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tions provide models of the same general form. Although the different systems have important special features (e.g., the conservation laws), surely we would like to communicate the more general idea that dynamics are described by differential equations and encourage students to discover the applicability of this approach to the dynamics of more complex biological systems through well-designed laboratory exercises. In a similar spirit, statistical physics and kinetic theory provide probabilistic models of the world, but Mendelian genetics is also a probabilistic model and an understanding of probability is at the heart of all practical data analysis.

Today, not only can we integrate subjects that share common mathematical structures, we can also integrate these abstract structures with their practical implementation through computation. If the students are taught to program and to use simple algorithms and if they learn to use high-level languages (e.g., Matlab or Mathematica), they can visualize and verify for themselves the mathematical ideas and thereby become comfortable with those they find less intuitive or more abstract. In statistics, for example, it is possible to begin by applying simulation and bootstrap algorithms (e.g., for finding P values). By starting in this way, students will more easily come to appreciate parametric methods and closed-form solutions and learn to understand and to use them appropriately.

We believe that integrating mathematics, computation, and the scientific context for these ideas will allow students in an

introductory course practical access to conceptual tools that are much more sophisticated than those currently taught in the standard first-year mathematics courses. Although real mastery over these ideas will require continuing reinforcement throughout the undergraduate curriculum (as is currently done for physical science students), a unified introduction can empower the students to explore ideas far beyond what is currently accessible to them.

A final and, in the context of biology, possibly the most important synergy derives from the judicious use of nonstandard examples for basic principles and methods of physics and chemistry. For example, it makes sense, in modern times, to introduce students to the idea of molecular motion and thermodynamics in solution rather than focusing only on the world of ideal gases. With affordable modern instrumentation, students can observe and record Brownian motion in a microscope, for example, and satisfy themselves quantitatively how this motion derives from invisible molecules bouncing around in the solution and even how many such molecules there must be. This hands-on approach has the advantage that the phenomena (and of course the underlying principles) are directly and obviously relevant to research in biology. In a similar vein, much of basic combinatorics, probability theory, and statistics can be presented in tandem with basic genetics, resulting a substantial saving in overall time when compared with separate courses in different departments. Again, the concurrent use

of computation will provide students with tools that will serve them well in all of their scientific careers thereafter.

Our proposal for an integrated introductory education for quantitatively oriented biologists really is an experiment in a more general problem: science education in the modern world. This is a problem whose solution will require collaborations among scientists who now reside in quite different departments and cultures; enthusiastic as we are, we also are cognizant of the difficulties that will no doubt arise. On the other hand, the necessary collaborations among the faculty from several disciplines may well set a wonderful example for students.

To conclude, we believe there is a great opportunity to construct a unified, mathematically sophisticated introduction to physics and chemistry, which draws on examples from biology wherever possible. Such a course would provide a coherent introduction to quantitative thinking about the natural world, and invite all students, including biologists of the future, to partake of the grand tradition, which flows from Galileo's vision.

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VIEWPOINT

Uses and Abuses of Mathematics in Biology

Robert M. May

In the physical sciences, mathematical theory and experimental investigation have always marched together. Mathematics has been less intrusive in the life sciences, possibly because they have until recently been largely descriptive, lacking the invariance principles and fundamental natural constants of physics. Increasingly in recent decades, however, mathematics has become pervasive in biology, taking many different forms: statistics in experimental design; pattern seeking in bioinformatics; models in evolution, ecology, and epidemiology; and much else. I offer an opinionated overview of such uses—and abuses.

Darwin once wrote "I have deeply regretted that I did not proceed far enough at least to understand something of the great leading principles of mathematics; for men thus endowed seem to have an extra sense." With the benefit of hindsight, we can see how much an "extra sense" could indeed

have solved one of Darwin's major problems. In his day, it was thought that inheritance "blended" maternal and paternal characteristics. However, as pointed out to Darwin by the engineer Fleeming Jenkin and others, with blending inheritance it is virtually impossible to preserve the natural variation within populations that is both observed and essential to his theory of how evolution works. Mendel's observations on

the particulate nature of inheritance were contemporary with Darwin, and his published work accessible to Darwin. Fisher and others have suggested that Fleeming Jenkin's fundamental and intractable objections to *The Origin of Species* could have been resolved by Darwin or one of his colleagues, if only they had grasped the mathematical significance of Mendel's results (1). But half a century elapsed before Hardy and Weinberg (H-W) resolved the difficulties by proving that particulate inheritance preserved variation within populations (2).

