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Mathematics + Cancer: An Undergraduate "Bridge" Course in Applied Mathematics*

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Abstract. Most undergraduates have limited experience with mathematical modeling. In an effort to respond to various initiatives, such as the recommendations outlined in [S. Garfunkel and M. Montgomery, eds., *GAIMME: Guidelines for Assessment & Instruction in Mathematical Modeling Education*, SIAM, 2016], this paper describes a course on the mathematical models of cancer growth and treatment. Among its aims is to provide a template for a "bridge" course between the traditional calculus and differential equations sequence and more advanced courses in mathematics and statistics. Prerequisites include a course in ordinary differential equations. Linear algebra is a useful corequisite but no previous programming experience is required. The content includes classical models of tumor growth as well as models for the growth of specific cancer types. Relevant research articles are provided for further study. Material for student projects and effective communication is supplied, as well as suggestions for homework assignments and computer labs. This paper aims to assist instructors in developing their own "Mathematics + Cancer" course.

Key words. mathematical modeling, cancer, differential equations, undergraduate education

AMS subject classifications. 97M10, 92C50, 34A99

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1. Introduction.

This paper describes an undergraduate course, accessible to students who have completed a standard sequence of calculus and ordinary differential equations, on the mathematical modeling of cancer. The content and format of the course are derived from the authors' experiences in advising undergraduates in a program funded by the National Science Foundation's Mentoring through Critical Transition Points (MCTP) initiative. Our objectives in developing this course are threefold. First, we are interested in providing a model of a "bridge" course between the traditional calculus sequence and higher-level courses besides the typical "introduction to proof" class. Second, our effort is an attempt to develop an introductory course in applied mathematics that addresses a compelling scientific and social prob-

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lem. We motivate the relevant mathematical ideas at a level that is intelligible to a broad student audience and in a way that will help students make informed choices about more advanced courses in statistics, probability, numerical analysis, partial differential equations, and dynamical systems, for example. Our third goal is to adapt some of the pedagogical features of an undergraduate research experience—reading papers from the primary research literature, completing a collaborative project, and giving a talk—to a semester course format.

Our course is also an attempt to respond to recent programmatic initiatives of professional mathematical societies, including those by the Mathematical Association of America's (MAA) Committee on the Undergraduate Program in Mathematics (CUPM) and by the Society for Industrial and Applied Mathematics (SIAM) and the Consortium for Mathematics and Its Applications (COMAP). The 2015 *CUPM Curriculum Guide to Majors in the Mathematical Sciences* [90] makes four "cognitive recommendations" for overall programmatic goals, stressing students' development of communication skills, ability to apply theory to applications, facility with technological tools, and "mathematical independence and experience [of] open-ended inquiry." The *Guidelines for Assessment and Instruction in Mathematical Modeling Education* (GAIMME) report [39] by the SIAM and COMAP working groups discusses "transferable skills" that undergraduates can develop in the context of a modeling course, including identifying tractable questions, using reliable sources, working collaboratively, and communicating effectively. The *Modeling Across the Curriculum* report [24], which was funded by a National Science Foundation grant to SIAM for "an initiative to increase mathematical modeling and computational mathematics in high school and college curricula," recommends developing accessible curriculum materials in addition to discussion of the modeling process.

Furthermore, by providing students with a research experience during a regular class, we are able to reach a diverse group of students who may not otherwise have the opportunity to participate in, for example, a supported project of the National Science Foundation's Research Experiences for Undergraduates (REU) Program [77]. Many REUs are inaccessible to minority, first-generation, and/or nontraditional students who, for financial, logistical, or child-care reasons, cannot attend an out-of-town program on a full-time basis for eight to twelve weeks. Our course represents an effort to provide a scalable, cost-effective alternative to a traditional REU. The enduring lessons the course aims to impress upon the students are similar to benefits students can obtain from participating in REUs: exposure to problem-solving experiences, awareness of STEM research fields and career options, and adding relevance to standard mathematics courses by applying theoretical knowledge to real-world cancer biology problems [72].

A final objective of this article is to motivate further efforts to develop courses with analogous goals on topics drawn from other areas of the mathematical sciences. We hope that the outline presented here, and the supplementary materials, will serve as a useful template.

2. Course Format and Overview. The course that we have developed meets for two 75-minute or three 50-minute periods per week over a 15-week semester. The first ten weeks or so use a "lecture-lab" format in which the main mathematical ideas are covered in a traditional lecture (one 75-minute or two 50-minute periods each week) followed by an informal computer lab whose exercises invite students to explore the ideas numerically. Homework sets, typically spaced every other week, emphasize the theoretical and analytical aspects in more detail. The last five weeks

of the course are devoted to student projects and presentations. Given the limits of time and prior student experience, projects generally focus on reproducing the results of a mathematical model described in a research paper (see section 4).

