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MATHEMATICS IN BIOLOGICAL APPLICATIONS

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ABSTRACT

BTEM (Biology, Technology, Engineering, Mathematics) is to cultivate scientific inquiry that requires coordination of both knowledge and skills simultaneously. Biology requires interdisciplinary approaches across different disciplines, such as engineering, computer science, physics, chemistry and mathematics to deal with higher level of complex problems, especially related to health, food, energy and environment which are becoming more dependent on other disciplines to collaborate in providing new applicantions, new methods, new techniques and new tools. Biology of genomics is for real, and it is indeed tremendously exciting as a result of dramatic improvements in underlying technologies.

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."

The principal goal of interdisciplinary approach for Biology, Technology, Engineering and Mathematics (BTEM) is to cultivate scientific inquiry that requires coordination of both knowledge and skills simultaneously. The dominant activity for BTEM is inquiry-discovery on the authentic problems. This is intended to enhance the students' abilities to construct their own knowledge through the relevant hands-on and minds-on activities. The essence of engineering is inventive problem solving. The Integration of advanced information communication technologies believed to be able to fulfill current Net Generation learning styles. Mathematics plays an important role as computational tools. The expected outcome of BTEM implementation is the inculcation of 21st century skills.

INTRODUCTION:

Interdisciplinary can be defined as a knowledge view and curriculum approach that consciously applies methodology and language from more than one discipline to examine a central theme, issue, problem, topic, or experience. One of the typical strategy used in the interdisciplinary approach is problem-centric, it connects knowledge from several disciplines to examine complicated real-life problems [1]. Interdisciplinary approach is implemented with the idea that subject-specific learning is neither important nor relevant to young school leavers in the twenty-first century [2].

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The 21st century biology requires interdisciplinary approaches across different disciplines, such as engineering, computer science, physics, chemistry and mathematics to deal with higher level of complex problems, especially related to health, food, energy and environment which are becoming more dependent on other disciplines to collaborate in providing new applicants, new methods, new techniques and new tools [3-5]. The new biologist of the twenty-first century should be: "The New Biologist is not a scientist who knows a little bit about all disciplines but a scientist with deep knowledge in one and a "working fluency in others". Teaching through this new interdisciplinary perspective requires new approaches, materials and pedagogies as well [6- 7, 4]. Solving complex, interdisciplinary problems will require that students go far beyond their biology content knowledge only. They are required to understand what connections exist across disciplines and how to make those connections. Preparing future biologist without offering them the exposure and experience with engineering and technology, will fail to survive in the competitive environment [8,7]. For this conceptual framework, the core knowledge is focus on biology discipline. Application of Information and Communication Technology (ICT) during T&L processes is highlighted in technology discipline; the skills includes surfing internet for relevant information, usage of e-tools for communication purposes and application tools provided by the Microsoft office (MS Words, MS Power point, MS Excel etc.).Technology has been immersed as part of the students' life with the integration of ICT in science T&L .Rapid advances in information technologies have changed the learning styles of many students of the Net Generation. These students have grown up in a world where technology is second nature to them [9]. Online social networking and electronic-based resources are increasingly being used to enhance student understanding and interest in biology [10]. ICT also encourage learning in a constructive context [11]. The fragmented or separated teaching of biology and mathematics has blocked the integration

"Algebraic Statistics for Computational Biology". have three related ideas: 1. that the language, techniques and theorems of algebraic geometry both unify and provide tools for certain models in statistics, 2. that problems in computational biology are particularly prone to depend on inference with precisely the statistical models amenable to algebraic analysis and (most importantly) 3. mathematical thinking, by way of considering useful generalizations of seemingly unrelated ideas, is a powerful approach for organizing many concepts in (computational) biology, especially in genetics and genomics.

Given a phylogenetic tree describing the evolutionary relationship among n extant species, one can examine the evolution of a single nucleotide along the tree. At the leaves, a single nucleotide is then associated to each species, collectively forming a single selection from among the 4^n possible patterns for nucleotides at the leaves. Evolutionary models provide a way to formalize the intuitive notion that random mutations should be associated with branches of the tree and formally are described via (unknown) parameters that can be used to calculate a probability for any pattern at the leaves. It happens to be the case that for most phylogenetic evolutionary model has the property that the probabilities for leaf patterns

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are *polynomials* in the parameters. The simplest example to consider is the tree with an ancestral node and two leaves corresponding to two extant species, say "B" and "M".

