Math 19a: Modeling and Differential Equations for the Life Sciences, Fall 2024, MWF 10:30–11:45

Course Head: Dr. John Wesley Cain ("Wes")
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Office Hours (tentative): Tuesdays 12:30-2:00, Fridays 12:30-2:00, or by appointment.
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Course Assistants (CAs): To be determined
Office Hours (tentative): To be determined
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Course Website: https://canvas.harvard.edu/courses/138217

Prerequisite: Strong command of single-variable calculus (Math 1b or equivalent)

Course Description: One of the primary goals of Math 19a is to facilitate comprehension of highly-quantitative research in the life sciences. To this end, Math 19a creates an interplay between reading journal articles in biology/medicine and introducing the necessary mathematical methodology. The mathematical content includes: Development and analysis of mathematical models; selected topics from multivariable calculus and matrix-vector algebra; differential/difference equations in one or more variables; and bifurcations in nonlinear dynamical systems. The biological content may include topics such as: Models of infectious disease transmission, biochemical kinetics and Michaelis-Menten formalism, ion channel kinetics and action potentials, interacting populations (competition, mutualism, predator-prey), biological waves, chemotaxis, and pattern formation. Topic selection may vary according to student interests and preferences. Probability and statistics are not emphasized in Math 19a, as those topics are more suited for Math 19b. However, the role of biological data in the development and revision of mathematical models is central to this course.

Course Goals and Learning Objectives: One of the major goals of this course is to understand how mathematics can be used to inform experimental protocol in biology and medicine. Often, laboratory experiments are expensive and time-consuming, and may involve the sacrifice of living organisms. For this reason, it is desirable to use mathematical models to make *educated* guesses regarding what sorts of experiments might be scientifically important. You will learn how to use models to predict future behavior based upon initial data and parameter estimates, and how to interpolate and extrapolate beyond what has been measured experimentally. You will learn to read primary literature in quantitative biology *fearlessly*, without glazing over (or skipping altogether) material featuring mathematical/theoretical modeling. As you read research articles, you will learn to test whether the predictions of deterministic models are consistent with the authors' experimental observations and, if not, how published data might help you reformulate a model based upon more realistic[1] assumptions.

Upon successful completion of Math 19a, you will have acquired a solid foundation of the following mathematical topics:

- Ordinary differential equations in one dependent variable. Qualitative analysis (equilibria, stability and bifurcation) and analytical solution techniques for separable and linear equations;
- Basic matrix-vector algebra, eigenvalues and eigenvectors;
- Ordinary differential equations in several (usually two) dependent variables. Solving linear, constant-coefficient systems. Qualitative analysis of planar systems (phase plane analysis, nullclines, equilibria, stability, bifurcation, linearization and the Jacobian, periodic solutions, homoclinic/heteroclinic orbits);

[1] Variations on the theme "All models are wrong but some are useful" have been echoed by scientists for many decades. During Math 19a, you will develop an ability to judge whether a given model is *useful* or not.

- Discrete-time models and difference equations: systems of one-dimensional mappings and qualitative analysis (fixed points, stability and bifurcation);
- Partial differential equations in one dependent variable: advection, reaction, diffusion and chemotaxis. Separation of variables and Fourier series solutions of linear initial-boundary value problems. Traveling wave solutions of nonlinear equations.
- Optional topics (time permitting): Global bifurcations and chaos; numerical methods for solving ordinary and partial differential equations.

You will highly prepared for any of the following courses commonly taken by Math 19a alumni: Introduction to Probability (STAT 110); Ordinary and Partial Differential Equations (APMTH 105); Nonlinear Dynamical Systems (APMTH 108); Mathematics in Biology (MCB 111); Linear Algebra, Probability and Statistics for the Life Sciences (MATH 19b); and Mathematical Biology-Evolutionary Dynamics (MATH 153).

