The 'Gift' of Mathematics in the Era of Biology

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Math and Bio 2010, whose table of contents can be found at `www.maa.org/mtc/mathbiotoc.html`, is the report of a project[1] called *Meeting the Challenges: Education Across the Biological, Mathematical and Computer Sciences*. The goal of this project was to explore strategies for integrating biology, mathematics, and computer science more effectively in the undergraduate curricula, and to alert faculty to the expanding and exciting challenges of interdisciplinary work in these fields.

Every day, findings in genetics, cell biology, ecology, medicine, and evolution excite our imaginations and expand opportunities for health and economic growth. *Math & Bio 2010: Linking Undergraduate Disciplines* envisages a new educational paradigm in which the disciplines of mathematics and biology, currently quite separate, will be productively linked in the undergraduate science programs of the twenty-first century. The paper reproduced here, "The 'Gift' of Mathematics in the Era of Biology," traces the history of interaction between mathematics and biology which has now blossomed into a challenging interdisciplinary enterprise.

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[1] *Meeting the Challenges* was a joint project of the Mathematical Association of America, the American Association for the Advancement of Science and the American Society for Microbiology funded by the Division of Undergraduate Education at the National Science Foundation and the National Institute of General Medical Sciences at the National Institutes of Health.

The "Gift" of Mathematics in the Era of Biology

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For most of the twentieth century, mathematics was seen as a close and natural partner of physics and engineering—a "wonderful gift," in physicist Eugene Wigner's memorable words, that we "neither understand nor deserve."[1] The mainstream of secondary and postsecondary mathematics education was channeled to nourish the roots of the physical sciences. The general public, notably including students and their parents, believed that only those who wanted to be engineers really needed advanced mathematics. From trigonometry through calculus and on into advanced calculus and differential equations, three to four years of students' mathematical study in grades 10–14 was designed to support the parallel curriculum in physics. Indeed, until well into the second half of the twentieth century, most universities required all mathematics majors to take a year of calculus-based physics.

Now, however, midway through the first decade of the twenty-first century, science has moved on. Biology has replaced physics as the next "big thing"—the crucible of innovation—not only in science but also in mathematics. "The mathematics involved in studying the genome and the folding of proteins is deep, elegant, and beautiful—all words that often were reserved only for pure mathematics in the past century," notes the Executive Director of the American Mathematical Society. "The sophisticated blending of mathematics and biology already is a spectacular new area of research that is certain to grow enormously."[2]

Some reverse the image and argue that mathematics is the next big thing in biology. Biologist Eric Lander, a principal leader of the Human Genome Project, speaks of "biology as information," as a vast library filled with the "laboratory notebooks of evolution," one for every species, with chapters for every tissue, each containing genome sequences as well as expressions of RNA and proteins.[3] All these volumes are written in code that can be deciphered only by use of sophisticated mathematical algorithms. Once read, sequences can be mapped to functions, and thence to malfunction (disease) and to the evolution of function and form in both organisms and species. According to Lander, the genetic revolution in

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[1] Eugene Wigner, "The unreasonable effectiveness of mathematics," *Communications in Pure and Applied Mathematics*, 13 (1960) 1–4.

[2] John Ewing. "The Next Big Thing in Mathematics." *The Chronicle of Higher Education*, September 20, 2002.

[3] Eric Lander, "Beyond the Human Genome Project: Biology as Information." *Genes, Genomes, and Medicine*, Columbia University Digital Knowledge Ventures. URL: `c250.Columbia.edu/genomes`.

Supporting Research in Mathematical Biology

Revolutionary opportunities have emerged for mathematically driven advances in biological research. Examples include:

- Evolutionary theory and practice arising from genomics advances;
- Statistical approaches to the discovery of genes that contribute to complex behavior;
- Modeling of complex ecological systems;
- Explanatory and predictive models of the cellular state;
- Cellular growth, motility, division, and membrane trafficking;
- Metabolic circuitry and dynamics;
- Population dynamics;
- Signal transduction;
- Informational molecule dynamics;
- New algorithms for phylogenetic analysis;
- Dynamics of pattern formation in development and differentiation;
- New approaches to the prediction of molecular structure;
- Improved algorithms for x-ray crystallography, NMR and electron microscopy;
- Simulations of human systemic responses to burn, trauma and other injury;
- Systemic effects of pharmacological agents and their genetic & environmental modifiers.

The National Science Foundation (NSF) and the National Institutes of Health (NIH) collaborate to provide support for research in cross-disciplinary areas such as these. Proposals are expected to identify innovative mathematics or statistics needed to solve an important biological problem. Work supported under this initiative must impact biology and advance mathematics or statistics. Thus, collaborations between mathematical and biological scientists are expected.

Officially called the Initiative to Support Research in the Area of Mathematical Biology, this program is a joint activity of the Division of Mathematical Sciences (DMS) in the Directorate for Mathematical and Physical Sciences (MPS) and the Directorate for Biological Sciences (BIO) at the National Science Foundation (NSF) and the National Institute of General Medical Sciences (NIGMS) at the National Institutes of Health (NIH). Further information is available at: www.nsf.gov/pubsys/ods/getpub.cfm?nsf04572.

biology contains keys to "the most remarkable library of information on this planet."

The relatively sudden emergence of biology as the dominant scientific partner for mathematics in both research and education has created major challenges for both disciplines. Biology research—and with it the emerging multibillion dollar biotech industry—is hampered by lack of scientists able to work in teams where both biological and mathematical skills are required. Biology education is burdened by habits from a past where biology was seen as a safe harbor for math-averse science students. Biology faculty need to learn about the new quantitative tools while at the same time teach students who are often refugees from mathematics. And while embracing the multitude of research opportunities offered by the new biology, mathematical scientists who were educated in the physics paradigm face the daunting prospect of learning to teach new cross-disciplinary courses and to conduct collaborative research with colleagues in life science fields awash in unfamiliar methodologies, vocabulary, and theoretical foundations. (Sidebars distributed throughout this paper illustrate a variety of responses to these challenges.)