Today, the H-W Law stands as a kind of Newton's First Law (bodies remain in their state of rest or uniform motion in a straight line, except insofar as acted upon by external forces) for evolution: Gene frequencies in a

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population do not alter from generation to generation in the absence of migration, selection, statistical fluctuation, mutation, etc. Subsequent advances in population genetics, led by Fisher, Haldane, and Wright, helped make the neo-Darwinian Revolution in the early 20th century. Current work on the one hand provides illuminating metaphors for exploring current evolutionary problems, particularly in molecular evolution, whilst on the other hand having important applications in plant and animal breeding programs (Fig. 1).

Before I embark on chauvinistic elaboration of other uses of mathematics in biology today, it is well to reflect on the varied encounters with mathematics that today's nascent biological researcher is likely to have as undergraduate and earlier. First encounters are usually with the simpler aspects of "pure mathematics" such as numbers, algebra, elementary trigonometry. Taught well, the emphasis is on clarity of thought, rigor, even elegance: "assume this, prove that." Taught badly, you get rote learning and mechanical tricks. No one taught well will ever forget the sheer wonder of $e^{i\pi} = -1$ (a magical result connecting two fundamental constants, e and π , and the ethereal square root of -1). But it can all seem rather abstract, or even off-putting (particularly if taught badly), and for some this will color attitudes to mathematics for the rest of their lives.

In the typical curriculum, applications come later, often in physics where the fundamentals are cast in mathematical terms (whence Einstein's reflection on the "unreasonable effectiveness of mathematics" in describing the natural world). Others will encounter applied mathematics in the form of probability theory and statistics—some through misspent youth playing bridge or poker, others more formally in the design of experiments to separate significant results from statistical fluctuations and other noise. Among the younger generation, many will have first met applied mathematics—often without realizing it—in computer games.

A paradigmatic account of the uses of mathematics in the natural sciences comes, in deliberately oversimplified fashion, from the classic sequence of Brahe, Kepler, Newton: observed facts, patterns that give coherence to the observations, fundamental laws that explain the patterns. These days, mathematics enters at every stage: in designing the experiment, in seeking the patterns, in reaching to understand underlying mechanisms. In biology, of course, every stage in this caricature is usually vastly more complex than in the early days of physics. But the advent of computers, and the extraordinary doubling of their capability roughly every 18 months for the past several decades, permits

exploration—and sometimes understanding—we could not have dreamed of 50 years ago.

Consider the role played by applications of mathematics in sequencing the human and other genomes. This adventure began with the recognition of the doubly helical structure of DNA and its implications, an oft-told tale in which classical mathematical physics played a central role. Brilliant biochemical advances, allowing the 3 billion-letter-long human sequence to be cut up into manageable fragments, were a crucial next step. The actual reassembling of the sequence fragments, to obtain a final human genome sequence, drew on both huge computational power and complex software, itself involving new mathematics. The sequence information, however, represents only

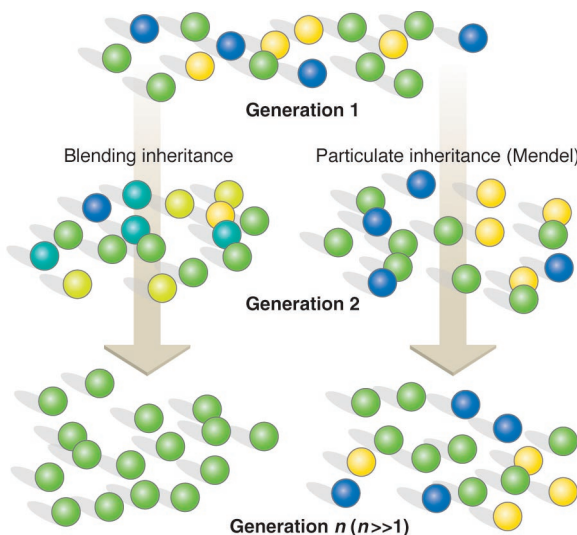


Fig. 1. Difference between the outcomes from blending and from particulate inheritance. In post-Mendelian terms, we assume a single diallelic locus, and hence three diploid genotypes (AA, blue; Aa, green; aa, yellow). Under particulate inheritance, the population's variability is preserved from generation to generation. In contrast, the conventional wisdom of Darwin's day saw offspring inherit a blend of parents' characteristics, here represented as the average of the two parental shadings. The result is that the variability diminishes in successive generations (the variance is halved each generation if mating is at random).

the Tycho Brahe stage. Current work on various genomes uses pattern-seeking programs to sort out coding sequences corresponding to individual genes from among the background that is thought to be noncoding. Again, elegant and sometimes novel mathematics is involved in this Keplerian stage of the "work in progress." We are only just beginning, if that, the Newtonian stage of addressing the deeper evolutionary questions posed by these patterns (not least, the surprising finding of how many genes we share with other species, and how numbers of genes appear to be uncorrelated with what we regard as complexity of the organism; rice, for example, appears to have more genes than we do).