Textbook: There is no required text for this course. Detailed lecture notes will be posted online. Additionally, we strongly recommend that you download the following books through the Harvard libraries website:

- J.D. Murray, *Mathematical Biology. I: An Introduction*, Springer, New York, 2002.
- J.D. Murray, *Mathematical Biology. II: Spatial Models and Biomedical Applications*, Springer, New York, 2003.
- J.P. Keener and J. Sneyd, *Mathematical Physiology I: Cellular Physiology*, Springer, New York, 2009.
- J.P. Keener and J. Sneyd, *Mathematical Physiology II: Systems Physiology*, Springer, New York, 2009.

Note: Harvard's library subscriptions allow you to download the electronic versions of these books for free! If you prefer hard copies, Harvard has an arrangement with Springer so that you can purchase the "My Copy" versions of these text at vastly reduced prices.

Biology Discussions; Resources Outside the Classroom: Each week, approximately one hour of our class time will be devoted entirely towards discussion of biological concepts from the assigned readings. these discussions are intended to help you integrate biological and mathematical concepts, and to help you achieve deeper understanding of the journal articles that we will be reading.

Outside of class, you are highly encouraged to visit the office hours of any course staff member. Besides the office hours offered by your course head, the CAs will hold office hours (likely in the evenings) to help you practice with mathematical concepts or to seek clarification regarding homework problems.

Readings: As mentioned above, one of the goals of the course is for you to be able to read and interpret articles in biology which employ the use of differential/difference equations. You will be assigned 1-2 articles to read per week. Do not expect to immediately understand everything in each article! The articles will be discussed in class to make sure that experimental protocol, mathematical modeling, and key take-away messages are clear. Many homework exercises will reference data sets and/or equations appearing in the required readings. Each midterm will contain at least three questions directly related to the readings.

Problem Sets: There is no question that the best way to learn math is by *doing* math, and homework exercises are an essential part of any math course. If you just go to a math class and watch the instructor work problems, but do not actually try doing any problems on your own, then there is very little chance you will really learn the subject. It is also very unlikely that you will do well on exams without working through homework problems ahead of time. While doing homework, do not just write down answers. Think about the problems posed, your strategies, the meaning of your computations, and the answers you get. The main point is not to come up with specific answers to the specific problems you are working on, but to develop an understanding of what you are doing so that you can apply your reasoning to a wide range of similar situations. It is very unlikely that later on in life you will see exactly the same math problems you are working on now, so learn the material in such a way that you are prepared to use your general knowledge of mathematics in the future, not just how to apply particular formulas for very specific problems.

We encourage you to form study groups with other students in the class so that you can discuss your work with each other; however, all work submitted must be written up individually. Make sure that even if you do work in groups, that you come away with the ability to explain everything you end up writing up in your homework.

Typically, there will be one problem set due each week, to be submitted via Canvas file uploads (PDF format preferred). Immediately after each submission deadline, we will post sample solutions on our course Canvas website. Please review these solutions while your recently-submitted problem sets are still fresh in mind, as this is a great way to (i) solidify/reinforce conceptual understanding and (ii) identify sources of confusion to ask course staff members about during office hours. (It's also very helpful for exam preparation.) Because homework solutions are posted immediately after the submission deadlines and the fact that falling behind in a math class is one of the most uncomfortable things you can do to yourself, homework *must* be submitted on time. **We will drop your lowest problem set score** when computing your overall homework grade. Please do not try to persuade a CA to accept a late homework assignment, as this goes against our academic integrity policy. Homework *must* be submitted electronically via Canvas and cannot be transmitted to CAs by other means (such as email). Moreover, claiming to have submitted the "wrong version" of an assignment via Canvas (or perhaps not all of the pages that you intended to submit) is never grounds for late submission of an assignment.

