Getting Started in Mathematical Biology

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Mathematicians are sometimes known in high school biology classes for their tendency to faint during dissections and their ability to cook experiments to fit straight lines. In spite of these impressions, mathematicians and biologists, including medical scientists, have a long history of working successfully together.

Sophisticated mathematical results have been used in and have emerged from the life sciences. Examples are given by the development of stochastic processes and statistical methods to solve problems in genetics and epidemics [1, 2] and in recent articles in these *Notices* on DNA topology and the genome project [3, 4]. Aristotle, Pythagoras, Fibonacci, Cardano, Fourier, Gauss, von Helmholtz, Riemann, Einstein, d'Arcy Thompson, Turing, Wiener, von Neumann, and Keller are other names associated with both significant applications of mathematics to life science problems and significant developments in mathematics motivated by the life sciences.

Mathematical biology, like mathematical chemistry and physics, is a highly interdisciplinary area that defies classification into the usual categories of mathematical research. The area lies at the intersection of significant mathematical problems and interesting biology. Work in the intersection is referred to here as being mathematical biology, but labels and the taxonomy of who works on what in this interdisciplinary field are unimportant. We have moved beyond the early question "Is it mathematics?" The value of mathematics comes partly from routine applications of statistics and calculus to solving life science problems, but more importantly from the sophisticated point of view it can bring to complicated real life problems.

Mathematical scientists and many more from physics, chemistry, engineering, and medicine have developed and used mathematical methods in biology problems, and so it is difficult to give an accurate sense of the scope of influence mathematics has had in biology. However, we try here to give a rough description of important areas for interaction, to illustrate some interesting research problems, to point out some known pitfalls, and to report some experiences of those getting into mathematical biology.

Activity in mathematical biology is at an all time high! Interest ranges from entry level undergraduate courses to advanced research by some of our best workers and from elementary and secondary education to the popular press [5, 6]. Some mathematics departments have significant strength in this area, and most major departments now have faculty working in collab-

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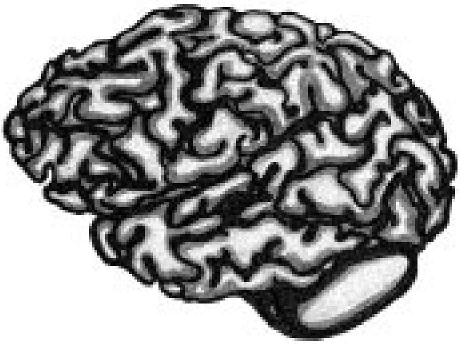
oration with life scientists. There are significant problems involving interesting mathematics in almost all areas of life and medical sciences that need the attention of mathematicians.

What are important areas of biology? The National Research Council [7] identified eleven major themes in biological research:

1. Cell organization
2. Ecology and ecosystems
3. Evolution and diversity
4. Genome organization and expression
5. Growth and development
6. Immune system, pathogens and host defenses
7. Integrative approaches to organism function and disease
8. Molecular structure and function
9. Neurobiology and behavior
10. New technology and industrial biotechnology
11. Plant biology and agriculture

Mathematics has influenced almost all of these areas.

The longstanding interaction between mathematical methods and biology is illustrated by one of the major problems facing neurobiology and behavior: How does a brain work? Mathematics has long played a role in studies of the brain, ranging from early work of von Helmholtz [8] who sought an energy-like function to describe physical and chemical bases of brain dynamics, through work of Norbert Wiener on Cybernetics (the study of biological control mechanisms [9]), to mathematical studies of the nervous system [10], and finally to quite recent work using mathematics to study consciousness [11].



Neurons, or nerve cells, are the basic building blocks of the nervous system and the brain. They are complicated, having electrical, mechanical, and chemical aspects. Their electrical activity is dominated by ionic currents passing through their membranes, and mechanical deformations of neurons and their interconnections are caused by contractile proteins in them. Neurons communicate primarily by passing powerful chemicals, called neurotransmitters, from one to another. There are many kinds of neurons, and what they do and how they work is still mostly unknown although significant progress is being made on these questions across many disciplines.

