Motivating Calculus with Biology

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NAME OF INSTITUTE: UNIVERSITY OF CALIFORNIA, DAVIS	
Size	32,000
Institution Type	Large comprehensive land grant university, offering bachelors through doctoral degrees, with four professional schools
Student Demography	Students majoring in the life sciences
Departmental Structure	Life sciences courses are taught in sixteen departments in two undergraduate colleges, with mathematics, statistics, and computer science in separate departments in two undergraduate colleges

Abstract

Applications of calculus concepts to real, data-driven biology problems provide students with a glimpse of the "unreasonable effectiveness" of mathematics in providing fundamental insights into biological processes. These applications can motivate key calculus concepts when chosen appropriately, provide a vehicle that links concepts throughout a calculus course. To illustrate this thematic development, I show how biological scaling laws and models of population growth link topics in precalculus fundamentals, derivatives, optimization, integration, probability, and differential equations.

Course Structure

- Weeks per term: 10-week quarter
- Classes per week/type/length: three 50-minute lecture class meetings per week
- Labs per week/length (if any): one 50-minute lab each week
- Average class size: 250 students
- Enrollment requirements: Entering students
- Faculty/dept per class, TAs: One mathematics faculty and 4 TAs.
- Next Course: N/A

Introduction

As Leo Breiman said, calculus has a right hand and a left hand.[2] On the right hand is the rigorous foundation of limits and infinitesimals. The left hand thinks physically in terms of rates of change and accumulated change. In the historical development of calculus, the left hand came first, driven by applications to planetary motions, classical mechanics, and optics. Only hundreds of year later did the rigor of the right hand enter and put calculus on a firm mathematical foundation. Given that calculus is the entry level mathematics course for most undergraduate programs, we as instructors are faced with the challenge of balancing the amount of time students spend with each hand. The right hand involves precise definitions and the derivation of properties of and relations between them. It exposes students to the elegance, power, and subtlety of mathematical rigor. The left hand involves developing and analyzing models to answer real world questions. It exposes students to the effectiveness of mathematics in describing the natural world. The right balance depends on the goals of the program. Hence, rather than presenting my personal view of the right balance of rigor and applications, I will illustrate how arming the left hand with biological applications can motivate and link a diversity of calculus concepts.

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[2] With apologies to Leo Breiman.

Why use biological applications? My answer comes in three parts. First, from a scientific perspective it is quite likely, in the words of Joel Cohen, that "Mathematics is biology's next microscope, only better; biology is mathematics' next physics, only better" (Cohen 2004). Mathematics can help extract patterns from large biological data sets and provide a theoretical framework for developing hypotheses for mechanisms underlying biological processes. Alternatively, the complexity of living things and how they interact is motivating the development of new mathematics. Calculus can provide students with their first exposure to the developing synergy between the two disciplines. Second, there are more students majoring in biology than physics (e.g., 64,611 biology bachelor's degrees conferred in 2004-05 versus 18,905 in physics). Thus, including some biological examples into calculus is likely to interest (and hopefully excite!) a larger number of students. Finally, there exists a rich collection of biological applications of calculus. Many of them require a minimal biological background, are supported by data sets, and can create biological themes that can be sustained throughout the calculus curriculum.

To illustrate how biological applications can motivate and connect calculus concepts, I present two classes of applications, scaling laws and population growth. My discussion of them is far from exhaustive and should be viewed as presenting the tip of the iceberg. Pedagogical suggestions are kept at a minimum. When discussing the topics in my classes, I have students (through an instructor-student dialog) identify the main questions, determine an appropriate set of assumptions, develop and analyze a model, and evaluate the model (e.g., comparing to a data set, interpreting the results from a biological perspective, etc.). After presenting the two applications, I provide a description of a topic from evolutionary biology—the growth-reproduction tradeoff—that could serve as a group project. The project combines ideas from scaling laws and population growth and can provide an opportunity for students to learn about collaboration, to delve deeper into an application, and to synthesize a diversity of calculus topics.