The Role of Data and Computing: As explained above, mathematical modeling and *in silico* studies can guide *in vitro* or *in vivo* experimental protocol. Whenever possible, the development of a mathematical model should be informed (see next paragraph) by real data. For this reason, some problem set exercises will incorporate real data sets, many of them from the articles you are asked to read. Some exercises will ask you to use data to estimate parameters, such as kinetic constants, appearing in differential equation models. Others will ask you to overlay model output with data sets and assess[2] goodness of fit, and whether a model is able to replicate the salient features of experimental observations. To facilitate such exploration, you will be asked to use the software package *Mathematica*, which you may download and install through Harvard's computing website. (Instructions will appear on your first problem set.)

Importantly, the most celebrated models of biological phenomena (such as the Nobel Prize-winning work of Hodgkin and Huxley) are not totally "data driven". Rather, they blend *mechanistic, biophysical* modeling with experimental measurements. In the case of Hodgkin and Huxley, the cell membrane was modeled as an electrical circuit: it acts as a capacitor (it separates electrically-charged ions) in parallel with variable resistors (i.e., voltage-gated ion channels). Using some basic theory of electrical circuits, Hodgkin and Huxley formulated a differential equation model for the membrane potential, and used voltage clamp data to estimate model parameters.

Final Project: You will critique and analyze a mathematical model in a research article of your choosing, subject to approval by your Course Head. As a high-risk but potentially rewarding alternative, you may formulate and analyze your own mathematical model of a biological/medical phenomenon of your choosing. Should you choose the latter option, it would be helpful if you could identify research articles that describe the phenomenon you propose to model. A preliminary proposal will be due in mid-October, and the final project will be due near the end of the University's Reading Period. Details will appear on the course website.

[2] Students interested in a formal introduction to relevant statistical methods are encouraged to take an introductory biostatistics course such as BST 202-203, as Math 19a does not introduce statistical tests, least squares regression, etc. In Math 19a, qualitative assessment of a model's ability to replicate data will help us (i) support/oppose hypotheses regarding mechanistic underpinnings of biological phenomena and (ii) identify realistic refinements of modeling assumptions, potentially leading to improved agreement with data.

Grading and Exams: There will be two midterm exams and a final project in lieu of a final exam. Your course grade will be determined as follows:

Component	Date	Percentage
Homework	see course website or Syllabus below	25%
Midterm I	Tuesday, Oct 08, 2024 from 7:00–9:30pm	20% or 30%*
Midterm II	Tuesday, Nov 19, 2024 from 7:00–9:30pm	20% or 30%*
Final Project	Tuesday, Dec 10, 2024 before 12:00pm	25%

*Your best midterm score will count for 30%, and your worst midterm score will count for 20%.

When we calculate your final grade at the end of the course, we will calculate a score on a 0-100 point scale using the scores that you have obtained during the course, and using the percentages given above. Your course grade will then be obtained using this table:

Numerical cutoff	Corresponding letter
92.5	A
89.5	A-
86.5	B+
82.5	B
79.5	B-
76.5	C+
72.5	C
69.5	C-
59.5	D
below 59.5	E

Academic Integrity: Discussion and the exchange of ideas are essential to doing academic work. For assignments in this course, you are encouraged to consult with your classmates as you work on problem sets. However, after discussions with peers (or course instructional staff such as tutors, TF/TAs, course assistants), make sure that you can work through the problem yourself and ensure that any answers you submit for evaluation are the result of your own efforts. In addition, you must cite any books, articles, websites, lectures, etc that have helped you with your work using appropriate citation practices. Similarly, you must list the names of students with whom you have collaborated on problem sets.

During the two in-class exams, all forms of communication (written, verbal, electronic, etc.) with non-course staff members is forbidden. Use of electronic devices during an exam is also forbidden. When completing the final course project, some students wish to contact authors of published research articles to request guidance and/or clarification. While this is usually appropriate, you must request permission from your course head before reaching out to subject matter experts external to our course staff.