The challenges for undergraduate education of what has come to be called the "New Biology" were forcefully articulated by the National Research Council in the widely acclaimed report *Bio 2010*.[4] This report unhesitatingly describes the digital transformation of biology as a "revolution," and offers far-reaching recommendations for how to synchronize undergraduate programs with the transformed reality of the new biology. The thesis of *Bio 2010* is that biology is not a separate science but an "integrative discipline" in which many aspects of the mathematical and physical sciences "converge to address biological issues."

Consequently, *Bio 2010* urges colleges and universities to create strong interdisciplinary curricula that integrate

[4] Committee on Undergraduate Biology Education, *Bio 2010: Transforming Undergraduate Education for Future Research Biologists,* National Research Council, National Academies Press, Washington, DC, 2003.

Workshops on the New Biology

A two-week intensive program introducing modern concepts in biology for mathematical and physical scientists took place in June, 2003 at the DIMACS Center, Rutgers University. Its goal was to introduce topics in molecular and cell biology that are relevant to those who wish to work at the interface of biology, mathematics, computer science, chemistry, and physics.

The first week, "The DNA Revolution," introduced the fundamentals of modern molecular biology, genetics, and biotechnology to participants who had little background in biology or biochemistry. It included a web-based primer of important biological information that covers chemical structures, biochemical processes, and classical genetics; a virtual laboratory with realistic exercises that illustrate the activities of modern-day bench scientists; and specially designed "hands-on" bioinformatics research projects. In addition, the tutorial examined scientific questions that interest present-day biomedical researchers, especially problems that can be addressed through quantitative approaches.

The second week reviewed cell biology—including energy generation, cell division, cell cycle control, cell communication, cytoskeleton, membranes, and intracellular compartments—and then summarized open questions. Major topics were illustrated by in-depth analyses of significant recent biophysical studies (e.g., mathematical models of cell and viral kinetics that explain the emergence of drug-resistant viruses). Participants became familiar with important websites useful to researchers and heard presentations on current research in fields at the interface of the biological, mathematical, and physical sciences.

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mathematical, information, physical, and life sciences. Defying the long-standing tradition of biology being taught as the least mathematical science, *Bio 2010* documents biologists' need for a strong foundation in the mathematical and information sciences. Indirectly, *Bio 2010* also implies an urgent need for a parallel change in the education of mathematical scientists: to be prepared either to teach or conduct research, today's students in the mathematical sciences need a strong foundation in the life sciences—just as their predecessors needed a strong foundation in physics.

These recommendations are not just parochial issues of concern to a small number of departments and students. One in six entering college students now expects to major in a biological, health, or life science. The number of graduates who major in the biological sciences is now greater than those in engineering or psychology. The quantitative and integrative challenges posed by the new biology herald changes coming to all undergraduate science in the first part of the twenty-first century. This is indeed a Big Thing.

Quantitative Biology: Origins

Even without understanding details, most people are well aware of the deep connections between the mathematical and physical sciences—from gravity to relativity, from quantum theory to string theory. Yet very few recognize similarly deep connections between the mathematical and life sciences. Even today when decoded genomes share headlines with speculations about dark matter, most people do not connect genomics with mathematical tools the way they do the theories of physics or astronomy. This bias in public perception—which influences students and schools—is in part the result of the physical-science orientation of traditional mathematics curricula. From their own education, adults have learned to see mathematics as comprising equations such as those used in physics (e.g., $E = mc^2$; $v = d/t$). But they have not learned to see mathematics as necessary for, or even relevant to, biology.

In one sense, this view is not unreasonable. With few exceptions, the mathematical and quantitative tools used to study biological processes have been only modestly effective, especially as compared with similar applications in the physical sciences. The reason is simple: Living organisms are vastly more complicated than lifeless matter. Quite naturally, the simpler problems of physics were solved before—a century or two before—those of biology. But now, at the beginning of the twentieth first century, scientists finally have received the "gift" of quantitative tools required to model biological processes with the same understanding as they have earlier achieved for physical systems.

In another sense, however, the widespread perception of biology as an exceptional science that does not speak the language of mathematics is a myth. Mathematics is the science of patterns,[5] and biology overflows with pattern. Visible examples are most obvious: spiral patterns in nautilus shells; intricate geometry of radiolaria skele-

[5] Lynn Arthur Steen, "The Science of Patterns," *Science* 240 (29 April 1988), 611–616.

tons; hexagonal structure of honeycombs; patterns on animal skin and butterfly wings; bilateral symmetry of most animal species; and much more.[6]

The great Scottish zoologist D'Arcy Thompson was the first person to argue persuasively that such patterns are due to mathematics, not instinct or genetics. "There are no exceptions to the rule that God always geometrizes. The problems of form are in the first instance mathematical problems, the problems of growth are essentially physical problems." In his classic monograph On Growth and Form,[7] Thompson used established principles of mathematics and mechanics to analyze skeletons and structure of living organisms. Through these examples he documented how the trail of evolution reflected the necessity of physical law, thus providing an explanation for how different life forms took on their varied shapes. His larger contribution was to break down the unstated assumption of the time that living things and inanimate objects occupied different scientific realms and were subject to different laws. For Thompson, both obeyed the laws of mathematics.

Other patterns are less visible but no less fundamental. During the eighteenth and nineteenth centuries, quantitative characteristics became increasingly important as measures of social well being. Censuses became common as a means of counting people and wealth, noting births, deaths, and immigration. Businesses counted and weighed natural assets such as wheat, timber, and livestock. World trade came to depend on projections of the size of natural populations such as wild game, crop harvests, and human population. Thus not only scientists but also business and political leaders all had increasing interest in quantification, particularly in the less visible patterns created by numbers that tally populations.

Surely one of the most widely recognized applications of mathematical principles to biology is Thomas Malthus' warnings about the calamitous consequences of population growth. Quoting himself in 1798, Malthus wrote "I said that population, when unchecked, increased in a geometrical ratio, and subsistence for man in an arithmetical ratio."[8] Malthus' "geometrical ratio" we now call exponential growth; even at modest rates, such growth is not realistic in the long run for any natural population. However, it is a very good model in certain circumstances, and is still the normative metaphor for discussions of population growth.