Scaling Laws

Scaling laws are a fundamental modeling concept in all the sciences. They describe how one quantity y (e.g,. respiration rate, strength, etc.) scales with respect to another quantity x (e.g,. body size). Scaling laws typically involve power functions $y \propto x^b$, a class of elementary functions that appear in most calculus courses. Although calculus students have seen them in pre-calculus, it is unlikely that they were exposed to modeling with them. Hence, revisiting these functions and their properties in modeling keeps students slightly off balance (i.e., they don't assume right away that this stuff is easy) and maintains their interest. I will illustrate how to motivate scaling laws in biology and how they can make repeated appearances throughout a calculus course.

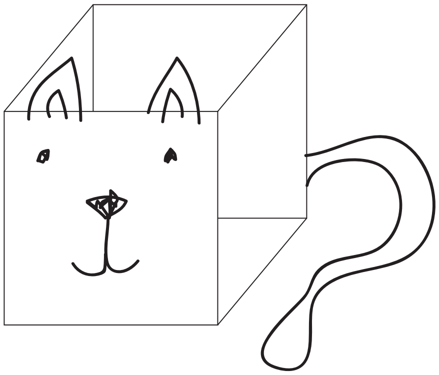

Figure 1: A Cubical Critter

J. B. S. Haldane's 1926 article, *On being the right size* (Haldane 1926), provides many wonderful examples of scaling laws in biology. For example, when discussing the challenges faced by large and small organisms, Haldane writes

> To the mouse and any smaller animal it [gravity] presents practically no dangers. You can drop a mouse down a thousand-yard mine shaft; and, on arriving at the bottom, it gets a slight shock

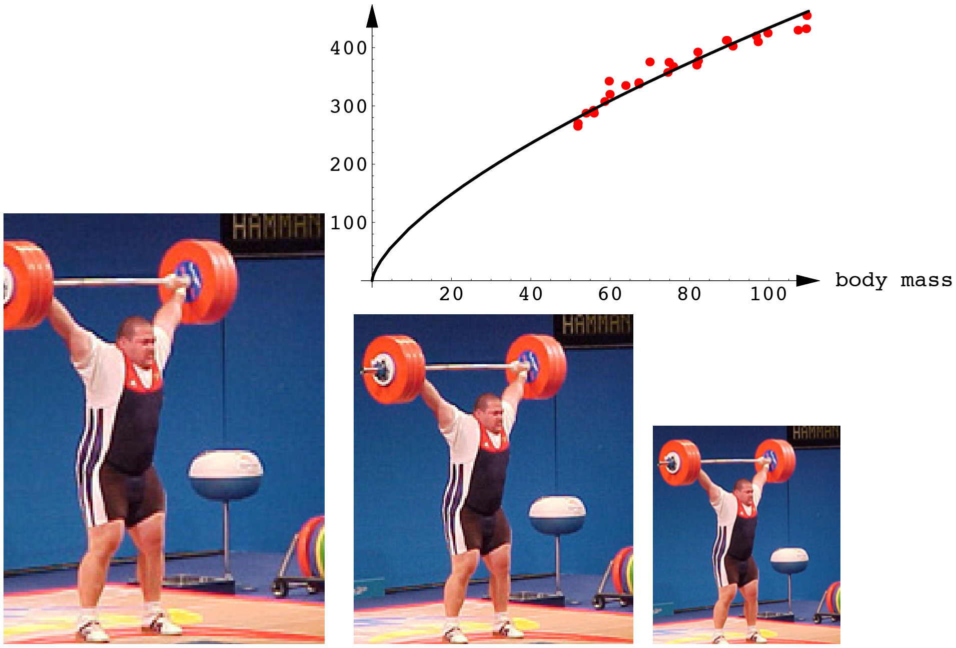

Figure 2: Geometrically similar weight lifters. The inset is a graph showing lifts of Olympic gold medalists as a function of their body mass. The fitted curve is $y = 20.15x^{2/3}$

> and walks away, provided that the ground is fairly soft. A rat is killed, a man is broken, a horse splashes. For the resistance presented to movement by the air is proportional to the surface of the moving object. Divide an animal's length, breadth, and height each by ten; its weight is reduced to a thousandth, but its surface only to a hundredth. So the resistance to falling in the case of the small animal is relatively ten times greater than the driving force.
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> An insect, therefore, is not afraid of gravity; it can fall without danger, and can cling to the ceiling with remarkably little trouble. It can go in for elegant and fantastic forms of support like that of the daddy-longlegs. But there is a force which is as formidable to an insect as gravitation to a mammal. This is surface tension. A man coming out of a bath carries with him a film of water of about one-fiftieth of an inch in thickness. This weighs roughly a pound. A wet mouse has to carry about its own weight of water. A wet fly has to lift many times its own weight and, as everyone knows, a fly once wetted by water or any other liquid is in a very serious position indeed. An insect going for a drink is in as great danger as a man leaning out over a precipice in search of food. If it once falls into the grip of the surface tension of the water—that is to say, gets wet—it is likely to remain so until it drowns. A few insects, such as water-beetles, contrive to be unwettable; the majority keep well away from their drink by means of a long proboscis.