The molecular approach to evolution posits that multiple sites together should be used both to estimate parameters associated with evolution along the tree, and maybe even the tree itself. If one assumes that nucleotides mutate according to the 4-state general Markov model with independent processes on each branch, and one writes p_{ij} for $\mathbb{P}(B = i, M = j)$ where *i,j* are one of *A,C,G,T*, then it must be the case that $p_{ij}p_{kl} = p_{il}p_{jk}$. In other words, the polynomial

$$p_{ij}p_{kl} - p_{il}p_{jk} = 0.$$

In other words, for *any* parameters in the 4-state general Markov model, it *has*to be the case that when the pattern probabilities are plugged into the *polynomial* equation above, the result is *zero*. This equation is none other than the condition for two random variables to be independent; in this case the random variable corresponding to the nucleotide at *B* is independent of the random variable corresponding to the nucleotide at *M*.

The example is elementary, but it hints at a powerful tool for phylogenetics. It provides an equation that must be satisfied by the pattern probabilities that does not depend specifically on the parameters of the model (which can be intuitively understood as relating to branch length). If many sites are available so that pattern probabilities can be estimated empirically from data, then there is in principle a possibility for testing whether the data fits the *topology* of a specific tree regardless of what the branch lengths of the tree might be. Returning to Mumford's description of algebraic geometry, the *variety* of interest is the geometric object in "pattern probability space" where points are precisely probabilities that can arise for a specific tree, and the "ring of polynomials with the geometric properties of the locus" are the phylogenetic invariants. The relevance of the ring lies in the fact that if *f* and *g* are two phylogenetic invariants then that means that $f(P) = 0$ and $g(P) = 0$ for any pattern probabilities from the model, so therefore $f + g$ is also a phylogenetic invariant because $f(P) + g(P) = 0$ for any pattern probabilities from the model (the same is true for $c \cdot f$ for any constant c). In other words, there is an *algebra* of phylogenetic invariants that is closely related to the *geometry* of pattern probabilities. As Mumford and Tate explain, Grothendieck figured out the right generalizations to construct a theory for *any* ring, not just the ring of polynomials, and therewith connected the fields of commutative algebra, algebraic geometry and number theory.

The simple example of the two taxa tree and delves deeply into the subject. Two surfaces (conceptually) represent the varieties for two trees, and the equations $f_1(P) = f_2(P) = \ldots = f_l(P) = 0$ and $h_1(P) = h_2(P) = \ldots = h_k(P) = 0$ are the phylogenetic invariants. The empirical pattern probability distribution is the point $\hat{P}$ and the goal is to find the surface it is close to:

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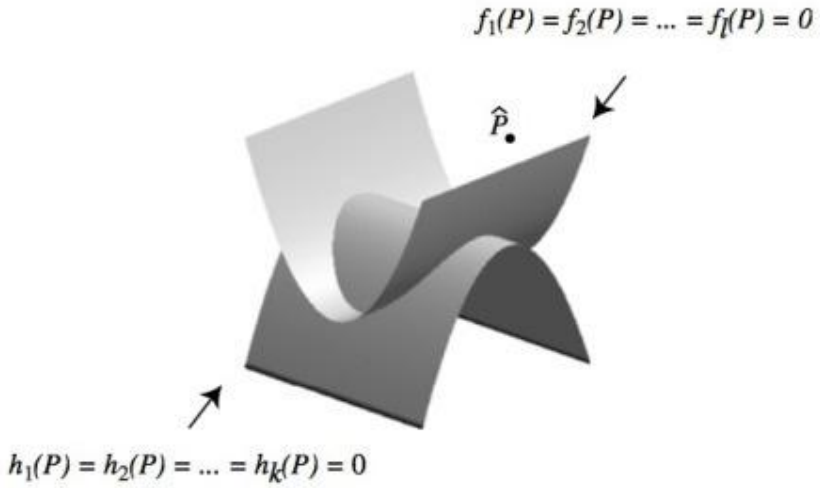

Figure 4.2 from Allman and Rhodes chapter on phylogenetic invariants.

Of course for large trees there will be many different phylogenetic invariants, and the polynomials may be of high degree. Figuring out what the invariants are, how many of them there are, bounds for the degrees, understanding the geometry, and developing tests based on the invariants, is essentially a (difficult unsolved) challenge for algebraic geometers.