Insofar as differential equations are used extensively to model the progression of cancer, students are assumed to have had a prior course in ordinary differential equations, such as might follow the second or third semester of calculus. (Linear algebra is a useful corequisite.) No previous programming experience is required. We have used MATLAB [100] for the computer lab exercises, but GNU Octave [41], Maple [67], *Mathematica* [110], and Python [22] are potential alternatives. Any platform that allows for interactive use and that includes an easy-to-use two-dimensional plotting facility should suffice.

Because one of our pedagogical goals is to give students experience in reading research papers, we have not used a traditional textbook. Nevertheless, instructors may wish to consider portions of texts by Wodarz and Komarova [109] and Kuang, Nagy, and Eikenberry [61] as background material for lectures. Our course so far has used ovarian cancer, prostate cancer, and glioblastoma multiforme as representative case studies, in part because of our research connections with oncologists specializing in these cancers. Table 4.1 lists some papers on these topics and others that, in the authors' opinion, have been suitable for case studies and student projects.

Few of the students have previously read an article in a research journal, so we provide some coaching. Our approach is to liken a research paper to the layers of an onion: first read the abstract, introduction, and conclusions for the basic gist; skim the methods and analysis section; then try to understand more details on subsequent readings. Greenhalgh's text, *How to Read a Paper* [44], is a useful supplement; the book focuses on the medical literature and is written for a general scientific audience.

Another goal of the course is to provide students with experience in communicating science beyond the written homework and blackboard problem presentations that are typical of first- and second-year college mathematics courses. We ask the students to articulate to their peers why their problem is important and interesting and to summarize their main findings in a short talk and/or poster format. Such training is common in graduate programs, but we think that nearly all undergraduates can benefit, insofar as analogous types of oral communication are necessary in most professional vocations.

3. Course Modules. In this section, we describe various modules of one to two weeks in length that can serve as subject material for lectures and computer labs. A sample syllabus, homework problem sets, and computer lab descriptions may be found in the supplementary materials.

Rarely a day goes by without newly published news articles on cancer, which can provide relevant material for class discussions. Cancer is the second most common cause of mortality in the United States (accounting for about one in every four deaths [5]). While cancer survival rates overall have increased in recent years, there has been no improvement for teenagers and young adults [21], for reasons that are unclear. New treatments are being tested constantly, and it is a challenge to stay current on the subject. We have tried to include one or two guest lectures by local research oncologists each term, as they can provide a clinical perspective on the challenges and legal and ethical obligations to patients when selecting standard and/or experimental treatments.

Since our course is offered within a mathematical sciences program, we focus on mathematical and statistical models of cancer. Nevertheless, we begin the course with

an overview of cancer biology. Hanahan and Weinberg [46] describe six "hallmarks" of cancer growth: sustaining proliferative signaling, evading growth suppressors, activating invasion and metastasis, enabling replicative immortality, inducing angiogenesis (growth of blood vessels), and resisting cell death.

3.1. What and Why Do We Model? Our main purpose is to discuss the role that mathematics and data play in understanding the dynamics of cancer, from the standpoint of an individual tumor to the burden of cancer at the population level. *What and why do we model?* can focus on the following questions:

Statistical models: What fraction of people will be diagnosed with cancer in the next year? How can one account for the increasing incidence of cancer with age?

Dynamical models: How does a population of cancer cells grow, spread, and evolve resistance to treatment in an individual patient?

The scale problem: What are the tumor dynamics at the cellular and tissue levels?

The data problem: What can we measure? How do clinical observations, such as medical imaging, relate to the underlying disease process? Insofar as many tumors are incurable, how can one measure the efficacy of treatment?

Policy: From a public health perspective, how much cancer might be preventable (e.g., by antismoking and antiobesity campaigns), how much is due to environmental exposures (e.g., sunlight, pollution), and how much is simply "bad luck" (i.e., arising from random somatic mutations)?

Prediction: Does a model using particular biological assumptions produce tumors that behave in a manner consistent with clinical observations? If not, then why not? Can we make short-term forecasts of tumor progression in an individual patient?

Hypothesis testing: How are statistics used to design clinical trials and to assess the efficacy of new treatments?

***In silico* clinical trials:** How might the sequencing of treatment (e.g., surgery before radiotherapy) affect the growth of a tumor under various hypotheses?

Throughout the course, we return to these ideas repeatedly to evaluate the mathematical models that are discussed. To validate the model equations, dimensional analysis and analysis of qualitative behavior and end behavior are studied as well as errors and data fitting. These analyses can be done during lectures or in the homework and computer labs (suggested assignments are given in the supplementary materials). References such as [13, 29], among others, that describe principles of mathematical modeling can be incorporated into class discussions.