To interpret these comments mathematically, we can begin by viewing all organisms as cubical critters characterized solely be their size differences (Figure 1). If L is the length of one side of the cubical critter, then it has a surface area of $6\,L^2$ cm^2,and a volume of L^3m^3. If we assume that the cubical critters are "ugly bags of mostly water,"[3] then a critter of length L weighs $m = L^3$ grams. Hence, surface area is proportional to $m^{2/3}$ and the ratio of mass to surface area is proportional to $m^{1/3}$. Hence, the larger you are, the harder you fall. Conversely, the ratio of surface area to mass is $m^{-1/3}$. Therefore, the smaller you are, the more water weight you carry per unit biomass when you get wet.

There are many data sets that can be modeled by scaling laws. One of my favorites is the mass lifted by an Olympic weightlifter versus his body mass (Figure 2). Assuming that Olympic weightlifters are geometrically

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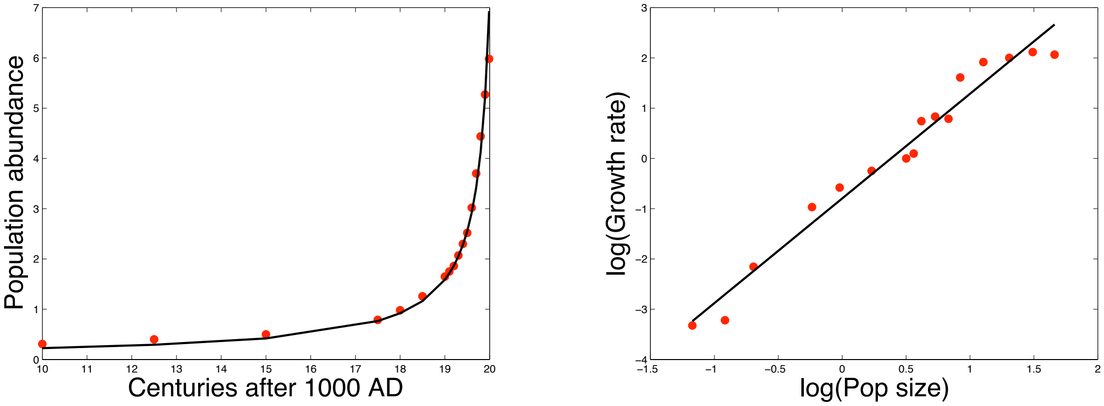
[3] Star Trek fans may remember this line as an alien's description of humans as mostly water encased in a bag of skin. The "ugly" part is a matter of extraterrestrial taste.



(a) (b)

Figure 3: World population growth from 1000 A.D. to 1999 A.D. Data are plotted in small circles and the solid curve is the model fit is the solid curve. In (b), growth rates are estimated by difference quotients and the best fitting line of a log-log scale is plotted.

similar and that strength is proportional to cross sectional area of the arm muscles,[4] we predicts that the mass lifted, call it y, should be proportional to $x^{2/3}$, where x is the body mass. To test the prediction, we can use linear regression on the log transformed data ($\ln y = \ln a + b \ln x$) to find the best proportionality constant a and exponent b. Linear regression yields an exponent close to $2/3$ and generates a reasonable fit to the data. Using this relationship, one can also try to choose the best weightlifter by giving each weightlifter a weight-adjusted score of lift divided by $x^{2/3}$. The one with the highest score should be the gold winner. Interestingly, for two of the Olympics represented in the data set, Naim Suleymanoglu was the gold winner. Suleymanoglu was the first Olympic weightlifter to win three gold medals. The World Sports Writers' Union has identified him as one of the Top 25 Athletes of the 20th Century; we can add mathematical support to their opinion with our use of scaling laws to compare weightlifters of different sizes.