In this Newtonian quest, mathematical models will help in a different way than in the

earlier stages. Various conjectures about underlying mechanisms can be made explicit in mathematical terms, and the consequences can be explored and tested against the observed patterns. In this general way, we can, in effect, explore possible worlds. Some hard-nosed experimentalists may deride such exploration of imaginary worlds. And such derision may have some justification when the exploration is in vaguely verbal terms. The virtue of mathematics in such a context is that it forces clarity and precision upon the conjecture, thus enabling meaningful comparison between the consequences of basic assumptions and the empirical facts. Here mathematics is seen in its quintessence: no more, but no less, than a way of thinking clearly.

A point that arguably deserves more emphasis than it usually gets is that, in such exploration of mathematical models, the understanding emerging from complex computer-based simulations can often be substantially less complete than that from the analytic methods of classical applied mathematics and theoretical physics. In the World War II Manhattan Project, the world's smartest theoretical physicists used a mixture of mechanical calculators (the computers of their day) and analytic approximation techniques to go from basic equations to the design of the atom bomb. At every stage in this process, there was preserved an intuitive understanding of the relation between the underlying physical assumptions and the results. Today, meteorological predictions are based on satellite data and the Navier-Stokes (N-S) hydrological equations, using computers whose power is beyond the wildest imaginings of an earlier generation. Amongst other things, we now believe that the nonlinear N-S equations can give so-called chaotic dynamics, where the sensitivity to initial conditions (the satellite data) is such that prediction beyond 10 to 20 days can be effectively impossible, no matter how powerful the

computer. In many ways, this has greatly increased our understanding of local weather prediction. But—an important but—a rigorous mathematical proof that the N-S equations have chaotic solutions, as distinct from computer simulations that look chaotic, is in effect one of the century-old unsolved Hilbert problems (and the Clay Foundation in Boston will give you 1 million dollars if you solve it).

More generally, the increasing speed and sophistication and ease of use of computers enables an increasingly large number of life scientists who have no substantial background in mathematics to explore "mathematical models" and draw conclusions about them. Such activity usually consists of representing sensible and evidence-based assumptions as the starting

point for a complicated and usually nonlinear dynamical system, assigning particular parameters (often in an arbitrary way), and then letting this complicated system rip. This represents a revolutionary change in such theoretical studies. Until only a decade or two ago, anyone pursuing this kind of activity had to have a solid grounding in mathematics. And that meant that such studies were done by people who had some idea, at an intuitive level, of how the original assumptions related to the emerging graphical display or other conclusions on their computer. Removing this link means that we arguably are seeing an increasingly large body of work in which sweeping conclusions—"emergent phenomena"—are drawn from the alleged working of a mathematical model, without clear understanding of what is actually going on (Fig. 2). I think this can be worrying.

This cautionary note can be fleshed out with a couple of examples. The first comes from HIV/AIDS in the mid-1980s, when Roy Anderson and I published the first, rough estimate of its likely demographic impact in some central African countries. The main unknown at that time was the probability, β , that an infected individual would infect a susceptible partner. Available data suggested that β depended relatively little on the number of sexual acts within a partnership. On this basis, we used a relatively simple model to suggest that the future demographic impact of HIV/AIDS could be severe in some such countries. In contrast, the World Health Organization and the Population Council in New York produced models that were much more complex, including very detailed demographic data, but where HIV transmission probability was treated as if for measles, compounding independently randomly for each individual sex act. Thus, in effect, their models assumed that, knowing nothing of the infective status of individuals, 1 sex act with each of 10 different sex workers was effectively equivalent to 10 acts with 1; our data-governed, but otherwise much simpler, model saw the former as roughly 10 times more risky. So it was not surprising that the later models, apparently "more realistic" by virtue of their computational complexity, suggested a less gloomy view than ours. Sadly, but understandably, our predictions have proved more reliable (3, 4).