3.2. Statistical Modeling of Cancer. Statistical and probabilistic analyses of data have been used for many years to understand the genesis of tumors. Our classroom discussion begins with two classic papers from the 1950s that demonstrate the value of mathematical analyses in unraveling the mystery of cancer formation.

Using the first reliable, comprehensive death registries in Western Europe and the U.S., Nordling [79] observed that the risk of dying from cancer was roughly proportional to the sixth power of age. If, for example, one crucial mutation sufficed to induce a cancerous tumor, and if there were an approximately constant probability p that a given dividing cell would incur such a mutation, then the death rate from cancer would be roughly constant with age. Consequently, Nordling explained the observed power-law relationship by suggesting that seven mutations were necessary, on average, for tumors to arise, assuming that the probability of the next mutation in the required sequence is approximately constant throughout life.

In 1954, Armitage and Doll [7] used death registries from England and Wales to examine the risk of cancer death by site as a function of age. They found that the death risk from colorectal, stomach, pancreatic, and esophageal cancers followed Nordling's power-law relationship reasonably well but that the death risk from lung, prostate, breast, ovarian, cervical, and uterine cancers did not. Armitage and Doll proposed a time-varying modification of Nordling's hypothesis. If the sth mutation ($1 \leq s \leq 6$) required for a given cancer occurs by age t_0, and cancer is diagnosed at some later age t, then they argued that cancer risk should be proportional to $t_0^{s-1}(t-t_0)^{6-s}$. Such a theory could explain the observed age-related incidence of cancers of the reproductive tract if the rate of initial mutations were a function of hormones or similar factor.

Armitage and Doll later refined their approach and proposed a two-stage theory of carcinogenesis [8]. Knudson's 1971 statistical analysis of retinoblastoma [56] (a pediatric eye cancer) suggested the existence of a tumor-suppressing gene. In 2014, Tomasetti et al. [103] applied a version of Armitage and Doll's approach and suggested that three driver gene mutations are required for lung and colorectal cancers.

A key public policy question concerns how cancer prevention and screening efforts should be prioritized. We focus one lecture on a review of Tomasetti and Vogelstein [104], which postulates that about 65% of the difference in lifetime cancer risk among various tissues can be explained by the average number of stem cell divisions within them. A subsequent paper [102], using data on 17 cancer types from 69 countries, corroborates the original findings and estimates the relative contributions of environmental, inherited, and random factors to the incidence of some common cancers. The authors' mathematical analysis concludes that "primary prevention is the best way to reduce cancer deaths" but also that many cancers are not preventable [102], so screening efforts will remain necessary.

3.3. Experimental Design and Hypothesis Testing. A discussion of the mathematics behind disease testing and clinical trials introduces students to the complexities of determining the extent to which treatments may be regarded as successful. Much of the content in this part of the course is classical, but many students have not had previous exposure to it. One objective is to interest students in more advanced courses in probability and statistics.

We begin this portion of the course with basic set theory including union, intersection, and complement of sets as well as the Inclusion-Exclusion Principle. This introduction leads into a discussion of what a sample space, event, and probability are. The next concept is conditional probability, which is the probability of event A occurring given that event B has occurred, or

$$P(A|B) = \frac{P(A \cap B)}{P(B)}. \tag{1}$$

An important theorem that follows is Bayes' theorem, which says that if $P(B) > 0$ and $P(B^c) > 0$ (where B^c is the complement of B), then for any event A such that $P(A) > 0$,

$$P(A|B) = \frac{P(B|A)P(A)}{P(B)} = \frac{P(B|A)P(A)}{P(B|A)P(A) + P(B|A^c)P(A^c)}. \tag{2}$$

One application of Bayes' theorem occurs in disease screening. For example, suppose that a test correctly identifies 95% of the people who are known to carry a

particular genetic mutation (i.e., the test's *sensitivity* is $P(+|M) = 0.95$) and that the test also rules out 99% of the population that does not have the mutation (the *specificity* is $P(-|M^c) = 0.99$). If the mutation is rare (e.g., the *prevalence* is $P(M) = 0.001$), then (2) can be used to show that the probability that one carries the mutation given a positive test (the *precision*, $P(M|+)$) is

$$(3) \quad P(M|+) = \frac{P(+|M)P(M)}{P(+|M)P(M) + P(+|M^c)P(M^c)} = \frac{0.95 \times 0.001}{0.95 \times 0.001 + 0.01 \times 0.999} \approx 0.087,$$

or about 8.7%, using the fact that $P(+|M^c) = 1 - P(-|M^c)$ and $P(M^c) = 1 - P(M)$. On the other hand, the probability that one does not carry the mutation given a negative test (the *negative predictive value*, $P(M^c|-)$) is greater than 99.9%. Examples like this illustrate why, based on a negative test, a doctor may be able to reassure a patient that he or she almost certainly does not have a given disease, and why another test is necessary to confirm a diagnosis otherwise.