There is a basic fill-and-flush dynamics in the ionic currents in neurons that has been captured by mathematical models. Hodgkin's and Huxley's Nobel Prize-winning work on nerve membranes proposed a model, though one not central to their work, of the form

$$\dot{V} + V = f(W, V)$$
$$T(V)\dot{W} + W = g(W, V)$$

where V denotes the voltage across a patch of nerve membrane and W is a vector of (phenomenological) recovery variables. When stimulated, V increases and causes the opening of ionic channels in the membrane that are described by the variables in W. Opening and closing of channels is triggered by V as it passes through various threshold values and the variables in W describe depolarization and recovery of the membrane. This is accounted for in the model by the form of the functions T, f and g. Models of this sort have been extensively studied by mathematicians. Notably, Lapicque (1907), van der Pol (1926), Littlewood and Cartwright (1940s), Levinson (1950), Smale (1960), and many others as reported, e.g. in [12].

Networks of neurons have been successfully studied as well. An important feature of neurons acting together is the timing of their activity. So, models have been devised that make accessible phase information and ensemble behavior.

These can be viewed in the following way. Consider the region of a neuron where voltage spikes are formed, and denote its voltage at time t by $V(\phi(t))$ where V is a voltage wave form ($\cos\phi$ is a reasonable choice) and ϕ is the voltage phase at time t. This typically has the (asymptotic) form $\phi(t) \approx \omega t + \phi_0$ where ω is the firing frequency and ϕ_0 is a phase lag or lead.

The equations

$$\dot{\phi} = a$$
$$\tau\dot{a} + a = \omega + \beta\cos\phi$$

describe the dynamics of such a neuron model. The variable a describes the cell's activity (here its firing rate) and ϕ the cell's action potential phase. The data τ, β, and ω describe a time delay, tuning and driving frequency, respectively. This model is in the spirit of the nonlinear pendulum (anharmonic oscillators), and it has been extensively studied in many contexts including mechanics, power systems, super conductivity, phase-locked loop integrated circuits, and quantum mechanics.

Networks of neurons can process information by passing appropriate signals on to other brain or body systems and they can store and retrieve information. Information may be in terms of chemical concentrations or in terms of electrical pulses.

A network of N such models is described by the system of differential equations

$$\begin{aligned}\dot{\phi}_j &= a_j\\ \tau \dot{a}_j + a_j &= \omega_j + \beta_j \cos \phi_j\\ &\quad + \sum_{k=1}^{N} (C_{k,j} f(a_k) + E_{k,j} V(\phi_k))\end{aligned}$$

for $j = 1, \cdots, N$ where $f(a)$ is an S-shaped function (e.g., $f(a) = 1 - e^{-a^2}$ for $a > 0$), or an $\cap$-shaped function, and the matrices C and E describe the network's chemical and electrical connections, respectively.

When $\beta = 0$ and $E = 0$, this network can be a gradient system with respect to the activities a, and the underlying potential function describes the remembered states of the system, and so it represents a kind of energy for the system. Work on spin-glass models and adaptive filters is in this direction [13].

Under other conditions, the system may have an invariant torus, say $a = A(\phi)$ of dimension N, and the flow on it can be a combination of stable torus knots (phase-locked quasi-periodic motions) and unstable ergodic behavior. Work on phase models is in this direction [12, 14].

The mathematical problems revolving around such systems touch on bifurcation, perturbation, and stability theories for dynamical systems [15], differential geometry, variational theory, and the geometry of knots. There is an abundant store of good mathematical problems residing in such systems.

Another rich direction mathematicians have taken toward brain dynamics began with work of Turing, McCulloch and Pitts [17], and Kleene. In these, a neuron is modeled as being a 0-1 device, so the state of a network at any instant is described by an array whose elements are zeros and ones. Turing machines [16, 18] and recursive function theory [19] are fundamental mathematical results related to this work. On the other hand, McCulloch's and Pitts's approach blended nicely with later developments of spin-glass models in physics and ultimately with recent developments of such models [20].

