regenerative, restorative, inward rectifying, outward rectifying, etc.
- fundamental aspects of physiologically important ionic currents including the potassium leakage current, the L-type voltage-gated  $\text{Ca}^{2+}$  current, the hyperpolarization activated cation current known as  $I_h$  (also called  $I_{sag}$ ), and others.
- Goldman-Hodgkin-Katz current equation; GHK voltage equation; their assumptions; their relationship
- interpreting bifurcation diagrams summarizing the number and/or stability of steady states of an ODE model

## Unit 2

- classical biophysics of the squid giant axon; the Hodgkin-Huxley model and equivalent circuit; ODE models with gating variables coupled to current balance equations
- voltage-clamp recording; interpretation of voltage-clamp recordings for the major ionic currents, e.g., the L- and T-type  $\text{Ca}^{2+}$  currents,  $I_{sag}$ ,  $\text{Ca}^{2+}$ -activated potassium currents, persistent sodium currents, etc.; inward vs. outward currents; currents activated via depolarization vs. hyperpolarization; transient vs. persistent currents; tail currents

- interpretation of experimental voltage-clamp and current-clamp recordings; the effects of various channel blockers and modulators (e.g., TTX, TEA); aspects of neurological channelopathies emphasized in readings; the role of calcium channels in higher-level brain function
- the Morris-Lecar model of the barnacle muscle fiber; physiological interpretation of dynamics in phase plane; type 1 vs. 2 excitability, e.g., whether action potentials are graded in amplitude or all-or-none; type 1 vs. 2 oscillations, e.g., the dependence of amplitude and frequency on the applied current when oscillations emerge
- phase plane analysis for 2D autonomous ODEs; direction fields; nullclines; horizontal vs. vertical trajectories crossing nullclines; identifying direction of flow in regions of phase plane between nullclines
- stable and unstable manifolds of a saddle; homoclinic and heteroclinic trajectories; attractors vs. repellers
- trajectories in 2D phase plane when one variable is faster than the other; excitability and (relaxation) oscillations in systems with separated time scales
- linear stability analysis and classification of equilibria in 2D systems; straight line solutions when eigenvalues are real and distinct; the trace-determinant plane; relationship between eigenvalues, trace, and determinant; evaluating the Jacobian at an equilibrium point
- interpreting bifurcation diagrams summarizing the number or stability of steady states (and periodic solutions) of an ODE model; saddle-node (fold), sub- and super-critical Hopf bifurcation, limit cycle fold, saddle node on an invariant circle (SNIC), saddle node loop (SNL; same as saddle homoclinic orbit) bifurcation; local vs. global bifurcations
- slow passage through different types of bifurcation; square-wave, elliptical, and parabolic bursters; physiological mechanisms of bursting (e.g., slow dynamics of a membrane current); the low-threshold calcium spike and post-inhibitory rebound bursting

## Unit 3

The content of Unit 3 varies quite a bit from year to year. Topics have included:

- Synaptic currents and intracellular communication
  - central pattern generators; in-phase and anti-phase synchronization; escape vs. release; slow synapses and counter-intuitive synchronization results; gap junctional coupling; electrotonic properties of dendrites
  - synaptic transmission; modeling of synaptic currents; ionotropic vs. metabotropic receptors; time constants and reversal potentials for AMPA, NMDA, GABA<sub>A</sub>, and GABA<sub>B</sub> receptors; drivers versus modulators; optical studies of individual synapses
- Network properties and systems neuroscience
  - thalamus: post-inhibitory rebound bursting; rhythmic bursting of thalamocortical (TC) relay neurons; complex interactions between excitatory and inhibitory burst-capable neurons; spindle waves in thalamic slice preparation; paroxysmal thalamic oscillations; role of thalamus in sensory gating

- cortex: four types of visually responsive cortical neurons; spike frequency adaptation
  - basal ganglia: basic anatomy; action selection; pathology leading to Parkinson's disease; deep brain stimulation as therapy for Parkinson's disease
  - population activity of neurons: synchronization and desynchronization of EEG and relationship between sleep/aroused states; place cells of hippocampus and relationship between spikes and theta waves; gamma oscillations in visual cortex during visual stimulation
  - leaky integrate-and-fire neurons and rate-based population models as alternatives to Hodgkin-Huxley-style conductance-based models
- Neuronal and cardiac calcium signaling
    - basics of calcium signaling; pumps versus exchangers; the IP3R and RyR; bell-shaped open probability curve of intracellular  $\text{Ca}^{2+}$  channels; fast  $\text{Ca}^{2+}$  activation and slow  $\text{Ca}^{2+}$  inactivation of intracellular  $\text{Ca}^{2+}$  channels
    - modeling of calcium responses; excitability, bistability and oscillations; the action of thapsigargin and ionomycin in experiment and theory
    - different types of propagating waves for bistable, excitatory and oscillatory media, localized calcium elevations, e.g., calcium puffs and sparks; puff/spark-mediated saltatory calcium waves; dendritic calcium signals, e.g., in synapses and dendritic spines
    - cardiac excitation contraction coupling; local versus global control of triggered calcium release; similarities and differences between neuronal and cardiac action potentials