Another widely known early foray into using quantitative methods to gain biological insight is Gregor Mendel's meticulous documentation in the 1860s of numerical patterns in inherited characteristics.

> "The ratio of 3:1, in accordance with which the distribution of the dominant and recessive characters results in the first generation, resolves itself ... into the ratio of 2:1:1. ... Since the members of the first generation spring directly from the seed of the hybrids, it is now clear that the hybrids form seeds having one or other of the two differentiating characters, and of these one-half develop again the hybrid form, while the other half yield plants which remain constant and receive the dominant or the recessive characters in equal numbers."[10]

Mendel's work not only described inheritance quantitatively, but made it possible to infer the notion of a gene—a minimal unit of heredity—long before physical genes were discovered. (This power of mathematics to predict scientific discoveries is not uncommon: the planet Neptune was predicted and ultimately discovered based on minute discrepancies between the theoretical and actual orbit of Uranus.)

Subsequently, arguments erupted over how recessive characteristics could survive eons of evolution. In 1908 British mathematician G. H. Hardy used simple high school mathematics—the binomial expansion—to infer from Mendel's analysis that the proportion of genes in a stable population will remain constant from generation to generation. "In a word, there is not the slightest foundation for the idea that a dominant character should show a tendency to spread over a whole population, or that recessive should tend to die out."[10] Now called the Hardy-Weinberg Law, this purely mathematical analysis helped resolve one of the early scientific objections to Darwin's theory of evolution.

More than a century earlier, the great eighteenth century Swiss mathematician Leonard Euler had established a similar stability result for the age distribution of populations. Uneven distribution of ages leads to uneven rates of reproduction of the population as a whole and can create "baby booms" and subsequent "busts." Euler showed that in the absence of external events such as immigration, the overall rate of growth of a population will even-

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6 John A. Adam, *Mathematics in Nature: Modeling Patterns in the Natural World*, Princeton University Press, Princeton, NJ, 2003.

7 D'Arcy Wentworth Thompson, *On Growth and Form*, Cambridge University Press, Cambridge, UK, 1917, 1942.

8 Thomas Malthus, *An Essay on the Principle of Population*, J. Johnson, St. Paul's Churchyard, London, 1798.

9 Gregor Mendel. "Versuche über Pflanzen-Hybriden." 1865. English Translation: "Experiments in Plant Hybridization." `www.biologie.uni-hamburg.de/b-online/e08_mend/mendel.htm`.

10 G. H. Hardy, "Mendelian Proportions in a Mixed Population," *Science*, 28:706 (Jul 10, 1908), 49–50.

Supporting Undergraduate Biology and Mathematics

The explosion of knowledge in the life sciences over the past twenty years cuts across all levels from molecules to ecosystems. Current research is often characterized by integrative and interdisciplinary approaches. At the center of this explosion of knowledge is a revolution in instrumentation, computational abilities, information systems, and mathematical tools.

A parallel growth in understanding has taken place in the mathematical sciences. Theoretical advances in complexity, dynamical systems, and uncertainty, coupled with advances in modeling and computational methods, have helped mathematicians and statisticians put ideas into action. These advances have expanded use of mathematics and statistics beyond the traditional fields of physical science and engineering. As that expansion has taken hold, the life sciences and other fields are posing new kinds of questions for the mathematical sciences, stimulating further the growth of mathematical ideas.

Thus the intersection of the biological and mathematical sciences is a fertile field for both sets of disciplines, where results in each area lead to advances in the other. However, there are comparatively few people able to work in this intersection. The Undergraduate Biology and Mathematics (UBM) program at the National Science Foundation (NSF) is designed to attract and prepare students for careers in this important crossroads of two major disciplines—mathematics and biology.

UBM programs are expected to:

- Be grounded in research activities involving both mathematical and biological sciences;
- Connect to regular academic studies, influencing the direction of academic programs for a broad range of students.
- Involve students from both areas in significant research experiences that connect to research at the intersection of the disciplines; and
- Show commitment to joint mentorship by faculty in both fields.

Individually, UBM projects will have a significant impact on the undergraduate programs of participating institutions. Collectively, they will strengthen the nation's research enterprise by providing new mechanisms for attracting a larger, more diverse group of students to careers that involve both the mathematical and biological sciences. Within this context, there is room for a variety of possible emphases, ranging from undergraduate research participation, through curriculum and faculty development, as well as internships outside the academic institution.

The Undergraduate Biology and Mathematics program is a joint effort of the Education and Human Resources (EHR), Biological Sciences (BIO), and Mathematical and Physical Sciences (MPS) directorates at the National Science Foundation (NSF). Further information is available at: www.nsf.gov/pubsys/ods/getpub.cfm?nsf04546.

tually stabilize: left to themselves, population distortions will subside. Euler did this by creating and solving a simple system of equations that represents the reproduction and survival rates for each age cohort.

But as Malthus argued, stable population growth cannot survive in the long run. Early in the nineteenth century the Belgian scientist Pierre François Verhulst suggested that each population has a theoretical long-term maximum that he called its "carrying capacity." As the population approaches its maximum, competition for resources tends to limit growth, thereby introducing negative feedback between size of a population and its rate of growth. In Verhulst's model,[11] the graph of population growth is no longer the dramatic (but unrealistic) unbounded exponential curve, but the "logistics" graph that begins exponentially but then tapers off as it approaches the carrying capacity.

As "survival of the fittest" theories came under scrutiny in the period following publication of Darwin's *The Origin of Species,* mathematically-minded biologists extended Euler's and Verhulst's equations to multiple species competing in a single ecosystem. In this endeavor, scientists consciously imitated the models of physical systems that had proven so successful in engineering and mechanics. For example, Alfred Lotka at Johns Hopkins University employed simultaneous difference and differential equations to represent the behavior of a complex ecosystem as a set of trajectories in n-dimensional space. Lotka studied evolution as "the mechanics of systems undergoing irreversible changes." Indeed, the sections of his 1924 monograph on what he called "physical biology" borrowed thematic headings from mainstream mechanics textbooks of that era: statics, kinetics, dynamics.[12]

[11] Pierre François Verhulst. "Recherches mathématiques sur la loi d'accroissement de la population." *Nouv. mém. de l'Academie Royale des Sci. et Belles-Lettres de Bruxelles*, 18 (1845) 1–41. "Deuxième mémoire sur la loi d'accroissement de la population." *Mém. de l'Academie Royale des Sci., des Lettres et des Beaux-Arts de Belgique*, 20 (1847) 1–32.