Finally, recent work on neurons has led to speculation that quantum mechanical aspects of them are related to consciousness, attention, and understanding. Thus, Schroedinger's equation and the paradoxes of quantum mechanics have come into discussions of brain dynamics as well. These exciting developments will blossom over the next decade and beyond, with possible connections to algebra, algebraic geometry, complex analysis, and topology through new mathematical theories that fill the gap between quantum mechanics and relativity [11, 21].

The impact of mathematical work on understanding the brain has been copious and significant, but not always obvious. For example, there is a direct bridge from von Helmholtz to Freud (oddly enough through a professor named Bruecke), who used the idea of psychical energy as a basis for his work on catharsis [22], and to Jung who investigated synchronicity [23]. Work by these psychoanalysts has fed back in many ways to influence scientific thought about the brain.

Can mathematicians and biologists collaborate? There are some basic problems to be overcome. R. Thom [24] identifies a possible philosophical obstacle to collaborations between life scientists and mathematicians. He points out that two principal approaches are taken toward modeling: ordinary language models, that are precise where data are known and suitably vague otherwise, and mathematical models that are reduced to minimal parts but still produce results consistent with experimental observations. In some senses, the issue is one between analysis and synthesis: one can synthesize a mathematical model and analyze its solutions, or one can analyze a phenomenon and synthesize a word model for it. Hopefully, iteration between these two approaches leads to useful descriptions of biological phenomena and new insights to mathematics. At various stages during this iterative process, the ordinary language model that is being analyzed and the mathematical model that is being synthesized are reviewed and updated. Resynthesis of the word model and analysis of the solutions of the mathematical model are included in this review.

This is not quite as simple as it might sound.

Following is a fanciful interaction between imaginary word and math modelers. While modeling in this illustration uses differential equations, the illustration could as well have been done with orientation reversing fission in some bacteria leading to a discussion of the dunce's cap in point set topology and back to discovery of three dimensional dynamics of cell division, or comparing two strands of DNA leading to a discussion of correlation matrices and Fourier analysis of them. This example is chosen because it involves widely known and straightforward mathematics. An interesting thing about joint work is the discovery of new mathematical problems, which this fictional dialog does not really capture. Still, the example does indicate the economy of word models and the convergence of theory and experiments, and it serves to identify some obstacles to collaboration.

Word: After a population of bacteria is exposed to an alternating starvation-nutrition regimen for a while, we observe that the cells synchronize their division times many generations into the future.

Math: Let $B(t)$ be the number of bacteria at time t. Then under steady conditions we have

$$\frac{dB}{dt} = AB$$

where $\log 2/A$ is the cell doubling time. If we use A as a control variable by alternately setting it to 0 and $A_{\max}$ to reflect starvation and nutrition, respectively, and then eventually setting it equal to $A_{\max}$ we see no mechanism for creating or sustaining oscillations. Are there time delays in the system?

Word: The life cycle of a bacterium is in four parts:

G_1, the first gap interval when we believe materials are taken up for metabolism and to prepare for DNA synthesis,

S, an interval during which DNA is synthesized in the cell,

G_2, the second gap interval in which the cells prepare for division,

Mitosis during which cell fission occurs. This interval is quite short compared to the others.

Math: Let p denote the cell cycle phase, and let p_1 and p_2 denote the boundaries between intervals, so G_1 corresponds to $0 \le p < p_1$, S corresponds to $p_1 \le p < p_2$, G_2 corresponds to $p_2 \le p < 1$, and cell division corresponds to $p = 1$. Let $u(p,t)$ denote the number of cells at cell cycle phase p at time t. Then conservation of bacteria implies

$$\frac{\partial u}{\partial t} + A\frac{\partial u}{\partial p} = 0$$

A denotes the ageing rate of bacteria, i.e., the rate at which they progress through the cell cycle. Cell fission is described by the boundary conditions

$$u(0,t) = 2u(1,t)$$

We can solve this model using the method of characteristics by solving the characteristic equations

$$\frac{dt}{ds} = 1$$
$$\frac{dp}{ds} = A$$

on the cylinder $\{(t, p \bmod 1)\}$ Again, we can use A as being a control variable, but when we analyze the model, we see no mechanism for bringing cells to similar phases or for sustained oscillations in cell division when A is eventually set to a constant $A = A_{\max}$.