We also devote a couple of class periods to null hypothesis significance testing, which is a standard topic in introductory statistics courses. Nevertheless, an introductory discussion of experimental design seems warranted, given the importance of clinical trials to cancer treatment and research and because many of our students have not yet had a course in statistics. We review the classical tests for differences between sample means (e.g., between an experimental group and a control group) and the computation of associated confidence intervals. Students also read about some of the criticisms of the classical approach (e.g., Cohen [20]) and common misconceptions about p values (e.g., Goodman [43]), which lend themselves to interesting classroom discussions. For example, in null hypothesis significance testing, the choice of the significance level is arbitrary, the results depend on the sample size, and one can fail to detect a treatment effect if the sample size is too small. Such *underpowered* trials are a real-world problem and potentially an ethical one, insofar as patients may continue to receive an inferior treatment. Furthermore, statistical significance does not imply clinical significance, because the classical approach does not quantify the effect size.

There are many other statistical topics that can be developed in greater detail, depending on the instructor's interest. One of our computer labs introduces the concept of bootstrap sampling [30], using an example from Efron and Tibshirani [31] to compute confidence intervals for hazard ratios of heart attack and stroke risk among men taking baby aspirin. Other topics might include selection and publication bias in clinical trials, power analysis of trial designs, sensitivity analysis and quantification of errors, ensemble forecasting, and the like.

Cancer data to use for statistical studies can be found on the Internet, for example, on web sites maintained by the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) [95], American Cancer Society [3], and the Centers for Disease Control and Prevention (CDC) [18].

3.4. Dynamical Models of General Tumor Growth. The ordinary differential equations emphasis in this course naturally starts with a discussion of growth models that can be applied to tumor cell proliferation. To build students' foundations in mathematical oncology modeling, we introduce historically-relevant models that have been used to analyze tumors' uncontrolled cell proliferation. While students learn about how the model equations are derived, it is useful to review important basic

concepts like separation of variables, direction fields, equilibrium points and their stability, the effect of initial conditions and parameters on the solution, and topics related to systems of ordinary differential equations such as phase portraits and eigenvalues and eigenvectors that are best illustrated with simple models. We suggest that this is done for each of the models we list below so that students see what is qualitatively and quantitatively different among the equations and what that could mean for tumor growth in the long run.

The clonal expansion of a mutant cell line, wherein one cell divides into two daughter cells, leads to the difference equation $x_{n+1} = \alpha x_n$ with initial condition x_0 and growth rate parameter α and to the continuous *exponential growth equation*,

$$\frac{dx}{dt} = \alpha x, \tag{4}$$

with initial condition $x(t_0) = x_0$. The dependence of the doubling time on α can be derived and analyzed.

Of course, resource and space limitations imply that no cell population can grow without bound. The *logistic equation*

$$\frac{dx}{dt} = \alpha x \left(1 - \frac{x}{K}\right) \tag{5}$$

introduces the notion of a *carrying capacity* K, as does the *regrowth model*,

$$\frac{dx}{dt} = \alpha \left(1 - \frac{x}{K}\right). \tag{6}$$

Both of these models are specific cases of cell growth rates given by the more general principle

$$\frac{dx}{dt} = \text{growth rate} - \text{death rate}. \tag{7}$$

The *von Bertalanffy growth model* [107] is derived from the observation that the pulse rate and metabolic rate (M) in mammals are often proportional to the animal's surface area (SA) rather than to the volume V of the body. Since $SA \propto V^{2/3}$, $M \propto V^{2/3}$. More generally, one may assume that $M \propto V^{\lambda}$ for some $\lambda \in [\frac{2}{3}, 1]$, which leads to the growth model

$$\frac{dx}{dt} = \alpha x^{\lambda} - \beta x^{\mu}, \tag{8}$$

where α and β are proportionality constants and the other parameters λ and μ are positive. The case where $\lambda = \mu = 1$ reduces to the exponential equation (4) and the case where $\lambda = 1$, $\mu = 2$ reduces to the logistic equation (5). The case where $\lambda = \frac{2}{3}$, $\mu = 1$ is called the *surface area model* [101].