[12] Alfred J. Lotka. Elements of Physical Biology. 1924; Reprinted as Elements of Mathematical Biology. Dover, 1956.

Verhulst's Model for Population Growth

In a capacity-limited population, the intrinsic rate of growth is diminished by the proportion of the capacity that has been used up. In symbols, as the population N approaches its maximum K, the rate of growth r will be reduced by $(N/K)r$. Thus the equation of unrestrained exponential growth

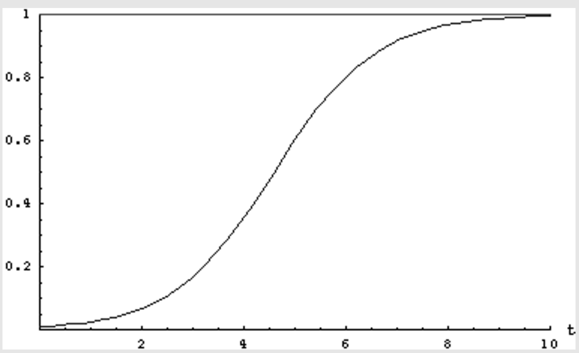
$$N(t + 1) = N(t)e^r$$

is replaced by

$$N(t + 1) = N(t)er(1 - N(t)/K).$$

Equivalently, the Verhulst model is often represented by the differential equation

$$dN/dt = rN(K - N)/K = rN(1 - N/K).$$



The most common application of Lotka's multi-species equations is to predator-prey situations where a dominant predator can so pressure its prey that the predator runs out of food, thence the predator population declines. With fewer predators, the prey rebound, and the cycle begins again. Classic long-term data documenting this phenomenon came from records of populations of Canadian lynx and snowshoe hares maintained for a century or more by the Hudson Bay Company. A similar analysis was carried out about the same time by the famous Italian mathematician Vito Volterra and his biologist son-in-law who was studying the stock of fish species in the Adriatic. Consequently, the predator-prey equations are now called the Volterra-Lotka equations.

Although these dynamical system models do a reasonable job of imitating certain patterns seen in actual populations (e.g., cycles of boom and bust), they are rarely very good at predicting events in real ecosystems. In one important study using single cell organisms competing for food and space, the Russian microbiologist G. F. Gause elaborated important differences between mathematicians' view of the Darwinian "stuggle for existence" and those found in nature. Gause showed, for example, that cyclic behavior is not an inherent characteristic of predator-prey competitions, but often arises in natural situations as the result of some external factor.[13]

Gaps between theoretical models and experimental reality remain high in the life sciences. Assessing the size of populations is an inherently mathematical task—far more promising as a quantitative activity than, for instance, assessing the health of individuals or the function of genes. Mathematicians, statisticians, and biologists have worked for a century to develop effective mathematical models in biology, and population models in ecology have proved to be one of the most productive areas. Yet the famed British biologist J. Maynard Smith notes that even here, in the most promising of subfields, "it is usually better to rely on the judgment of an experienced practitioner than on the predictions of a theorist."[14]

Quantitative Biology: Expansion

These classic examples from the nineteenth and early twentieth centuries demonstrate that the image of biology as a non-quantitative science is a bit misguided. Contrary to popular myth, biology *is* amenable to quantitative methods—some areas more so (e.g., epidemiology, demography), others less so (cell biology, physiology). Moreover, just as Newton's effort to understand gravity led him to the development of calculus, scientists who investigate biological problems often find themselves inventing new mathematics (e.g., the Volterra-Lotka equations).

One indication of the breadth of intersection between mathematics and biology can be gleaned from the subject headings of *Mathematical Reviews* under the topic of biology. These span the entire spectrum of biology from molecular to ecological:

Animal behavior	Genetics
Biochemistry	Medical applications
Biomechanics	Medical epidemiology
Biomedical imaging	Molecular biology
Biophysics	Molecular structure
Biostatistics	Neural biology
Cell biology	Neural networks
Cell movement	Pharmacokinetics
Cellular processes	Physiological flow
Developmental biology	Physiology
DNA sequences	Plant biology
Ecology	Population dynamics
Enzyme kinetics	Protein sequences
Epidemiology	Signal processing
Evolution	Taxonomy

[13] G. F. Gause, *The Struggle for Existence*, The William & Wilkins Co., 1934; Dover, 1971.

[14] J. Maynard Smith, *Models in Ecology*, Cambridge University Press, 1974.

Environmental Biocomplexity

Complexity pervades biology and puzzles mathematicians. From matching segments of DNA to tracing electrical waves in the heart, the problems posed by biology often move well beyond the methods mathematicians have yet invented. Environmental science runs into the brick wall of complexity before it has rounded the first turn.

From the scientific perspective, environmental problems require integration of ever-changing data from biological, physical, and social systems. For example, ameliorating the impact of an airborne pollutant requires knowledge of its impact on the body, of its dispersal in the atmosphere, of the human causes of the pollution, of its economic and social costs, and of the consequences of any proposed program to bring about a change. Any one of these investigations alone would be complicated enough; together they merit the special label of "environmental biocomplexity."

From a mathematical perspective, complexity means something more than merely complicated. Phenomena that exhibit nonlinear dynamic behavior, or random fluctuations, or interactions of different scale are prone to chaotic behavior which is characterized by a special kind of unpredictability in which minute differences beyond our ability to observe or measure create noticeable differences in future phenomena that may be rather distant in time or space. This kind of complexity imposes limits on our ability to understand causes and to predict consequences.