We can revisit scaling laws when computing derivatives. For instance, what is $\frac{d}{dx}\Big|_{x=100} 20.15x^{2/3}$ and what does it mean? A calculation for Olympic weight lifters reveals that this derivative is approximately 2.9 kg per kg. Hence, a 1 kilogram increase in the mass of a 100 kg Olympic weight lifter results in an approximately 2.9kg increase in the mass he can lift. Even better, we can introduce the notion of elasticity: the relative change in y due to a relative change in x. More precisely, the *elasticity* of $y = f(x)$ at $x = a$ is $f'(a)\frac{a}{f(a)}$. For scaling laws, $f(x) = ax^b$, the elasticity is simply b. Hence, for the Olympic weightlifters, a 10% increase in weight results in approximately a 6.7% increase in the mass lifted.

We can also introduce optimization problems involving scaling laws, but before doing that, lets consider two examples of scaling laws in differential equations. The first example involves the *Science* paper, "Doomsday: Friday, 13 November A.D. 2026," published in 1960 by three electrical engineers at the University of Illinois (Foerster et al. 1960). World population growth data from 1000 A.D. to 1960 A.D. suggests that if N is the population size, then the population growth rate $\frac{dN}{dt}$ is proportional to N^{1+b} for some positive constant $b > 0$ and some proportionality constant $a > 0$. Letting t denote centuries after 0 A.D., plotting the log of the growth rate of world population (estimated by difference quotients) yields a roughly linear plot (Figure 3b). Using linear regression, we estimate $a \approx 0.4507$ and $b \approx 1.0827$. Solving the differential equation $\frac{dN}{dt} = a\,N^b$ yields a solution of the form $N(t) = (a\,b(T-t))^{-1/b}$ where T is the time at which, in the words of a Pogo cartoon, "everyone gets squeezed to death". Since we have estimates of a and b, we can use nonlinear least squares regression (a nice calculus exercise in of itself!) to find the value of T that gives the best fit to the data set (Figure 3a). The value turns out to be $T \approx 20.24$ for the U.N. estimates of

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[4] The assumption of geometric similarity is obviously violated for the heaviest weight class as they have no weight restriction and therefore have no reason to keep their body tight. For this reason, the fit to the 2/3rd law only seems to hold when you exclude this weight class from the data.

world population growth. Hence, one gets the updated Doomsday prediction of 2024. The reliability of the prediction and the limitations of the model makes for a good classroom discussion.

The von Bertalanffy equation, which describes the growth of an organism, is another example of a differential equation that uses scaling laws. To derive it, consider a cubical critter with length L. If we assume length is measured in centimeters and the critter is mostly made of water, then its mass M is L^3 grams. If it ingests food at a rate proportional to its surface area and respires at a rate proportional to its mass, then

$$\frac{dM}{dt} = aL^2 - bL^3$$

where a and b are positive proportionality constants. Since $M = L^3$, we obtain

$$\frac{dM}{dt} = 3L^2 \frac{dL}{dt}.$$

Combing the equations yields

$$\frac{dL}{dt} = k\left(L_\infty - L\right)$$

where $k = b/3$ and $L_\infty = a/b$. Thus, somewhat magically, the growth of an organism can be described by a linear differential equation. With it, the student can be given many fun examples and questions. For instance, the von Bertalanffy curve was used to examine growth patterns in body length and mass of female and male polar bears (*Ursus maritimus*) live-captured near Svalbard, Norway (Derocher and Wiig 2002). With information about the parameters and body sizes at different ages, we can discover various properties about the pronounced sexual dimorphism of body size. We can ask questions such as “At what length is the body mass increasing most rapidly?” (The answer is 2/3 of L_∞.) An extension of this problem is discussed in Section .