An interestingly different but rather common sin is exemplified in a risk-assessment study commissioned by the U.K. Government a few years ago to help determine whether to ban beef-on-the-bone (T-bone steak; hereafter BOTB) in the aftermath of the BSE or "mad cow" epidemic. Three factors are involved in any assessment of the likely number of cases of vCJD in humans prevented by such a ban: the number of infected animals still liable to enter

the human food chain, after the precautionary measures taken earlier; the amount of infected meat additionally removed by banning BOTB; the probability, P , of contracting vCJD after eating, say, 1 g of infected meat. Of these three, the first can be estimated fairly reliably (certainly to within a factor 10). The second can be estimated to stupefying precision, which indeed forms the bulk of the report. The infection probability, P , is essentially unknown. So the study ran computer simulations, with an arbitrary distribution of P values ranging over six orders of magnitude. For any one assumption about the P value, you could roughly assess the number of vCJD cases saved by banning BOTB by a calculation on the back of an envelope. In the published study, however, these arbitrary

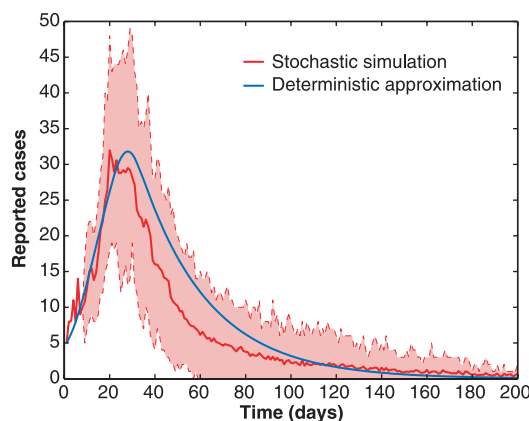


Fig. 2. The predictions for the numbers of animals infected with foot-and-mouth disease, under a controlled program that combines culling with reactive vaccination. The red curve shows the mean, and the shaded region the range, for simulations of a detailed stochastic model in which spread of infection is modeled using the actual spatial distribution of farms in England and Wales. The blue curve is from a highly simplified "toy model," using gross averages of relevant parameters. The comparison between the simple model, in which the dynamics can be clearly understood, and the complex computer simulations is illuminating both for the similarities and the differences (the latter helping to explain why, in reality, local outbreaks continued to erupt many months after the endpoint predicted by deterministic models). Reprinted with permission (10).

assumptions were magically transmogrified into a probability distribution by passage through a big computer. The resulting 95% "confidence interval" included the possibility of saving one life. This, along with other considerations, led to the ban. Of course, an alternative assessment could have asked what is the ratio of the cases of vCJD saved by banning BOTB to the number of cases—at that time hard to estimate—coming down the pipeline from cattle that entered the human food chain at the height of the epidemic, before effective measures were taken. This ratio depends mainly on the number of cattle still entering the human food chain to the number entering at the epidemic's height, with the great uncertainty in P canceling out of the ratio. On this basis, you

would conclude that for every case of vCJD prevented by banning BOTB, you were looking at 100,000 (give or take a factor 10!) cases of vCJD yet to come from the earlier epidemic. Put another way, given the best guess of a few hundred cases of vCJD from the earlier epidemic, the ban prevented 10^{-3} of a case. The public, with admirable common sense, saw the ban as silly, and they were right. Sadly, examples of the application of statistical "confidence intervals" to distributions resulting from making arbitrary assumptions about essentially unknown parameters, and then endowing this with reality by passage through a computer, continue to proliferate.

The history of useful mathematical models, and of mathematics more generally, varies among different areas in the life sciences. I referred earlier to population genetics; ecology and immunology provide two further, and interestingly different, examples.

Ecology is a relatively young subject, and much early work was largely descriptive. Seminal studies by Lotka and Volterra explored mathematical metaphors for competition and other interactions among species, but things did not really take off until the 1960s, when Hutchinson and MacArthur began to ask focused and testable questions in the idiom of theoretical physics: How similar can species be yet persist together. How do the patterns of species' interactions within a food web affect its ability to withstand disturbance. Why are some natural populations relatively steady from year to year, others cyclic, and others fluctuate widely (5)? At first, some ecological empiricists resented *arrivistes*, who had paid no dues of years of toil in the field, presuming to mathematicize their problems (sometimes sweeping aside arguably irrelevant, but certainly much loved, details in the process). Others welcomed the newcomers too uncritically. Look at the ecology texts of 50 years ago, and you will find very few equations. Today's, by contrast, contain a blend of observation, field and laboratory experiment, and theory expressed in mathematical terms. I think this reflects the maturing state of this vital subject, although it still has more questions than answers. The mathematical traffic, moreover, has not been all one-way: Some of the seminal developments in chaos theory were prompted by ecological problems (6, 7).

