

REVIEWS

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Biology in Time and Space: A Partial Differential Equation Modeling Approach. By James Keener, American Mathematical Society, 2021. 308 pp., ISBN 978-1-4704-5428-9, \$99.00

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A question mathematical modelers are getting some relief from in these pandemic times is “what is the real utility of a mathematical model for medicine, or biology in general?” The value of mathematics applied to physical systems has persisted unchallenged for hundreds of years, but the application of mathematical principles to biological systems has remained controversial at least as far back as Turing’s model of pattern formation proposed in 1952 [7]. We are naturally suspicious of the limitations in reducing such complexity. However, this reluctance has diminished as we have been confronted by a deadly infectious disease about which little was known, yet predictions needed to be made in order to slow the spread. “Mathematical modeling” has become part of the public lexicon. Convincing biologically-inclined students of the value of a quantitative approach and, conversely, attracting students inclined toward computer science and physics to apply these techniques to problems in medicine, both became a whole lot easier. Every calculus and differential equations class I have taught since the spring of 2019 has featured infectious disease modeling as a theme, from estimating the reproductive number of SARS-CoV-2 from case data to SIR modeling, and students have been incredibly receptive to exploring such timely and authentic problems. Problems like these, as we’re now all too aware, require an interdisciplinary approach that we should be fostering in our students if we want to see solutions over the coming years.

How many mathematicians are truly interdisciplinary? A *Nature* special issue on the topic published in 2014 poses this very question to scientists (even including a fun self-quiz) and the editorial of the issue adds this clarification of interdisciplinarity: “...it is not mere multidisciplinary work — a collection of people tackling a problem using their specific skills — but a synthesis of different approaches into something unique” [2]. Useful mathematical models are composed of more than mathematics: a “good” model of infectious disease spread, for example, that provides actionable public health information, takes spatiotemporal data as input that is now available via GIS, cell phone tracking, or even social media tracking to say nothing of the biological and medical knowledge required. Developing such models obviously requires familiarity not just with partial differential equations (PDEs), but with epidemiology, GIS, social media data extraction, and various programming languages. A specific example of this, again, is pandemic preparedness and a “modernization” of the SIR model of infectious disease spread to build in a global mobility framework [4]. Further, multiscale mechanistic models are becoming the gold standard, and can require levels of models including ODE, PDE, and agent-based. We need people who are trained across these areas and, even more importantly, who have some experience speaking the language of multiple disciplines in order to foster collaboration. A 2019 article by Keisuke Okamura revisited the importance of interdisciplinarity to give some verifiable evidence that scientific research impact increases with the number of distinct disciplines in-

volved [3]. To give a personal example, I've had a collaborative research project with a developmental biologist fail because we couldn't agree on the meaning of the word "output"! As someone who came to biological applications late in my education, I could have been spared some growing pains by a text like *Biology in Space and Time: A Partial Differential Equation Modeling Approach* by James Keener. I saw Keener speak on modeling diffusion in biological systems as a graduate student in 2016, at the Biology and Medicine Through Mathematics Conference, when I was just beginning my research in mathematical biology, and I remember being energized by his ability to capture the fundamentals of such diverse processes as quorum sensing and mitosis all with variations on the same equation: $u_t(x, t) = Du_{xx}(x, t)$. Exciting connections like this abound in the text and I can imagine my students being as excited as I was by questions it leads to, such as "how is an electrical circuit like a nerve axon?"

The text contains that "synthesis of different approaches" mentioned above, combining elements of statistics and probability, computer science, physics, biology, and, of course, plenty of solid applications of multivariable differential equations. The intended audience, according to Keener, is the advanced undergraduate student with courses in multivariable calculus and ordinary differential equations under their belt, as well as some exposure to probability theory and stochastic processes. Some programming experience is also helpful, since numerical rather than analytical solution methods are the focus. A diligent student could probably get by with minimal to no previous knowledge of stochastic processes and Matlab, however, with the support of the instructor. A Matlab primer is included in the appendix to complement the codes used throughout the book.