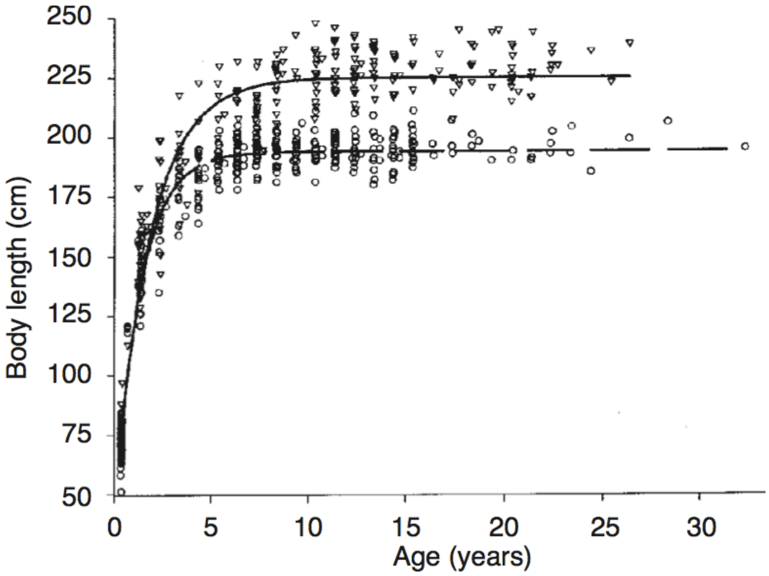

Figure 4: The von Bertalanffy curve fitted to age and body length
Data for female (○, dashed line) and male (▽, solid line) polar bears *Ursus maritimus* captured in the Svalbard area. (Derocher and Wiig 2002)

Population growth

Modeling the growth of populations has a long rich history in mathematical biology. The richness occurs because the populations may consist of drug particles, viral particles, cells, or multicellular organisms. Hence, models of population growth have applications to genetics, ecology, evolution, immunology, physiology, and epidemiology. The models can connect calculus topics (e.g., elementary functions, optimization, differential equations, and probability density functions) and can be tested using widely available data. To illustrate their utility, I will focus on tumor growth and the spread of diseases and rumors.

A tumor is an abnormal population of cells (i.e., tissue) created when the natural balance of cell division and death is disturbed. Slow growing harmless tumors are called benign, while harmful faster growing tumors are called malignant. The simplest model of tumor growth is one of exponential growth and decay: $V(t) = V(0)e^{at}$ where $V(t)$ is the volume of the tumor at time t and a is its per-capita growth rate. Although exponential growth can not continue unabated, there are many data sets supporting this simple model during the initial phase of tumor growth. For instance, Looney and colleagues (Looney et al. 1975) used exponential growth and decay to model untreated rat tumors and strongly radiated rat tumors. Using linear regression,[5] the per-capita growth rates for non-radiated and strongly radiated tumors can be estimated as illustrated in Figure 5a. With them, we can compute the doubling time for the untreated tumors (a little over a week) and the half-life for the strongly radiated tumors (approximately 12.5 days).

Malignant tumors can be treated with radiation therapy and chemotherapy. For both, rarely is a single treatment is sufficient. Typically, the first treatment reduces the tumor, but eventually it begins to regrow, as not all cancerous cells have been killed. Since chemotherapy and radioactive therapy have many harmful side effects, determining the timing between treatments and their intensity is important. Treatments have to be sufficiently intense to cause a reduction in the tumor size, but not so intense as to place the patient at great risk from side effects. After a treatment, ideally the next treatment should occur just before the tumor starts to regrow. Estimating the time until tumor regrowth is a great optimization problem. Consider, for example, an experimental study (Demidenko 2004) in which two groups of mice with tumors were treated with the chemotherapeutic drug cisplatin. Prior to the therapy, the tumor consisted of proliferating cells (also known as clonogenic cells) that grew exponentially with a doubling time of approximately 2.9 days. Each mouse was given a dosage of 10mg/kg of cisplatin. At the time of the therapy, the average tumor size was approximately 0.5 cm^3. After treatment, 99% of the proliferating cells became quiescent cells. Quiescent cells do not divide, and decay with a half life of approximately 5.7 days. With these assumptions, the tumor volume t days after therapy is given by

$$V(t) = 0.005e^{0.24t} + 0.495e^{-0.12t}.$$

Taking derivatives reveals that V decreases until $t \approx 10.84$ days and then begins to grow again. This prediction is close to what the data reveals (Figure 5b).