When it comes to genomics journalists write about revolutions,precision medicine, curing cancer and data deluge. But the biology of genomics is for real, and it is indeed tremendously exciting as a result of dramatic improvements in underlying technologies (e.g. DNA sequencing and genome editing to name two).we can believe it is true that despite what is written about data deluge, experiments remain the primary and the best way, to elucidate the function of the genome. Data analysis is secondary. But it is true that statistics has become much more important to genomics than it was even to population genetics at the time of R.A. Thequantitative sciences for biologyplaying important role for mathematics.

Of course sometimes theorems are important, or specific mathematical techniques solve problems and mathematicians are to thank for that. Phylogenetic invariants are important for phylogenetics which in turn is important for comparative genomics which in turn is important for functional genomics which in turn is important for medicine.

Computational biology where it is not yet clear what “right” thinking should be despite the experts working hard at it, and that is useful to highlight because of the people involved: With the vast amount of human genomes being sequenced), there is an increasingly pressing fundamental question about how the (human) genome should be represented and stored. This is ostensibly a computer science question: genomes should perhaps be compressed in ways that allow for efficient search and retrieval, but I’d argue that fundamentally it is a math question. This is because what the question is really asking, is how should one think about genome sequences related mostly via recombination and only slightly by mutation,

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The math-bio combination has been an exercise in extremes. There was an identified need to more quantitative analysis and modeling in the biosciences. But most of the attention has focused on mathematics and statistics. Forgotten are the legions of physicists, chemists, and engineers who in my opinion could have had a much more direct and immediate impact on biology. Somehow a biologist, when told basic math is required (maybe calculus!?) would then seek out a mathematician.We can see how most problems would not intrinsically interest a mathematician, but that a physicist would find "nice." Basically, biologists in general do not have a high enough resolution on the other physical sciences.

In the end though, We can say what is most dangerous is a biologist who thinks they understand mathematical modeling, rather than the other way round. They go off and do the "math" or modeling or analysis themselves, spreading wrongness. This 9 steps back, and 10 steps forward approach should have been better mitigated early on.

We do think that the language barrier is MUCH higher between math and biology than it is between physics and biology, or say, chemical engineering and biology.We think, this whole effort of quantifying the biosciences, was carried about rather inefficiently by not planning and understanding what all fields had offer. This is why there is some division between physics and math approaches to biology.

Other mathematical habits we also found valuble were going around and just inventing arbitrary structures and seeing what happens. Allied with this is the experience of creating a set of definitions (a group) or a set of constraints (having only one and self as factors) and then figuring out all the examples that follow these and exploring the variety you get. (i.e. def of platonic solid or prime number of group gives you some wild variety but not infinitely chaotic variety) it is this background that gives me the intuition that of course given the properies of bacteria they can have evolved into all life on earth, or given the properties of chemical interactions, two dozen different elements can spontaneosly form into life.

All areas of biology are so full of crazy complexity that thinking about them would benefit from having had the experience of making the abstractions one does in basic mathematics (the nested sequence of number spaces, the crazy habits of things like studying functions between number spaces and then .. what the hell .. make a number space out of functions… Topology...).Statistical genetics and statistics have had a long association (both disciplines share common founders such as R.A. Fisher) so the relation between stats and the stochastic data analysis end of genomics has a history. In much of genomics, stochastic models and data analysis methods that incorporate randomness are required. The stochastically oriented people in math departments have traditionally been probabilists, to be flip if you take a probabilist and make them do data analysis and inference you get a statistician . [8] proposed a principle in which another NN yield input control law was created for an under incited quad rotor UAV which uses the regular limitations of the under incited framework to create virtual control contributions to ensure the UAV tracks a craved direction. Utilizing the versatile back venturing method, every one of the six DOF are effectively followed utilizing just four control inputs while within the sight of un demonstrated flow and limited unsettling influences. Elements and speed vectors were thought to be inaccessible, along these lines a NN eyewitness was intended to recoup the limitless states. At that point, a novel NN virtual control structure which permitted the craved translational speeds to be controlled utilizing the

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pitch and the move of the UAV. At long last, a NN was used in the figuring of the real control inputs for the UAV dynamic framework. Utilizing Lyapunov systems, it was demonstrated that the estimation blunders of each NN, the spectator, Virtual controller, and the position, introduction, and speed following mistakes were all SGUUB while unwinding the partition Principle.