Immunology offers a somewhat different picture. Here there are truly remarkable advances in describing and understanding, at the molecular level, how individual viruses and other infectious agents interact with individual immune system cells. And on the basis of such knowledge, so brilliantly detailed on the molecular scale as almost to defy intuitive comprehension, we can, for example, design drugs that suppress viral replication. Chemotherapy

against HIV is one notable example. At the same time, however, there is as yet no agreed explanation for why there is so long, and so variable, an interval between infection with HIV and onset of AIDS. Indeed, I guess that many researchers in this field do not even think about this question. But I suspect the answer may necessarily involve understanding how whole populations of different strains of HIV interact with whole populations of different kinds of immune system cells, within infected individuals. And understanding the nonlinear dynamics of such a system will require mathematical models with similarities to and differences from those that have helped us understand population-level problems in ecology and infectious diseases (8). It may even be that the design of effective vaccines against protean agents like HIV or malaria will require such population-level understanding. As yet, this mathematically theoretical aspect of immunology is even less to be found in textbooks than were mathematical models in ecology texts a generation ago. I venture to predict that the corresponding immunology texts will indeed look different in 20, or even 10, years' time.

In short, mathematical models have proved to have many uses and to take many forms in the life sciences. We all, by this time, acknowl-

edge the usefulness of statistical recipes to help design and analyze experiments. More familiar in some areas than others are the benefits of mathematical studies that underpin pattern-seeking and other software that is indispensable in elucidating genomes, and ultimately in understanding how living things assemble themselves. Very generally useful are still-unfolding advances that illuminate the frequently counter-intuitive behavior of nonlinear dynamical systems of many kinds.

Mathematics, however, does not have the long-standing relation to the life sciences that it does to the physical sciences and engineering. It is therefore not surprising to find occasional abuses. Some have been sketched above. Particularly tricky are instances in which conventional statistical packages (often based on assumptions of an underlying Gaussian distribution—the central limit theorem) are applied to situations involving highly nonlinear dynamical processes (which can often lead to situations in which “rare events” are significantly more common than Gaussian distributions suggest) (9). Perhaps most common among abuses, and not always easy to recognize, are situations where mathematical models are constructed with an excruciating abundance of detail in some aspects, whilst other important facets of

the problem are misty or a vital parameter is uncertain to within, at best, an order of magnitude. It makes no sense to convey a beguiling sense of “reality” with irrelevant detail, when other equally important factors can only be guessed at. Above all, remember Einstein's dictum: “models should be as simple as possible, but not more so.”

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REVIEW

Evolutionary Dynamics of Biological Games

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Darwinian dynamics based on mutation and selection form the core of mathematical models for adaptation and coevolution of biological populations. The evolutionary outcome is often not a fitness-maximizing equilibrium but can include oscillations and chaos. For studying frequency-dependent selection, game-theoretic arguments are more appropriate than optimization algorithms. Replicator and adaptive dynamics describe short- and long-term evolution in phenotype space and have found applications ranging from animal behavior and ecology to speciation, macroevolution, and human language. Evolutionary game theory is an essential component of a mathematical and computational approach to biology.

Evolution through natural selection is often understood to imply improvement and progress. A heritable trait that confers to its bearer a higher fitness will spread within the population. The average fitness of the

population would therefore be expected to increase over time. This is often pictured as a steady ascent on a so-called fitness landscape. The landscape metaphor suggests some solid ground over which the population moves. This paradigm (1), which is also widespread in the theory of genetic algorithms (2), neglects one-half of the evolutionary mechanism: Although the environment selects the adaptations, these adaptations can shape the environment. By moving across a fitness landscape, populations change that landscape (Fig. 1).

This is particularly clear if several populations interact, because each population

can be part of the fitness landscape of the other. A host's successful immune response to a pathogen, for instance, will exert selection pressure leading to adapted strains of pathogens, and vice versa (3–5). But even within a single population, the fitness of a trait often depends on the prevalence of that trait: The selective advantage of a given tree height, for example, depends on the heights of neighboring trees. Similarly, the success of a given sex ratio depends on the overall sex ratio in the population.

Therefore, the fitness landscape is shaped by the phenotypic distributions of the involved populations. As the population moves through the fitness landscape, new peaks and valleys form, channeling its further motion. This viewpoint affects not only the intuition of evolutionary biologists but also their theoretical tools. The proper technique for describing uphill motion on solid ground is optimization theory, a set of mathematical techniques developed in the past 300 years, mostly to solve physical or technical problems. If the adaptive steps, however, imply changes in the environ-

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