While exponential growth can provide a reasonable description of population growth when the population is not too large, it clearly can not be sustained indefinitely (e.g., a quick internet search and computation with the exponential model of the untreated mouse tumor shows that the tumor will be the size of the earth in approximately 670 days!). This can be illustrated in a classroom by simulating the spread of a rumor or disease amongst the students. Randomly choose a person in the classroom to infect with the rumor or disease. To see how the disease or rumor spreads, invoke an iterative procedure. At every iteration, ask everyone that is infected to randomly choose another individual in the classroom (e.g.,by using a random number generator). If the person chosen is not infected, the person becomes infected. Everyone that is infected remains infected. Record the fraction of infected. Iterate until everyone is infected. Doing this in a class of 29 gave the data shown in Figure 6a. While an exponential growth model does a reasonable job of describing the first four iterations, it grossly overestimates the number of infected in the long term (the dashed curve in Figure 6a). If $y(t)$ denotes the fraction of infected individuals by time t, then the exponential growth model $y(t) = y(0)e^{at}$ satisfies the differential equation

$$\frac{dy}{dt} = a\,y,$$

which explains why a is called the per-capita growth rate of the population; i.e., $a = \frac{dy}{dt}\frac{1}{y}$ whenever $y \neq 0$. The problem with this model is that as the infection spreads, the fraction of those uninfected decreases and, consequently, the per-capita growth rate of y must decrease as y increases. The simplest assumption is to

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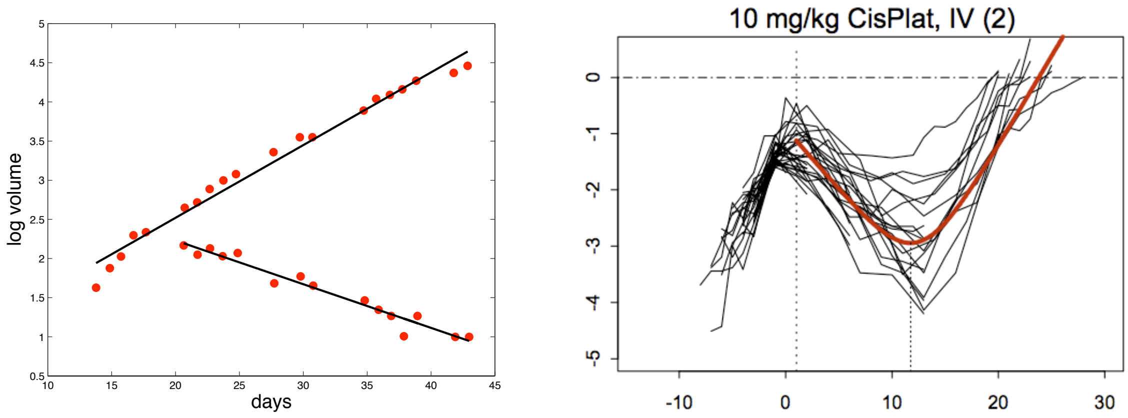
[5] Even if one does not have immediate access to the data, it is easy to digitize the image from the paper and extract the data using a variety of utilities that are available as free ware.



(a) (b)

Figure 5: Tumor growth in rats: (a) growth of untreated tumors and the decay of tumors treated with 3750R of radiation data (Looney et al. 1975) (Linear regression yields per-capita growth rate estimates of $a = 0.0929$ for a non-radiated tumor and $a = -0.0558$ for a tumor with a strong radiation treatment of 3750R); (b) tumor size for mice treated with cisplatin (Demidenko 2004).

assume that the per-capita growth rate is proportional to the fraction of uninfected individuals. If r denotes the proportionality constant, then we set at the logistic equation

$$\frac{dy}{dt} = r\, y(1-y) \qquad y(0) = 1/29.$$

For the classroom data, we can estimate r from the exponential growth phase of the data. Solving the differential equation using separation of variables and partial fractions yields

$$y(t) = \frac{e^{rt}}{28 + e^{rt}}$$

(see the solid curve in Figure 6a). Using this function, we can estimate when two-thirds of the population was infected. How accurate is the prediction? How does the answer depend on r?