After an introductory chapter that reviews prerequisites and a second chapter that discusses modeling in general, most subsequent chapters either expand on or introduce a class of partial differential equations used in modeling biological processes. Most texts on the topic, such as Walter A. Strauss's classic undergraduate text *Partial Differential Equations: An Introduction* [6], cover the wave equation, the heat/diffusion equation, and the Laplace equation, and are structured around derivations and analytic solution methods with applications to physical systems. The context of a typical boundary value problem in a PDE text might be measuring temperature x at time t on a long insulated wire touching a block of ice at each end, or vertical displacement u of a string at time t . In contrast, Keener's text begins with the diffusion equation in Chapter 3 and moves on to the bistable equation, Burger's equation, advection-reaction, and advection-diffusion, where some of the models include stochasticity as well. The context of most problems is also different: for example, we are interested in measuring the concentration of pheromone u at time t emitted by an ant traveling down a long tube and flux of oxygen in muscle fibers. Numerical solution methods are the heart of the text, and topics like nonlinear PDEs and bistability get more than usual coverage because they are widely used in the actual practice of modeling biological systems. Only Chapter 4 features primarily analytic solution methods, since most biological problems are too complex to be solved in this way, yet spending some time on these methods builds intuition.

Each individual chapter presents mathematical and statistical derivations, Matlab code for simulation, and biological applications problems, and I can imagine selecting these materials depending on student preparation and interest. For example, at my liberal arts institution where even upper level mathematics courses can be populated with primarily non-mathematics majors, I might choose to focus class time on building understanding of partial differential equations via running the numerical simulation codes and solving exercises and applications, while assigning videos and readings before each class to build mathematical intuition and walk through some of the derivations. A

class composed of more mathematically oriented students could easily be structured in the opposite manner, centered on some of the rigorous mathematical analysis of each equation—the breadth of approaches covered for each of the PDEs presented in the text allows a lot of flexibility in the classroom to suit the audience.

In the introduction to the book, Keener states “...it is often the case as illustrated here that processes transpire according to the same principles and therefore their mathematical descriptions have common features that can inform each other even though the vocabulary describing the details is vastly different.” Chapter 3 is a good example of this, where the diffusion equation is arrived at via three derivations ranging over the concrete (flow of a chemical between boxes), the statistical (random walk, with expected value and variance), and the biological/physical (the cable equation model of flow of voltage between neurons). Each derivation is brief, but is further explored in the end of chapter exercises, and there is a lot here to engage the student who is excited to discover connections between seemingly unrelated phenomena. As someone who uses active learning in the classroom and reviewed this text with an eye toward teaching an undergraduate PDE course with it, I can envision assigning students to attempt to derive a mathematical description of the flow of a chemical between boxes as a warmup before class. In class, I would first take Keener’s suggestion of getting students to physically simulate Brownian motion to build some intuition about the diffusion process. Next, we would spend a day or two discussing circuits and how they can be used to model flow of voltage between neurons with the diffusion equation.

Chapters 4 and 5 expand on the diffusion equation (no pun intended). In Chapter 3, we discovered that a key feature of a diffusion process beginning at the origin is that its expected value is zero for all time and its variance is a linear function of time. In Chapter 4, this leads us to consider how we might leverage these properties to calculate an “effective diffusion” for biological processes that are not completely explained by diffusion—and this gives us a nice example of the value of numerical simulation. The problem of modeling the run and tumble motion of bacteria is presented with the question of whether it is a diffusion process: it turns out that it is one if the mean squared displacement of bacteria is a linear function of time. How can we check this? By developing a mathematical description, coding it in Matlab, and running simulations as any applied mathematician would do! The reader of Keener’s book is walked through this process and then again walked through development of an agent based model. This is an example of how the text goes beyond training students to solve PDEs in the classroom to supporting their development as a researcher. My main memories of an undergraduate PDE course consist of using the separation of variables to solve various Cauchy problems related to the heat and wave equations; what I recall taking several weeks of that course is covered in about 9 pages in Chapter 5 on solutions to the diffusion equation. The focus is instead on the numerical methods that would actually be used in practice. All of this is tied together at the end of the chapter with an application that presents the perfect opportunity for some interdisciplinary collaboration: measuring the diffusion coefficient of molecules using FRAP (fluorescence recovery after photobleaching). This experimental technique fluorescently labels the molecules and then bleaches a circular region with a laser beam so that diffusion of fluorescent molecules back into the bleached area can be tracked over time. Modeling this involves numerically solving the diffusion equation on a circular domain, so that the student must discretize $\frac{\partial u}{\partial t} = \frac{D}{r} \frac{\partial}{\partial r} \left(r \frac{\partial u}{\partial r} \right)$, where u is the concentration of fluorescent molecules, D is the diffusion coefficient, and r is the radius. They will then think about how the experimental setup must be reflected in the boundary conditions, since bleaching occurs in the circular region only at $t = 0$, $u(r, 0) = 0$ and $u(R, t) = U_0$ for $0 < r < R$. This would make a great lab or mini-project: use an established for-