Generative artificial intelligence (GenAI) tools such as ChatGPT can sometimes help you explore a concept, but beware—these tools can give answers that sound confident regardless of whether they are correct. You should never ask such tools to solve your homework problems.

Redistribution of any of our course materials (class notes, readings, homework assignments, exams, project materials, and so on) is strictly forbidden unless written permission from your course head is granted.

Disabilities Requiring Accommodation: If you need accommodation or assistance for a documented disability, please contact the course head as soon as you can so that we can make the necessary arrangements. Please note that accommodations for extended time on homework assignments and/or use of electronic devices during exams (including phones, calculators, or computers) do **not** apply to this course. Refer to

https://dao.fas.harvard.edu

for more information.

Syllabus[3] for Math 19a, Fall 2024

Date	**Due**	**Math Topics**
Wed 09/04		Course Orientation and Preview, terminology
Fri 09/06		First-order differential equation (DE) models
Mon 09/09	Reading 1	Solving separable DEs, solving linear DEs
Wed 09/11	PS00	Qualitative analysis, phase line, equilibria, stability
Fri 09/13	Reading 2	Bifurcations, intro to planar systems, phase plane
Mon 09/16		Planar systems: equilibria, nullclines
Wed 09/18	PS01, Reading 3	Lotka-Volterra systems (predator-prey, competition, symbiosis)
Fri 09/20		SIRS models and/or biochemical kinetics models
Mon 09/23	Reading 4	Vectors, matrices, and systems of DEs
Wed 09/25	PS02	Linear, constant-coefficient systems
Fri 09/27	Reading 5	Eigenvalues and eigenvectors
Mon 09/30		Eigenvalues and eigenvectors, continued
Wed 10/02	PS03, Reading 6	Complex eigenvalues
Fri 10/04		Nonlinear systems, partial derivatives and tangent planes
Mon 10/07		Review for first mid-term exam
Tue 10/08	**Exam 1**	(room to be determined) from 7:00pm–9:30pm
Wed 10/09	PS04, Reading 7	Jacobian matrices, stability of equilibria
Fri 10/11		Linear stability analysis, trace/determinant plane
Wed 10/16	PS05, Reading 8	Bifurcations in nonlinear systems of DEs
Fri 10/18		Periodic orbits and Hopf bifurcations
Mon 10/21	Reading 9	Periodic, homoclinic, and heteroclinic orbits
Wed 10/23	PS06	Discrete-time systems, one-dimensional mappings
Fri 10/25	Reading 10	Fixed points, stability, bifurcations in discrete-time systems
Mon 10/28		Higher-dimensional mappings, fixed points, stability
Wed 10/30	PS07, Reading 11	Partial differential equation (PDE) models in the biosciences
Fri 11/01		Diffusion/advection/reaction systems
Mon 11/04	Reading 12	Diffusion/advection/reaction systems continued
Wed 11/06	PS08	Initial-boundary value problems
Fri 11/08	Reading 13	Separable PDEs
Mon 11/11		Separable PDEs and Fourier Series
Wed 11/13	PS09, Reading 14	Fourier Series Continued
Fri 11/15		Stability of equilibria
Mon 11/18		Review for second mid-term exam
Tue 11/19	**Exam 2**	(room to be determined) from 7:00pm–9:30pm
Wed 11/20	PS10	Reaction-diffusion equations, traveling wave solutions
Fri 11/22		Traveling wave solutions continued
Mon 11/25		Chemotaxis, review of PDE unit
Mon 12/02		Waves of invasion, pursuit, and evasion
Wed 12/04	PS11*	Research in biomathematics
12/05–12/10		Reading period
Tue 12/10	**Final Project**	Final project is due at 12:00pm

[3]The dates listed here are approximate, so don't worry if there are times when we're a bit ahead/behind what the syllabus indicates. Due dates for certain readings or problem sets may be adjusted in order to keep your workload as uniform as possible!
*You **cannot** select the last problem set of the semester as the assignment you elect to "drop".