The *Gompertz growth model* [42] arose from an actuarial accounting of the number of people alive as a function of their age. This model assumes that the population $x(t)$ grows according to an exponentially decaying birth rate $g(t)$,

$$\frac{dx}{dt} = g(t)x(t), \tag{9a}$$

$$\frac{dg}{dt} = -\alpha g(t). \tag{9b}$$

Let $g(0) = g_0$ be the initial population's net fecundity. Substituting the solution of (9b) into (9a) yields the relation

$$\ln x(t) = \ln x_0 + \frac{g_0 - g(t)}{\alpha},$$

where $x(0) = x_0$ is the initial population size. Since $g(t) \to 0$ as $t \to \infty$, it follows that $\ln x(t) \to \ln x_0 + g_0/\alpha$ as $t \to \infty$. If $\lim_{t\to\infty} x(t)$ is interpreted as the carrying capacity K, then $x(t) \to K$ as $t \to \infty$. Thus, $g_0 = \alpha \ln (K/x_0)$, which implies that $g(t) = \alpha \ln (K/x(t))$, so (9a) becomes the Gompertz growth model,

$$\frac{dx}{dt} = \alpha x \ln\left(\frac{K}{x}\right). \tag{10}$$

Other derivations of (10) are possible [61, 101]. An important early attempt to validate the Gompertz equation qualitatively with laboratory data can be discussed as an introduction to calibration, inference, and prediction in the context of deriving, testing, and applying mathematical models of tumor cell proliferation [62, 63].

A discussion involving which model equations appear more physically relevant on qualitative and quantitative levels can be held after analyzing the ordinary differential equations. Numerical simulations of these different growth functions can be explored in a computer lab such as those described in the supplementary materials for quantitative comparison of solutions. Further investigation of these models is most appropriate when considering specific cancers (instead of general tumor cell proliferation models like in this section), which is done for the remainder of the course.

3.5. Mathematical Models of Chemotherapy and Surgery. After general tumor growth models are introduced, we then move into a discussion of how the effects of treatment can be described by a deterministic model. Surgery, chemotherapy, radiotherapy, and immunotherapy are examples of common treatments that can be included in mathematical models. One specific example is the ovarian cancer model of Kohandel, Sivaloganathan, and Oza [58].

The American Cancer Society [5] estimates that there will be 22,530 new cases of ovarian cancer and 13,980 deaths in the United States in 2019. Most of these cases occur in women past menopause, and the most common type is ovarian epithelial cancer, accounting for approximately 95% of the cases. Currently, chemotherapy and surgery (laparotomy) comprise the two main treatments for Stage IIIC/IV ovarian cancer, in which the tumor is larger than 2 cm in diameter and has metastasized beyond the abdomen. A key question is: *Does the order of treatments matter?*

A recently concluded, large multicenter randomized clinical trial sought to study the differences in survival between surgery prior to chemotherapy versus chemotherapy prior to surgery [106]. While in clinical settings, the usual therapeutic strategy is to perform surgery before chemotherapy, it was found that the reverse sequence is not inferior. What can mathematical models tell us about the difference in the order of treatments?

Consider the generic model of tumor growth (7), where $x(t)$ is the tumor cell population at time t. The growth rate prior to treatment can be modeled by any of the right-hand sides of (4), (5), (8), or (10), denoted by function $f(x)$.

The death rate, denoted $P(t, x)$, describes the pharmacokinetic and pharmacodynamic effects of chemotherapy on the cancer. Various cell-kill hypotheses have been studied and are useful for students to compare and test for model validity, such as the

log-kill hypothesis [91], in which chemotherapy kills cancer cells at a rate proportional to their population,

$$P(t,x) = cx, \tag{11}$$

the *Norton–Simon* hypothesis [80, 81], in which chemotherapy kills cancer cells at a rate proportional to their growth rate,

$$P(t,x) = cf(x), \tag{12}$$

and the $E_{\max}$ model [49], in which chemotherapy kills cancer cells at a saturable rate,

$$P(t,x) = \frac{cx}{x+\delta}. \tag{13}$$

Treatment produces a *response* when the death rate is strictly larger than the growth rate.

To include the effects of surgery in the model, we observe that surgery affects the number of tumor cells, and thus the initial condition of the differential equation. Kohandel, Sivaloganathan, and Oza [58] explore mathematical models of the two different treatment orders, termed adjuvant chemotherapy and neoadjuvant chemotherapy.

Adjuvant chemotherapy refers to the case where chemotherapy is given following the primary therapy (here, surgery, performed instantaneously at $t = t_s$). Suppose the tumor initiates at $t = 0$ and grows untreated until surgery. Then

$$\frac{dx}{dt} = f(x), \qquad t \in [\,0, t_s], \tag{14a}$$

$$x(0) = X_0, \tag{14b}$$

where f is the growth model. Assume that surgery removes all but e^{-k} of the tumor at $t = t_s$; then the tumor population $x_c(t)$ after surgery under chemotherapy until final time t_f is modeled by