The hallmark of a vital link between science and mathematics is a symbiotic relationship in which each draws strength from the other—posing challenges, raising questions, suggesting promising avenues of investigation. Many examples can be cited to illustrate that biological problems have stimulated important advances in the mathematical sciences, even as mathematical models have slowly improved in their ability to address biological problems with success and insight:

- In 1874, Francis Galton and H.W. Watson reported public concern about "the decay of families of men who occupied conspicuous positions in past times ... Surnames that were once common have since become scarce or have wholly disappeared." To test the widespread opinion that a "rise in physical comfort and intellectual capacity is necessarily accompanied by diminution in fertility," Galton and Watson developed a stochastic branching process to determine the likelihood of extinction of surnames under purely random conditions. They determined that this common conclusion had been "hastily drawn,"[15] and in the process introduced a new quantitative tool for use in analyzing evolutionary behavior.
- Later, in trying to understand how strongly the characteristics of one generation were evident in succeeding generations, Galton developed rudimentary ideas of regression and correlation.[16] These ideas were placed on firm mathematical footing by his younger colleague Karl Pearson.[17] The most commonly used tools of today's statistics (correlation, regression) are direct descendents of ideas introduced in these experiments.
- Imaging technology has made great strides in the last two decades and has become an indispensable tool both for biology and medicine. Many factors combined to bring this about, not least advances in sensitivity of radiation detectors and increases in speed and power of computers that reconstruct three-dimensional images from two-dimensional data. Undergirding these modern computer methods is a strategy developed nearly half a century earlier by the Czech mathematician Johann Radon that showed, in essence, how to reconstruct images of objects from pictures of its shadows.[18] This Radon Transform is the central idea that made Computed Axial Tomography (CAT scans) possible.
- One of the more widely known examples of biological questions leading to new mathematics involves Benoit Mandelbrot's 1975 invention of fractals, abstract objects of fractional dimension that offer better models for life forms (trees, leaves, veins, lungs) and other natural shapes (coastlines, mountain ranges) than do the shapes of Euclidean geometry or curves of Newtonian calculus.[19] Iteration, a mathematical process that mimics the way natural organisms grow,

[15] Francis Galton and H. W. Watson, "On the probability of the extinction of families," *Journal of the Anthropological Institute*, (1874) 134–144.

[16] Francis Galton, *Natural Inheritance*, Macmillan and Co., London, 1889.

[17] Karl Pearson, "Mathematical Contributions to the Theory of Evolution. III. Regression, Heredity and Panmixia," *Philosophical Transactions of the Royal Society of London,* 187 (1896) 253-318.

[18] Johann Radon. "Über die Bestimmung von Funktionen durch ihre Integralwerte längs gewisser Mannigfaltigkeiten," *Berichte über die Verhandlungen der Sächsischen Akademie,* 69 (1917) 262-277.

[19] Benoit Mandelbrot, *Les objets fractals: forme, hazard et dimension,* Flammarion, Paris, 1975.

is the key to fractals. Notwithstanding that fractals have become part of popular culture and *New Yorker* cartoons, their utility has been thoroughly demonstrated in many parts of science.

- For decades, randomized double blind experiments have been the "gold standard" of clinical studies of proposed treatments for disease. Increasingly, however, patient advocates—often including the investigative scientists themselves—chafe under rigid protocols that deny some patients access to promising drugs until after the experiment is completed. An influential coterie of medical scientists are now using Bayesian statistics—a controversial eighteenth century approach that takes into account accumulating results[20]—to reconcile traditional statistical inference with current demands of ethics.[21]
- One of the many mysteries of biology that mathematics has helped explain is how a small homogeneous ball of embryonic cells can develop the dramatic differentiated patterns of a leopard's skin or a butterfly's wings. The answer, first formulated by the brilliant British computer theoretician Alan Turing, can be found in the interaction of chemicals whose concentrations during morphogenesis (embryonic development) alternately inhibit or activate each other. Turing used "reaction-diffusion equations" for these interacting chemicals to show how it is possible for patterns such as those found on skin to be created during the development of an embryo.[22]
- The mystery of morphogenesis extends from two-dimensions of skin patterns to differentiation of tissues and overall shape of the three-dimensional organism. What physical processes could conceivably enable such variety to emerge from uniform beginnings? Biologists can explain differences in tissue function by genes that are switched on or off, but this doesn't resolve the geometric puzzle about control of tissue boundaries. In searching for clues to this enigma, French mathematician René Thom, "one of the most original mathematical thinkers of the twentieth century,"[23] extended Turing's idea of biochemical attractors and derived seven possible geometric forms of morphogenesis that he termed "catastrophes."[24]
- Policy challenges associated with management of renewable resources has led to a whole new interdisciplinary field known as mathematical bioeconomics.[25] Fisheries, for example, need limits on allowable catches, seasons, and locations in order to ensure a stable population of fish as well as sufficient harvest to make the industry profitable. This has led to development of various models of optimal control theory that take into account variables such as aging, multiple species, capital investment, and stochastic events.
- Even though the heart is often viewed as a mechanical pump, reality is complicated by interaction of blood with flexible heart valves and muscular heart walls. Charles Peskin and colleagues at New York University have pioneered a mathematical model that regards the cardiac tissue as a part of the fluid in which additional elastic forces are applied. With the aid of an innovative "immersed boundary" method created to solve the equations of fluid motion under these circumstances, the NYU group can view a simulated beating human heart in order to study how it works, and how during heart attacks, it fails.[26]
- Shortly after defibrillators became visible in television emergency rooms, they began appearing on airplanes and are now being promoted for well-equipped home medicine chests. But no one can explain exactly why they work. James Keener at the University of Utah is one of several mathematicians attempting to build effective mathematical models of how electrical waves move across the heart to induce healthy rhythmic beats.[27] So far neither mathematicians nor biologists seem to have figured it out, but together they are making much more progress than either could alone.

This inventory of interaction between mathematical and biological sciences could go on for pages. However, those cited here are sufficient to document several important features of the relationship:

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[20] Thomas Bayes, "Essay towards solving a problem in the doctrine of chances," *Philosophical Transactions of the Royal Society of London,* 53(1763) 370–418; reprinted in *Biometrika,* 45:3–4 (Dec. 1958) 293-315.