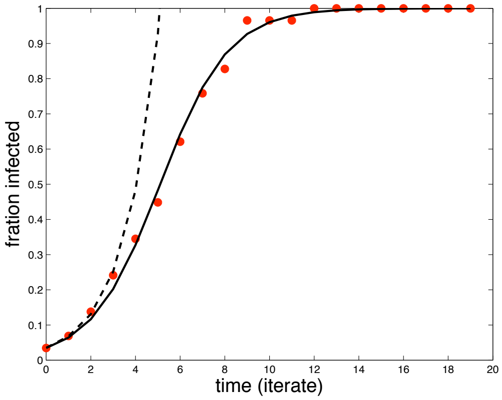


Figure 6: The spread of a rumor in a classroom of 29 individuals: actual data (circles), exponential growth model (dashed curve), and logistic growth model (solid curve).

Population growth curves can provide a nice introduction to cumulative distribution functions (CDFs), probability density functions (PDFs), and other statistical concepts. For instance, consider the exponential decay of a strongly radiated tumor. If $V(t) = V(0)e^{-at}$ is the volume of the tumor at day t, then the fraction of cells lost by day t is given by

$$F(t) = \begin{cases} 0 & \text{if } t \leq 0 \\ 1 - e^{-at} & \text{if } t > 0. \end{cases}$$

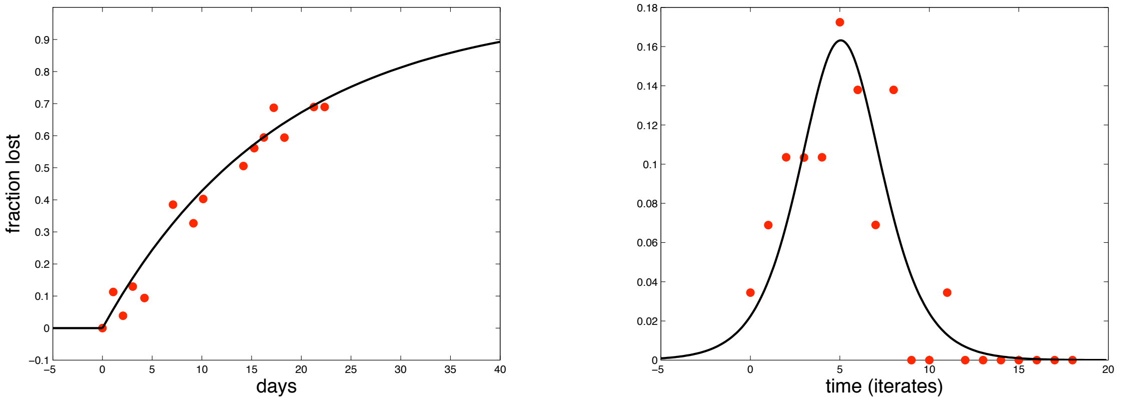
Differentiating yields the associated PDF

$$f(t) = \begin{cases} 0 & \text{if } t \leq 0 \\ a\,e^{-at} & \text{if } t > 0. \end{cases}$$

If $y(t)$ is the fraction of individuals infected with our classroom rumor by time t, then it is easy to verify that $y(t)$ is a CDF of the logistic distribution with PDF

$$y'(t) = ry(t)(1 - y(t)) = \frac{28\,r\,e^{rt}}{(28 + e^{r\,t})^2}.$$

Using the CDFs, we can answer a variety of questions. At what time is half of the classroom infected? What fraction of tumor is lost by the third day? Using PDFs and improper integrals, we can find the expected time for the loss of a particular tumor cell (i.e., $\frac{1}{a}$ days, which provides another interpretation for the parameter a) or the expected time for an individual in the classroom to become infected using the symmetry of the logistic distribution. Working with CDFs and PDFs provides an opportunity to review both parts of the fundamental theorem of calculus, as getting a CDF from a PDF involves integration and getting a PDF from a CDF involves differentiation.



(a) (b)

Figure 7: CDFs and PDFs for decay of tumors and spread of rumors: (a) the empirical CDF (circles) and the model (solid curve); (b) the empirical PDF (circles) and the model (solid curve). Source of data as in Figures 5 and 6, respectively

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Projects: Putting it all together!

Projects provide students with an opportunity to pull together and apply the calculus concepts they have learned and an opportunity to collaborate. Here I will illustrate one project, optimal investment into reproduction and growth, that pulls together several of the applications from this article.