mula to estimate the diffusion coefficient of a molecule given appropriately normalized time-course data (for example, this article contains data on diffusion of SARS-Cov-2 neocapsid protein [5]), then use the estimate to run simulations with the provided Matlab code and compare results. Better yet, ask your colleagues in the biology department for data or even if your students can take a "field trip" to collect data in their lab - I'm fortunate enough to have a colleague that allows this "wet lab" experience for my undergraduate research and calculus students and it seems to deepen their understanding of the modeling process significantly.

Chapter 6 begins the discussion of reaction-diffusion equations as modeling such things as dispersal of populations experiencing growth or decay. This gives a concrete feel to some of the properties of diffusion; for example, homogeneous Dirichlet boundary conditions on growth and diffusion of a population on a finite domain take on a somewhat more visceral meaning when they correspond to instantaneous death for organisms leaving the space. Further, the behavior of solutions begins to gain some additional meaning within this setting. By this point, students have seen that the general solution to the diffusion equation contains an exponential term and a trigonometric term, but having experienced the confusion of students in how to interpret this in a general way I can see the value of considering these solutions contextually .

Chapters 7 and 8 cover the bistable equation

$$\frac{\partial u}{\partial t} = D \frac{\partial^2 u}{\partial \xi^2} + kf(u).$$

In this scenario, in addition to experiencing diffusion, a concentration or population u also has a reaction rate that at first slowly increases to some threshold, jumps, and then decays. When we investigate the biological systems modeled, we find that such diverse systems as spread and control of ecological pests, the dynamics of action potentials along nerve axons, and calcium waves in cell signaling have the common feature of switching behavior. The constraints on the function f give two stable equilibria u_0 and u_2 that lead to this behavior, and the way in which the text guides us through the solution process provides a good example of the structure of each chapter. Simulations using Matlab code motivate the search for traveling wave solutions when we notice that some trajectories appear as a fixed shape traveling with constant speed. Based on the numerical hint, we are told to expect solutions of a certain form, and the analysis proceeds from there as we search for the appropriate value for the traveling wave coordinate, calculate speed of propagation, and find the threshold that the initial stimulus needs to overcome to initiate traveling waves. The visualization of solutions generated by numerical methods as we perform the intensive work of analytic solution is a highlight of the text, and it's hard to imagine working through it without Matlab. In particular, most of the plots of solutions contain trajectories for many time points simultaneously so that using the included code to manipulate visualizations could improve interpretability.

In Chapter 9, the advection/transport equation is introduced with structured population modeling, where differences among individuals can impact population change. We can model, for example, $u(a, t)$ as the number of people of age a at time t and model the population demographics as an advection plus decay process $\frac{\partial u}{\partial t} = -\frac{\partial u}{\partial a} - \mu(a)u$, assuming a death rate of $\mu(a) \geq 0$. If we move forward in time by Δt , then individuals in the age range $[0, a]$ age (are "transported" in time units) by Δt since aging happens at the same rate that time passes, less that portion of the population that has died. This introductory example, which is refreshingly different from the usual "transport of a pollutant down a stream", is then extended to age-dependent red blood cell production