[21] Jennifer Couzin, "The New Math of Clinical Trials," *Science*, 303:5659 (6 Feb. 2004) 784–786.

[22] Alan Turing, "The Chemical Basis of Morphogenesis." *Philosophical Transactions of the Royal Society of London*, B237 (1952) 37–72.

[23] Jean-Pierre Bourguignon, "René Thom: 'Mathématicien et Apprenti Philosophe,'" *Bulletin of the American Mathematical Society*, 41:3 (July 2004) p. 273–274.

[24] Rene Thom, "Une théorie dynamique de la morphogénèse," In E. H. Waddington (Ed.), *Towards a Theoretical Biology,* Vol. I: Prolegomena, Edinburgh University Press, Edinburgh, 1968, pp. 152–166.

[25] Colin W. Clark, *Mathematical Bioeconomics: The Optimal Management of Renewable Resources*, John Wiley & Sons, New York, 2000.

[26] Frank C. Hoppensteadt and Charles S. Peskin, *Modeling and Simulation in Medicine and the Life Sciences,* Second Edition, Springer-Verlag, New York, 2002.

[27] Dana Mackenzie, "Making Sense of a Heart Gone Wild," *Science,* 303:5659 (6 Feb. 2004) 786–787.

From Molecular Regulatory Networks to Cell Physiology

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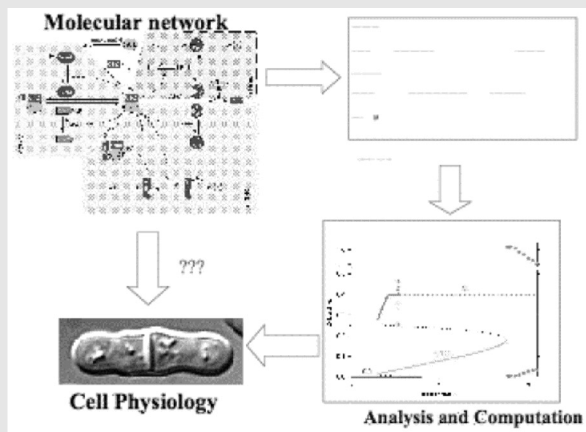
The living cell is a miniature biochemical machine that harvests material and energy from its environment and uses them for maintenance, growth and reproduction. These processes are carried out by macromolecular machines (enzymes, transport proteins, structural proteins, motor proteins, etc.) whose structures are encoded in nucleotide sequences (DNA and mRNA). The activities of these macromolecules are controlled and coordinated by regulatory networks of great complexity and exquisite effectiveness. These networks collect information from inside and outside the cell, process the data, and direct cellular responses that foster the survival and reproduction of the cell.[i]

How these regulatory systems work is no more or less apparent from their network diagrams than is a complex piece of electronics from its schematic wiring diagram. In the same way that electrical engineers create accurate mathematical representations of wiring diagrams and use these equations to design new devices, cell biologists now recognize the need for quantitative (mathematical and computational) modeling in order to understand how molecular regulatory systems control cellular responses. Only with this understanding can they re-engineer these control systems for industrial and medical purposes.[ii]



The regulation of growth, DNA synthesis, mitosis and cell division in eukaryotes is a prime example of what is called the "new biology" because of the central role of the cell cycle in all of cell physiology, because much is known about the underlying molecular regulatory system, and because of the immense importance of cell reproduction in health (cancer) and biotechnology (tissue engineering). A research group led by John Tyson (Virginia Tech) and Bela Novak (Budapest Univ. of Technology & Economics) uses nonlinear differential equations to represent wiring diagrams and provide reliable connections between the molecules and cell cycle physiology.[iii] By mathematical analysis (bifurcation theory) and numerical simulation, these researchers are building comprehensive, accurate, predictive models of cell cycle regulation in yeast cells, frog eggs, and multicellular organisms.

Research of this sort requires a sophisticated understanding of many fields: physiology, molecular cell biology, biochemical kinetics, dynamical systems theory, and numerical analysis, for starters. To provide such training, graduate programs in "computational biology" are springing up across North America, but the next generation of quantitative life scientists must start their preparation earlier. New interdisciplinary curricula for intelligent and highly motivated undergraduates are desperately needed. Such curricula could allow carefully chosen and guided students to put together courses from diverse fields, rather than to meet the expectations of traditional academic disciplines. To provide some structure, the program of study should be directed toward a specific research project in the final year. The exact combination of courses chosen by any student is not so important as is the interdisciplinary nature of the experience, which gives students confidence to cross boundaries in order to tackle cutting edge problems in the life sciences.

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[i] D. Bray, "Protein molecules as computational elements in living cells," *Nature* 376 (1995) 307–312.

[ii] L.H. Hartwell et al., "From molecular to modular biology," *Nature* 402 (1999) C47–52.

[iii] J.J. Tyson et al., "Network dynamics and cell physiology," *Nature Rev. Mol. Cell Biol.* 2 (2001) 908–916.

1. Quantitative methods have always been part of biology.
2. Mathematical and statistical models are employed in biology at all scales from microscopic (molecular) to macroscopic (environmental).
3. All realms of the mathematical sciences—geometry, statistics, algebra, computer science, analysis, probability—share significant boundaries with the biological sciences.
4. Biological questions have motivated major advances in many parts of the mathematical sciences.
5. Finally, as biologists amass increasing amounts of data, the numerous connections between mathematical and biological sciences are becoming stronger and more essential.

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In short, even apart from the genomics revolution, the gap between mathematical theory and biological reality is rapidly closing. After a century's struggle, mathematics has become the language of biology.

The New Biology: Data, not Disciplines

All the examples mentioned above share one further feature: they have nothing to do with genomics or bioinformatics. They are about all the other parts of biology. Indeed, no part of the biological terrain has been immune from the influence of statistics and mathematics: from molecules, cells and organs to organisms, populations and ecosystems, quantitative methods have been put to productive use in biology for well over a century, and continue so to this day.