$$\frac{dx_c}{dt} = f(x_c) - P(t,x_c), \qquad t \in [t_s, t_f], \tag{15a}$$

$$x_c(t_s) = e^{-k}\left(\lim_{t\to t_s^-} x(t)\right). \tag{15b}$$

The final tumor size following treatment is

$$x_{SC} = x_c(t_f). \tag{16}$$

Neoadjuvant chemotherapy refers to the case where chemotherapy is the initial treatment, beginning at $t = t_c$ (surgery follows at $t = t_s$). Again supposing that the tumor initiates at $t = 0$ and grows untreated until chemotherapy begins, we have

$$\frac{dx}{dt} = f(x), \qquad t \in [\,0, t_c], \tag{17a}$$

$$x(0) = X_0, \tag{17b}$$

and the treatment model becomes

$$\frac{dx_c}{dt} = f(x_c) - P(t,x_c), \qquad t \in [t_c, t_s], \tag{18a}$$

$$x_c(t_c) = x(t_c). \tag{18b}$$

Surgery occurs at $t = t_s$ and again removes a fraction e^{-k} of the remaining tumor, which yields a final tumor population of size

$$x_{CS} = e^{-k}\left(\lim_{t\to t_s^-} x_c(t)\right). \tag{19}$$

Which sequence of treatments yields the smallest tumor (or whether there is any difference) depends on the untreated tumor growth model $f(x)$ and the chemotherapy model $P(t, x_c)$. Analytical results can be obtained in some cases, and numerical methods must be employed in others depending on which cell-kill hypothesis is studied. This example lets students test the results of various assumptions about the growth and treatment models (which includes the option of having students create their own possible models) to determine which ones might be physically relevant and to perform some parameter sensitivity experiments as outlined in the homework and computer labs in the supplementary material.

3.6. Mathematical Models of Prostate Cancer Treatment. Prostate cancer is one of the most common tumors in men. (The American Cancer Society estimates a 1 in 9 lifetime risk, with 174,650 new cases of prostate cancer in 2019 and 31,620 deaths [5].) During the 1930s and 1940s, surgeon Charles Huggins showed that castration (orchiectomy) in men with locally metastatic prostate cancer usually causes dramatic regression of the disease. His results proved that most prostate tumors are hormone dependent (as are normal prostate cells [37]) and provided some of the first evidence that certain cancers were potentially controllable by chemical means. Similar results were eventually shown for most breast cancers [50]. Huggins shared the Nobel Prize in Medicine in 1966 for this discovery [4].

Castration remains the standard of care for locally advanced prostate cancer, although nowadays the treatment is usually pharmacological rather than surgical [94]. So-called androgen deprivation therapy (ADT) is typically highly effective, but it can cause serious side effects, including bone loss, diabetes, and heart and kidney problems [94]. Moreover, the tumor almost always evolves resistance to ADT, and there is no consensus regarding the choice and efficacy of subsequent treatment options [23].

ADT is typically given continuously until resistance occurs. Some clinical trials are investigating the use of intermittent therapy, whereby patients receive ADT until serum levels of a tumor marker (typically prostate-specific antigen, or PSA) drop below a predetermined level, at which point ADT is discontinued until the patient's PSA levels rebound. The cycle continues until the tumor demonstrates resistance (e.g., PSA levels fail to drop sufficiently after a certain time interval). The hope is that intermittent ADT will reduce side effects and delay resistance [51, 1].

There are several challenges in devising mathematical models of ADT. One wishes to capture the initial rapid regression of the cancer in response to ADT as well as capture the evolution of resistance. Ideally, one would like to find a model that can quantify a typical patient's treatment response, and, in the case of intermittent ADT, predict whether another cycle is likely to be effective for a given patient.

One model of the initial response of prostate cancers to ADT borrows from an ecological model of population growth under resource constraints, popularized by Droop [28]. In this view, there is a minimum *cell quota*, $q_{\min}$, of some essential nutrient Q below which the population $x(t)$ begins to shrink:

$$\frac{dx}{dt} = \mu\left(1 - \frac{q_{\min}}{Q}\right)x. \tag{20}$$

Here $q_{\min}$ may be regarded as a physiological constant, and μ is a (positive) net proliferation rate. If $Q > q_{\min}$, then the term in parentheses is positive and x increases, but if $Q < q_{\min}$, then x decreases, possibly rapidly. Here we regard x as the population of prostate cancer cells and Q as the cells' internal supply of androgen (or associated metabolite).