All organisms have a finite amount of energy at their disposal and must divide it into three fundamental biological processes: growth, maintenance, and reproduction. Since natural selection tends to weed out organisms with lower fitness (e.g., total number of offspring produced per individual), we would expect natural selection to favor organisms that divide their energies to optimize the number of offspring produced. According to Gadgil and Bossert (1970)

> If fitness is being measured entirely in the currency of offspring, the advantage of devoting resources to maintenance and growth is only insofar as this enhances the reproduction at further stages in the life history. Maintenance is essential to enable an organism to survive to these stages. Growth may enhance both survival and reproductive ability. A continuous increase in fecundity with size is well known in fishes, where gonads comprise a fairly constant proportion of the body weight. A basic challenge confronting all organisms is at what point in their life should they invest into reproduction rather than growth. On the one hand, by growing to a larger size an individual may be able to collect more resources and, thereby, produce more progeny than if it remained smaller. On the other hand, by waiting too long to start producing young, an individual may die before producing any young. Using models, one can investigate how various factors such as per-capita mortality rates, size-specific respiration rates, and size-specific consumption rates influence the optimal time to start investing energy into reproduction.

To explore optimal reproductive schedules, consider an individual that experiences a constant risk of dying. In other words, the probability of an individual surviving to age t, call it $l(t)$, is exponentially distributed with a hazard rate of a, i.e., a mean life expectancy of $1/a$. Assume that during its growth phase (i.e., before the switch to its reproductive phase), the individual's growth is determined by the von Bertalanffy growth equation

$$\frac{dL}{dt} = k(L_\infty - L) \qquad L(0) = 0,$$

where $L(t)$ is the length of the organism at time t, L_∞ is its asymptotic size, and $k > 0$ is a proportionality constant determining the rate of growth.As discussed earlier, this equation accounts for maintenance costs with the $-k\,L$ term. Its solution is

$$L(t) = L_\infty \left(1 - e^{-k\,t}\right).$$

Suppose at age T, the organism invests of all its growth in reproduction. The rate of growth of mass at this age is

$$\begin{aligned} \left.\frac{d}{dt}\right|_{t=T} L(t)^3 &= 3L(T)^2 L'(T) \\ &= 3\left(L_\infty\left(1 - e^{-kT}\right)\right)^2 k L_\infty e^{-kT}. \end{aligned}$$

Hence, if we assume that its rate of production of progeny is proportional to its growth rate at age T, then its birth rate for $t \geq T$ is

$$b(T) = \alpha\left(1 - e^{-kT}\right)^2 e^{-kT},$$

where α is a proportionality constant. The total number of progeny expected to be produced by the individual is

$$\begin{aligned} R_0 &= \int_T^\infty (t - T) b(T) e^{-at} a\, dt \\ &= \beta e^{-(k+a)T}\left(1 - e^{-kT}\right)^2 \end{aligned}$$

for an appropriately defined constant $\beta > 0$. Solving for the time T that maximizes R_0 yields

$$T = \frac{1}{k}\ln\left(1 + \frac{2k}{k+a}\right).$$

This shows that higher hazard rates (i.e., larger values of a) lead to smaller optimal T values. Hence, organisms with shorter life expectancies should reproduce sooner rather than later. Taking the limit as $a \to 0$ results in $T = \frac{1}{k}\ln 3$. This corresponds to the time at which the organism reaches two-thirds of its limiting length and, consequently, corresponds to the time at which its mass grows most rapidly. Hence, according to this model, organisms should begin to invest in reproduction when they reach two-thirds of their limiting size. We can verify that T is decreasing with the growth rate parameter k. Thus, organisms that grow faster should reproduce sooner. To see that this simple model is just the tip of the iceberg, students should be encouraged to conduct a literature search to see what else has been done.

Discussion

Many of the perspectives and ideas in this article stem from almost two decades of teaching calculus and a decade-long collaboration with Wayne Getz and Karl Smith on writing a calculus text (Schreiber et al. 2012). This upcoming text, *Calculus for the Life Sciences* with John Wiley and Sons, is based on and elaborates on many of the ideas presented here. It highlights how biological phenomena naturally motivate and pull together all the key ingredients of differential and integral calculus. Texts like this and the diversity of pedagogical approaches described in this MAA volume can result in the next generation of biology students seeking out further connections between mathematics and the life sciences and will help the next generation of faculty to facilitate this process.

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