and epidemics in which transmission rate depends on time since infection (as is the case with SARS-CoV-2). All systems are solved analytically here, using the method of characteristics, and each solution carries a punchline that illuminates an aspect of biology. For example, when modeling age-structured populations we find that if the "fitness" of a population, as measured by the age-dependent reproduction rate, is below a certain level it cannot be sustained. Simulation methods for advection equations are then covered, including how to numerically implement the method of characteristics, followed by Burger's equation for nonlinear advection and the possibility of multivalued solutions that pops up for many real nonlinear processes, and then three more detailed presentations of model development and solution finish the chapter. It's hard to imagine spending less than a couple of weeks on this rich topic that does not usually get much attention in an undergraduate course.

Diffusion augments advection in the following chapter where the run and tumble motion of bacteria that appeared in Chapter 4 can now occur at differing rates in either direction along a line. This can no longer be modeled with simple diffusion, giving a great opportunity to show students how we build on previous ideas to extend models. Ornstein-Uhlenbeck processes model constrained motion of a particle as a mass-spring system and epidemic spread in this chapter. Like many examples of stochasticity in the text, the topic seems intuitive enough that I can see a student with minimal background in probability doing just fine as long as they are familiar with some basic concepts in statistics. For example, just as we see in modeling diffusion-only processes, we can pretty easily shift from taking the deterministic steps we're accustomed to, $dx = vdt$, to taking steps $dx = vdt + \sqrt{2Dt}\mathcal{N}(0, 1)$ which can be understood as simply adding noise that scales with the variance as a linear function of time. Similarly, when random walks are referenced throughout the text the context is so intuitive that not much background may be needed. Exposing students to modeling randomness in the natural world is critical. And teaching them to use code and other tools that they don't yet fully understand is an important part of "getting used to" the business of fumbling in the dark a bit to solve problems. Welcome to real math!

Chapters 11-14, as Keener notes in the introduction, do not introduce new mathematics but instead present a series of biological processes and ask "how do we model this and learn something useful given our existing knowledge?" Topics include movement of cells and organisms along chemical gradients (Chapter 11), spatial pattern formation in animals, plants, and cells (Chapter 12), invasive species dynamics (Chapter 13), and quorum sensing and flocking (Chapter 14). I particularly like the end-of-chapter exercises for these applications, which include modifying the Matlab code and also exploring the impact of modifying model parameters - they feel like the playful reward for doing all the heavy lifting of the previous chapters. With seven distinct biological applications that extend the PDEs learned previously, groups of students could be assigned one each to present as a final project.

Full disclosure on my perspective: I worked through this text with the simultaneous viewpoint of (a) an undergraduate student, since I have not worked much with PDEs since I was a teaching assistant for an undergraduate course about a decade ago, and (b) a professor intending to use the text in a special topics course. From either perspective, reading this text was an education: there are so many rabbit holes to go down that I expect to have a difficult time developing a syllabus that can be covered in one semester! So much is covered that many of the derivations and techniques presented are brief and readers may need to review their differential equations from other sources. For example, the part of Chapter 6 dedicated to the Fisher equation includes topics such as nondimensionalization, linearization, the Jacobian, bifurcations, both stable and unstable manifolds, traveling wave solutions, and a comparison theorem. All in just twelve

illustrated pages. That is a lot of mathematical ground to cover, but the big picture of how to approach these problems comes across; as von Neumann famously said regarding the method of characteristics "...in mathematics, you don't understand things. You get used to them." Here, we "get used to them" chapter by chapter by solving a variety of problems using the same methods. Along the way, we gain not only practice and familiarity but a sense of connection across wide branches of human knowledge that motivates the effort.

Students who learn the material in this book, and embrace its spirit through the models referenced throughout the application problems, will be deeply rewarded in their understanding. For my part, I am looking forward to having some exceptionally prepared undergraduate research students the summer after teaching a sequence of differential equations with the new modeling focused text from SIMIODE [1], which provides a brief introduction to PDEs, followed by a partial differential equations course using this text.

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