A very simplified model of ADT can be constructed by supposing that Q is a time-varying function that depends on the present serum level of androgen, $A(t)$, which can be measured clinically (and is manipulated pharmacologically during treatment). We suppose that the tumor cells' internal androgen supply grows according to the present serum androgen level and is consumed by the cellular metabolism at a net rate given by

$$\frac{dQ}{dt} = c_1 \left(\frac{A}{A + \nu} \right) - c_2 Q. \tag{21}$$

The constants c_1, c_2, and ν are chosen so that, at pretreatment levels of serum androgen $A(t)$, the right-hand side of (21) is approximately zero; initially, $Q(t_0)$ and μ are chosen to yield net growth of tumor that is positive but clinically realistic. When ADT reduces A to a fraction of its pretreatment level, dQ/dt becomes negative, $Q(t)$ eventually drops below $q_{\min}$, and the tumor responds accordingly. Treatment resistance might be modeled by supposing that ν is not constant but gradually declines, perhaps at the rate $\nu' = -\beta\nu$ for some positive constant β, which eventually renders $Q(t)$ independent of A.

A more sophisticated model by Portz, Nagy, and Kuang [83] postulates the existence of two tumor phenotypes, treatment-sensitive and treatment-resistant, that depend on internal cell quotas of androgen in a Droop-like manner and that can also mutate from one phenotype to the other depending on treatment pressure. The model, which consists of five ordinary differential equations, also estimates the tumor's production of PSA. It is possible to estimate parameters for this model that yield time series of PSA that are roughly consistent with those observed from individual patient cases in a clinical trial [1]. This model is described in more detail in the supplementary materials and in [83]. One of the most challenging computer labs in the course asks students to program the Portz–Nagy–Kuang model (with suitable constants) in MATLAB and to drive it using clinically observed levels of serum androgen, $A(t)$, in individual patients to reproduce some of the results in [83].

3.7. Mathematical Models of Glioblastoma Multiforme. The final case study in our course involves glioblastoma multiforme (GBM), which is the most common primary brain tumor in adults and, unfortunately, has a poor prognosis [78]. The location of the tumor can affect patients' neurological symptoms. Insofar as these tumors are highly diffusive as well as proliferative, a partial differential equation model is necessary. We include a brief introduction to the diffusion equation as the last mathematical topic in the course.

Typical models of GBM growth express the rate of population growth as the sum of a diffusive term and a proliferation term, which leads to a reaction-diffusion model of the form

$$\frac{\partial u}{\partial t} = \nabla \cdot (D \nabla u) + g(u). \tag{22}$$

In the simplest formulation, D is a constant and $g(u)$ is an exponential or logistic growth term [96, 97]. Normally, (22) is simulated in three dimensions on an anatomically accurate brain domain, but such a numerical implementation is too difficult

for a course of this nature. Instead, we study (22) along an interval, which might be regarded as a model of diffusive migration of glioblastoma cells along a bundle of nerve fibers.

The usual diffusion equation (with $g(u) = 0$) permits a discussion of the classical methods of separation of variables for various initial and boundary conditions. GBM rarely metastasizes beyond the central nervous system [45] or penetrates the skull, so no-flux boundary conditions are appropriate for (22). Students simulate (22) numerically in the one-dimensional formulation using finite differences as a system of ordinary differential equations (the method of lines) in two computer labs focusing on different growth terms and boundary conditions. It is possible to include a discussion of medical imaging, such magnetic resonance imaging (MRI), which is used clinically to determine the extent of GBM tumor growth, and its implementation using, for instance, the book by Epstein [35] as an auxiliary resource.

Reaction-diffusion equations also have applications in models of avascular tumor growth and tumor angiogenesis [6, 17, 66, 87]. Discussion of partial differential equations models could lead to students' interest in advanced techniques and analysis as well as numerical methods.

4. Final Projects and Assessments. As mentioned above, one of our objectives is to incorporate elements of an undergraduate research experience into the course. For this reason, in lieu of a traditional final examination, we require the students to present a 15-minute talk and write a final report on a preselected research paper. A digital or paper poster may be prepared in addition to or instead of the oral presentation. Typically, the paper is one that involves derivation, simulation, and analysis of an ordinary differential equation model of a tumor or related disease process. Table 4.1 lists some recent papers that we have found to be suitable for this purpose. Alternatively, students may select another paper with approval from the instructors; we strongly prefer papers that allow students to pursue some type of simulation or statistical analysis of data. We have emphasized ordinary differential equation models for simplicity and in view of the students' prior mathematical preparation. The following are some specific activities that we suggest students might do in their projects:

- Read the paper fully and be able to give an oral synopsis of the main results.
- Replicate the steps of deriving the mathematical model.
  - Explain the biological and mathematical evidence for the model.
  - Find analytic solutions of the ordinary differential equation model.
  - Determine equilibrium points and their stability.
- Reproduce the main numerical simulations by coding up the model.
  - Reproduce figures showing the results of numerical simulations.

The objective of the project is for students to reproduce some of the main results of the selected paper. We encourage (but do not require) students to work in teams of two. Often, one of the students is better at programming and the other is more confident in front of a classroom audience (as may be the case for students who are not native speakers of English). To assist students in their preparation, we include a lecture on how to give an effective talk, including poise, dress, voice modulation, slide format, and hand gestures. (There are many related resources on the Internet, and Higham's text [48], which also discusses technical writing, and Alley's text [2] are useful supplements.) We also require the students to rehearse their talk at least twice with other members of the class.