Nevertheless, these models were rarely able to describe or predict with sufficient precision to answer specific research questions, nor were they able to demonstrate theorems of power comparable to those that undergird mathematical physics. Biological models were, quite literally, mostly of theoretical interest. More often than not, they suggested how things might behave rather than demonstrating how they would behave; they created hypotheses to test rather than conclusions to verify. For this reason, throughout the twentieth century mathematical biology was very much a niche discipline, fundamental to neither field and typically overlooked by both.

In recent years, of course, all this has changed. One reason is the recognition of genomes as the Rosetta Stone of life. For the same reason that the National Security Agency employs hundreds of mathematicians to crack intelligence codes, the biological research community now needs thousands of mathematical scientists to read information hidden in the genetic code.

A second reason is the powerful role of computer-enhanced visualization for research, diagnosis, and treatment. No longer are we limited to human eyesight enhanced by optics alone. Now we can "see" inside the body, even to the point of studying the shapes of molecules and witnessing internal organs. There are good evolutionary reasons why our minds can grasp more through a visual image than through words or data. Images enhance enormously each investigator's ability to "see," and therefore to understand.

A third reason is the revolutionary impact of networked databases. Data from millions of experiments reside in hundreds of thousands of computers all over the world. Like detectives who use networked fingerprint databases to solve decades-old crimes, biological investigators can now use the Internet to make connections and draw scientific conclusions from a vast international data warehouse. Networking magnifies enormously each investigator's scientific reach and resources.

The currency of the new biology is data—terabytes of data that are beginning to fill Eric Landers' imagined library of life. Traditional mathematical and statistical methods such as those described above—the cornerstones of twentieth century science—relied on a "reductionist" belief that the nature of complex processes can be explained by, derived from, or reduced to simpler and more fundamental laws. Examples of this paradigm include the triumphs of classical physics—Kepler's, Newton's, and Maxwell's laws—and the explanatory theories of multiple regression and factor analysis in subjects as wide ranging as evolution and education.

But in the new biology, data is king. In addition to verifying predictions of a mathematical model or statistical hypothesis (continuing the "old" biology), much current research is carried out by direct examination of data. Reversing the cycle of the "scientific method" in which theories are tested against data, these new methods begin (and often end) with data. The deluge of sequencing

Matching Grants for Genomics instrumentation

LI-CORR Biosciences of Lincoln, Nebraska offers a Genomics Education Matching Fund program (GEMF) to help colleges and high schools establish or enhance their programs in genomic studies. The GEMF program is to be used to acquire LI-COR DNA sequencing instruments and software for use by students studying molecular biology and related fields. The goal of the program is to help students get hands-on training in using cutting edge technology, to help educators improve their courses in practical application of genomics, and to increase the number of students prepared in genomics for both the job market and graduate work. LI-COR genomic analysis systems are used for a variety of research applications including sequencing, microsatellites, AFLPR and reverse genetics research.

LI-COR awards grants to eligible institutions on a matching funds basis. Eligible institutions must demonstrate how they will incorporate the LI-COR DNA analysis system to teach undergraduate or high school students. Additionally, schools may use the instruments for faculty and student research programs. Further Information is available at: www.licor.com/bio/Undergrad/matching_funds.jsp

Creating Courses that Integrate Biology and Mathematics

A one-week workshop in July, 2003 at Hope College in Holland, Michigan focused on courses and materials that integrate mathematics and biology in ways that benefit students from both disciplines. Participants consisted primarily of interdisciplinary teams including faculty from both the biological and mathematical sciences.

The workshop was designed to help participants better understand the uses of mathematics in current biological research and to help them develop appropriate interdisciplinary courses on their own campuses. It focused on key steps in this process:

- Establish collaborations between mathematicians and biologists;
- Create a course that attracts students from both disciplines;
- Find and develop curricular resources; and
- Incorporate appropriate software and/or experiments.

Participants received a variety of supporting materials, including resources used in existing mathematical biology courses, biology research papers that use quantitative methods, and the NRC report *Bio 2010.* Each participant completed a pre-workshop assignment from these resources. During the workshop participants developed a course syllabus and supporting curricular materials, worked through sample biology experiments, and completed sample computer exercises using modeling software such as STELLA. Participants are collectively creating a resource guide to be shared with others interested in developing similar courses.

Organizers:
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information has already led to improvement in crops, treatment of diseases, and revision in our understanding of the tree of evolution. Genetic data are used to prosecute criminals and document the migration of peoples; digital pictures help researchers find drugs that bind to biologically active sites; and networked computers enable specialist consultation across cities and continents.

Data, however, do not honor disciplinary boundaries. They are what they are, without labels that say "biology" or "physics" or "mathematics." So a data-intensive science tends to be an interdisciplinary science. Indeed, many signs suggest that science disciplines in general are converging, "drawn together by common mathematical and computational paradigms" and because areas of greatest current interest "transcend traditional academic disciplines."[28] Unquestionably, these changes are having their strongest impact in biology:

> How biologists design, perform and analyze experiments is changing swiftly. Biological concepts and models are becoming more quantitative and biological research has become critically dependent on concepts and methods drawn from other scientific disciplines. The connections between the biological sciences and the physical sciences, mathematics, and computer science are rapidly becoming deeper and more extensive.[29]

Thus the educational challenge of the new biology has two related but somewhat different dimensions. One is to recreate undergraduate biology as an interdisciplinary science, the other, to build high-capacity two-way bridges to the mathematical sciences.

Focusing on What Works

Changes in biology compel corresponding changes in biology education. Two fundamental issues are of central scientific importance:

- How to prepare students for a world where scientific boundaries are of diminishing importance.
- How to integrate the biological and mathematical sciences in students' undergraduate education.

A third is of utmost practical importance, namely:

- How to increase the number of biology students who are mathematically proficient and experienced in interdisciplinary work.

This latter issue is a direct consequence of the increasing importance and changing nature of biology. If biology

[28] Judith A. Ramaley. "Meeting the challenges in emerging areas." Keynote Lecture, Meeting the Challenges workshop, Feb. 27, 2003. URL: `http://www.maa.org/mtc/`.