Is there something in the cell cycle that could lead to convergence of the characteristics, and so bring several cell lines to division at nearly the same time?

Word: After some experimentation, we see that during starvation the cells seem to progress through the synthesis stage even though there are no external nutrients.

We deduce that cells do not start synthesis until they have enough material to complete it.

Math: Keen observation! So A can change with p, too: We write $A = A(p,t)$. Then

$$\frac{\partial u}{\partial t} + \frac{\partial}{\partial p}(A(p,t)u) = 0$$

For $p \in [p_1, p_2)$ we set $A = c$, a constant corresponding to the observed rate at which a cell passes through synthesis, and in G_1 and G_2, we set $A = \alpha$, which we will use as a control variable. During starvation, we set $\alpha = 0$ and during nutrition $\alpha = \alpha_{\max}$.

Now, we see that during starvation the characteristics will accumulate at the end of the S phase. This is a mechanism for converging cell lines. Since there is no mechanism for changing synchrony under steady nutrition, synchrony will be sustained into the future.

The project is wrapped up by experimental determination of relevant rates, calculation of optimal starvation-nutrition cycling to synchronize all cell reproduction in the shortest time using the model, experimental corroboration of suggested optimal schedules, generation of model control charts to use as diagnostic tools to test the differences between bacterial species and genetic types, computation of the rate at which synchrony might be lost if noise is introduced, and production of a written record of the work, perhaps for publication.

This is not to say that collaboration will stop at this point since there are numerous new experiments and mathematical problems suggested by the project.

It is clear that there are a number of points in this interaction where philosophical differences, unsuccessful mathematical modeling or analysis, or incomplete experiments could block success. Among the impediments to joint projects are the following:

First, there is legitimate reluctance by life scientists to invest effort in understanding preliminary mathematical characterizations of a phenomenon when they could be “just going ahead and doing the experiments”.

Second, there are linguistic barriers. For example, the precision of word models depends on interpretation of the words. One sees scientists disagreeing over the interpretation of data (How can you interpret my data correctly? You never did a rotation in my lab!). In addition to interpretations, there are other communication barriers: Often mathematical modelers do not appreciate the subtlety and complexity of word models; on the other hand, biologists often do not "speak mathematics". Various languages enable one to create new words of increased precision that is not so easy in other languages. Finally, there are cultural differences to be aware of. For example, modes for funding graduate students and postdocs in the two disciplines are quite different. Mathematics often supports students through the use of teaching assistantships while for the most part biologists support their graduate students through grants. The pressures on both sides shape attitudes of researchers as to how "blue sky" an approach one can take.

Third, there are some deep-seated conflicts between rationalists and irrationalists dating back at least to the Enlightenment [25] that manifest themselves when one threatens to mathematize some biological phenomena. For example, work on consciousness is sometimes dismissed as being too close to God.

Finally, even when the iterative process between word and math models converges, it can be difficult to communicate the results effectively to both audiences.

Meetings of combinations of mathematicians, biologists, and engineers are now frequent, and they attract excellent minds (e.g., [35, 36]). These are important for helping to develop common languages for communication between biologists and mathematical scientists, and so for breaking down some of these barriers. We need more such meetings—especially seminars in university and industry settings.

Is one approach better than the other? There are compelling reasons for pursuing both word and math models. Obviously, new biological facts are needed to be uncovered through experiments, and the results must be communicated in accurate and accessible ways. Word models are entirely appropriate.

On the other hand, mathematics has proven to be useful in many important ways.

First, there are many developments in both biology and in mathematics that have benefited by iteration, not always in phase, between biologists and mathematicians. Irregular solutions of nonlinear difference equations arising in ecology models [26] eventually were explained by mathematicians in subsequent work on chaos [5]. Early developments in probability theory motivated by studies of Mendel's and Darwin's theories of genetics and evolution [1] led to development of statistical methods that now form a major part of descriptions of most experiments. They also (should) play a major role in the design of experiments [27]. These developments over the past seventy-five years have established mathematics as being important in suggesting, designing, and interpreting experiments.