Students are required to select a paper at least one month before the end of the semester. Toward the end of the term, we set aside one week of class time solely for

Table 4.1 *List of research journal articles that can serve as topics for undergraduate writing/ research-based projects organized by type of cancer. Mathematical models in the papers are ordinary differential equation models.*

Type of Cancer	**Papers**
General Growth	Benzekry et al. [11] Gentry and Jackson [40] Ku-Carrillo, Delgadillo, and Chen-Charpentier [60] Laird [62, 63] Sarapata and de Pillis [89] Talkington and Durrett [99]
General Treatment	de Pillis, Gu, and Radunskaya [26] Feizabadi and Witten [36] Jain and Jackson [53] Kozusko et al. [59] López, Seoane, and Sanjuán [64] Murphy, Jaafari, and Dobrovolny [74] Nagy [75] Sachs, Hlatky, and Hahnfeldt [88] Talkington, Dantoin, and Durrett [98] Wilson and Levy [108]
Bladder	Bunimovich-Mendrazitskya et al. [15, 16]
Brain	Sturrock et al. [93]
Breast	Eladdadi and Isaacson [32, 33] Enderling et al. [34] Miller et al. [70] Mufudza, Sorofa, and Chiyaka [73] Roe-Dale, Isaacson, and Kupferschmid [85]
Cervical	Brown and White [14]
Colorectal	Bjerknes [12] de Pillis, Savage, and Radunskaya [27] Johnston et al. [54]
Leukemia/Lymphoma	Clapp et al. [19] Marciniak-Czochra et al. [68] Michor et al. [69] Moore and Li [71] Nanda, de Pillis, and Radunskaya [76] Paquin et al. [82] Roesch, Hasenclever, and Scholz [86] Stiehl, Lutz, and Marciniah-Czochra [92]
Lung	Kang et al. [55] Rhodes and Hillen [84]
Melanoma	Kogan, Agur, and Elishmereni [57]
Pancreatic	Louzoun et al. [65]
Prostate	Baez and Kuang [9] Gallaher et al. [38] Hedican, Kemper, and Lanie [47] Jain and Friedman [52] Tosoian et al. [105]
Renal	dePillis et al. [25]

open office hours, in which the students can work on talks and simulations with input from an instructor. Sometimes, a paper contains a minor error or is not specific about the precise values of model parameters used to generate a figure; in such cases, we suggest workarounds (and sometimes have emailed the authors for clarification).

In the final report, students are asked to include some sample simulations (MATLAB code can be included as an appendix) and to explain in their own words how the model is derived, the main assumptions involved, and the interpretation of the principal numerical results. Usually this can be done in 8–12 pages, and we provide guidance on providing citations and avoiding plagiarism. Beier, Gevertz, and Howard [10] describe approaches to preparing students for a research/writing experience, examples of specific questions that students can address when working on projects with mathematical models of cancer, and some ideas for assessment.

5. Discussion. In this paper we present material that can be used to develop an undergraduate course in mathematical modeling of cancer growth and treatment. In particular, general growth models such as exponential, logistic, von Bertalanffy, and Gompertz growth are introduced as well as models of ovarian cancer, prostate cancer, and glioblastoma multiforme. Probability and statistics topics are also covered. Following the content on cancers, resources for effective reading and communication of research are given as well as a list of research journal articles suitable for student projects. In the supplementary materials, a sample syllabus, homework assignments, and computer labs are provided. This toolkit will be beneficial to those instructors interested in developing or supplementing a mathematical modeling course.

Student response to the course has been mostly positive; preliminary feedback from students indicates that the course material was found to be very interesting and engaging. The Mathematics + Cancer course has been taught three times, in Fall 2013, 2015, and 2017. Evaluations were lowest the first time the course was taught, as there was a learning process for the instructors as well as the students regarding the topics and mathematical level. Among the positive comments in students' anonymous course evaluations include the novelty of the topics, relevance of mathematics to the "real world," and the opportunity to give a talk on a paper of interest. Not all students liked the MATLAB exercises, and one (who was not a native English speaker) expressed frustration about some of the medical and biological terminology.

No student has ever complained that the pace of the course was too slow! Our advice to instructors who would like to offer a course of this nature is to start slowly: a review of the basic concepts of exponential growth and decay, half-life and doubling times, etc., is welcome. It is wise to define biological terms more than once; concepts such as phenotype, signaling, "wild type," chromosome, receptor, fitness, mutation, etc., can be explained and their implications developed over the course of several lectures. We provide further information and data on student evaluations of the course in the supplementary materials.

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