[29] *Bio 2010,* op cit, p. 1.

What Works in Undergraduate Science Education

A thriving 'natural science' community is an environment where:

Learning is experiential and steeped in investigation from the very first courses for all students through capstone courses for students majoring in science, technology, engineering, and mathematics (STEM).

Learning is personally meaningful for students and faculty, making connections to other fields of inquiry, is embedded in the context of its own history and rationale, and suggests practical applications related to the experience of students.

Learning takes place in a community where faculty are committed equally to undergraduate teaching and to their own intellectual vitality, where faculty see students as partners in learning, where students collaborate with one another and gain confidence that they can succeed, and where institutions support such communities of learners.

— *What Works: Building Natural Science Communities*, Vol. I. Project Kaleidoscope, Washington, DC, 1991.

were only an esoteric corner of science of limited practical importance, society could probably rely on the few who emerge from the current educational system with strong backgrounds in both mathematics and biology. But the opposite is true. It is not only the science of biology but also its manifold applications in agriculture, medicine, biotechnology and now bioterrorism that will suffer without a significant increase in the number of graduates who are professionally literate in both the mathematical and biological sciences.

Questions about better approaches to biology education are an important part of higher education's broader need to revitalize in the face of challenges posed by changing world conditions. One expression of this agenda is the Greater Expectations undertaking of the Association of American Colleges and Universities (AAC&U).[30] The greater expectations urged in this project are motivated by the increasing interconnection of knowledge in a rapidly changing world that knows no disciplinary boundaries. In many respects, they extend the expectations of the New Biology across the curriculum.

A similar but more focused effort has urged educators in grades 10-14 to pay greater attention to quantitative literacy (QL) for all students.[31] As a deluge of data has forced biology to embrace more sophisticated mathematical tools, so increased reliance on data in other fields is having similar effects. If more students finished secondary school with good quantitative tools, college biology courses could incorporate models requiring a greater degree of mathematical sophistication. Even fluency and comfort with ratios and percentages would be a positive step, not to mention more advanced topics. As important, if biology courses embraced mathematical and quantitative models of biological phenomena, they would make their own significant contribution to students' quantitative literacy. Two support networks seek to advance the QL agenda: the National Numeracy Network[32] and a Special Interest Group on Quantitative Literacy[33] of the Mathematical Association of America.

Experience teaches that we cannot predict very well who among the 1.5 million entering college students will have the motivation and capacity for productive careers in the life and health sciences. Many students who flee science and mathematics have as much potential as those who stay.[34] Current patterns of early filtering—first select for science interest, then separate mathophiles from mahophobes—hardly works for the old biology, and clearly fails for the new biology. College is a period of awakening; most students change career interests and intended majors, especially during the first two years. Lower disciplinary boundaries facilitate this exploration. So too does teaching that is investigative, experiential, and connected (see sidebar).

Teaching for a multi-, inter- or non-disciplinary world will require reshaping education at all levels. Current faculty have been trained in disciplines, not across disciplines. Although deep disciplinary knowledge has been a strength of twentieth century science that focused on fundamentals (e.g., physics and chemistry), such narrowness is a handicap now that the frontier of science has

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30 *Greater Expectations: A New Vision of Learning as a Nation Goes to College,* Association of American Colleges and Universities, Washington, DC, 2002.

31 Bernard L. Madison and Lynn Arthur Steen, *Quantitative Literacy: Why Numeracy Matters for Schools and Colleges,* National Council on Education and the Disciplines, Princeton, NJ, 2003.

32 `www.math.dartmouth.edu/~mqed/index.html`

33 `www.css.tayloru.edu/~mdelong/qlsigmaa/frames.html`

34 Elaine Seymour and Nancy M. Hewitt, *Talking About Leaving: Why Undergraduates Leave the Sciences,* Westview Press, Boulder, CO, 1997.

moved on to integrative areas such as genomics, neuroscience, and ecology. Disciplines establish distinctive vocabularies, procedures, and standards for truth. They also build budgets and bureaucracies, both on campus and in the external worlds of policy and funding. If biology is to thrive as the interdisciplinary science that it has become, all these impediments will have to be overcome, if not eliminated. Sidebars throughout this paper illustrate how different organizations are addressing this important challenge. In addition, the National Research Council has begun summer workshops in support of *Bio 2010*[35] that will lend increased credibility to the effort to break down disciplinary silos.

The struggle to integrate the biological and mathematical sciences in students' education faces impediments that are arguably even greater than the general challenge of interdisciplinary study. As noted above, mathematics and statistics have long histories of modeling biological processes, but equally long traditions of separation in education. Because mathematical models are difficult for both students and instructors, because many were (as we have also noted) of limited effectiveness, and because so much biology could be taught by taxonomic and wet-lab methods without significant quantitative challenges, biology came to be seen by everyone as the least mathematical science. Once perceived this way, self-selection made it that way. Students entered the life sciences in part to limit their exposure to advanced mathematics. When they became professionals, the example of their own career and, often, their advice to students continued this tradition.

This era has passed. Whether they study molecules, cells, or ecosystems, future biologists will clearly need to understand and use sophisticated quantitative and computational tools. So too will anyone dealing with the societal impact of the new biology (genetically engineered crops, epidemics, antibiotic-resistant pathogens, bioterrorism,…). This includes every college student, not only future biologists. It is as important that ordinary citizens understand the new biology as that specialists do. Citizens who elect legislators, police officers who deal with threats, business leaders who make economic decisions, and school board members who set educational policy all need sound understanding of twenty-first century biology. In the new biology, evidence is as often mathematical as observational, as often quantitative as descriptive. In 2010, mathematics and biology will be just as entwined as were mathematics and physics in 1910. We may then marvel, as Wigner did in an earlier era, at the unreasonable effectiveness of mathematics as a tool for explaining how living things function.

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[35] William Wood and James Gentile. "Meeting Report: The First National Academies Summer Institute for Undergraduate Education in Biology." *Cell Biology Education,* 2 (Winter 2003) 207–209.