Second, the power of mathematics to synthesize models and analyze their solutions is important, for example, in determining boundaries between equilibrium and nonequilibrium biology. For instance, the Kermack-McKendrick threshold theorem gives a dimensionless parameter that is useful in determining when a population is at risk for propagation of a disease resulting in an epidemic [28, 29, 30]. Similar problems are ubiquitous where risk analyses are derived and applied, for example to pesticides [21, 31].

Third, a mix of analysis and geometry brings to biological problems methods that are useful for the study and visualization of higher dimensional structures. For example, joint work on tomography by mathematicians and radiologists has been and continues to be highly successful [32, 33].

Finally, (for this list at least) mathematical models make it possible to bring high-speed computers to bear on biology problems. Large scale applications at present are in the design of drugs and analysis of genome organization [33, 34].

How to get into mathematical biology? Fortunately for us, biology is more descriptive than mathematics, and most of us can pick up a general biology text and understand the underlying ideas and concepts presented there. This is not the case for many biologists with regard to books on differential equations or probability theory, for example. Sensitivity to these issues facilitates collaborations with life scientists.

Here are some suggestions for starting work on problems in mathematical biology.

Why might a biologist be interested in working with a mathematician? It was once put to me this way—You don't know [much] about the experiments so you won't get in my way, and you can probably write great lab reports! Expect some good-humored abuse, but find a biologist who is interested in the possibilities that mathematics might offer to his or her area of research. Do some homework on the area to lay a basis for communication. While this sometimes doesn't work at all (maybe at best you are asked to perform a chi-squared analysis of some data or to write a computer program to do least squares estimations), often it pays off handsomely. A good place to start for leads might be with the chairperson of the local biology department.

What areas of mathematics might be useful in biology? Essentially all areas. Traditional areas arising in mathematical models include bifurcation, perturbation, and stability methods for dynamical system. Topological methods for knots arising in DNA dynamics and structure and in torus flows related to phase-locking of oscillators are important. In addition, input-output analysis of systems (e.g., energy budgets, ecology, physiology, systematics), pattern recognition algorithms (e.g., medical diagnosis), mechanics of artificial limbs, continuum mechanics of organs (e.g., visco-elasticity, fluid flows), electronic circuits to replace parts of our nervous systems (TV vision, electronic hearing, artificial olfaction, etc.), and even quantum mechanical aspects of brain function as noted earlier are rich areas for mathematical investigation.

Start joint seminars for people from both sides (math and biology). A mathematical biology seminar for undergraduates is usually very popular with students, and there are useful texts available [38, 39, 40, 41, 42]. Also, consider organizing a meeting for the American Mathematical Society, the Society for Industrial and Applied Mathematics, or the Society for Mathematical Biology.

Select projects that have interesting mathematics in them and that address significant biological problems. While this is often difficult to see, there are many significant biology problems that can benefit from high-level mathematical results and at the same time generate new mathematics.

Once a problem area is identified that interests you, invest some time in seriously studying the biology. This can be done by sitting in appropriate courses, working together with postdocs or students in biology labs, or in collaboration with faculty, or by yourself in the library. A good book series that introduces mathematical topics in a wide variety of life science areas is the *Cambridge Studies in Mathematical Biology* [37]. You can also get ideas for where to go for problems and references by contacting friends through e-mail or telephone.

Try to publish in journals dealing with the biological area of interest. This is not easy, but it sets high standards for biological content. This might require learning new ways to write mathematics, for example, deferring derivations to a technical appendix, and it often requires co-authorship with a biologist.

It is interesting and useful to learn new areas and to meet other scientists who approach problems from points of view different from mathematicians. It is also interesting to see how their laboratories, departments, and funding sources function. Mathematical biology provides unusual opportunities for making contact with biologists in ways that can result in useful new knowledge about us and where we live.

The areas touched on in this article are not meant to be exhaustive. I am happy to say that such a project is virtually impossible because of the huge literature involved. Also, the choice of references in this article is rather idiosyncratic. It is done by design to indicate some contributions and directions that are not widely known among mathematicians. The default in many people's minds about mathematical biology is the Volterra-Lotka-Kolmogoroff system or results from Rashevsky's school. We see here that there are many other people involved in mathematical biology. You could be too.

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