Molecular biology has historically been deterministic and did not use mathematics. This changed with sequencing technology and the need for alignment tools.The alignment questions and problems are very algorithmic and quickly fell under the purview of computer science. Now where discrete math, algorithms, theoretical computer science divides between computer science and math is another issue.We can say that even in computer science the more applied end has been more involved in genomics.

Until the need for theory in biology becomes obvious to biologists, and until the need for collaboration with the life sciences becomes obvious to the mathematics community, we have no choice but to rely on a small “coalition of the willing” to do the sort of work. The problem that we don’t see often stated is that there is a minimal level of mutual understanding of each other’s fields that is needed for these areas of fruitful collaboration to be identified. And because mathematics and biology are so divergent, this is very difficult to achieve. There is a significant asymmetry here too – a mathematician can learn a lot of biology much more easily than a biologist can learn a lot of math (that’s why there are so many mathematicians who successfully moved into biology), because biology is mainly broad, while math is very deep.But for the full potential to be realized, it is necessary for biologists to learn more math, which can only be meaningfully achieved at the training level (starting as early as high school, not at the graduate level). we have seen mathematicians saying the the role of the mathematician is to provide tools for the scientists to use in their research. Well, that can only work out if the scientists know what tools are available, and this is not at all the case at the moment because of the huge upfront cost associated with learning advanced math. we know that in general, “knowing more math” might help me with research. the problem is that we don’t really know what math and neither I, nor anyone can learn all the math in the world (because the subject is really huge), much less at depth Physics and math have had a fruitful relationship because the subjects have never been that far apart, and because there is a commonly and fairly well understood, quite large and deep body of mathematics that a theoretical physics needs to learn, that was arrived at in much better times for science in general. In biology we can’t even start bridging the gap, and because of how messed up institutionally and culturally biomedical research is right now, that’s not going to change any time soon.Both the biologist and mathematician seek to feel relevant by applying their training to real problems. What is often not understood about mathematics is that abstraction is about analogy. When one talks about the “commutative law” x*y = y*x one notes that

itapplies to addition and to multiplication, so part of an anlogy.

To a mathematician reality is just a special case.” Biology is a very special case of reality. I tell my students that mathematics is that which is true on every universe. Intelligent beings in a universe without DNA will rediscover schemes. You don’t have to like abstraction or be good at it to recognize its importance—this is true even for mathematicians.

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Thought experiment: replace some of the math jargon in the obituary with words like "enzyme" or "chromosome". This would be acceptable to nature and a lot of pretty fair scientists would have only a vague working idea of exactly what these things are and what their precise structure is.

If the unit of physics is an atom, then the unit of life is a cell; but a cell is infinitely more complex. A cell in mammals typically contains 300 million molecules. Some are very large, such as the DNA molecules, which consist of many millions of atoms. But a cell is not just a huge collection of molecules. The cell maintains control and order among its molecules as exemplified, for instance, in the DNA-RNA-protein machinery. A cell absorbs nutrients and generates biomass to perform specific functions, such as secreting chemicals or engulfing pathogens; it adapts to its microenvironment by moving toward sources of nutrients or by remaining quiescent when resources are scarce, and a cell replicates when conditions are favorable. Consequently, mathematical modeling of cellular processes is quite challenging [12]. Furthermore, since the human body has 1013 cells of different types and functions continuously talking to each other, it is quite clear that mathematical models of biological processes are extremely challenging. Even the most successful models can be expected to deal only with limited situations, ignoring all but the most essential variables. Work in mathematical biology is typically a collaboration between a mathematician and a biologist. The latter will pose the biological questions or describe a set of experiments, while the former will develop a model and simulate it.

Ischemic Wounds Chronic wounds represent a major public health problem worldwide, affecting 6.5 million individuals annually in the United States alone. Vascular complications commonly associated with problematic wounds are primarily responsible for wound ischemia (shortage of blood flow), which severely impairs healing response. Recent experiments with a porcine model to study healing in a preclinical approach were conducted by Roy et al. [13]. In those experiments a full-thickness bipedicle dermal flap was developed first, such that blood supply was isolated from underneath the flap and from two long edges, as shown in. One circular wound was then developed in the center of the flap (ischemic wound) and another on the normal skin (nonischemic wound) of the same animal as a pair-matched control. In order to determine therapeutic strategies that may help heal ischemic wounds, Xueet al. [14] developed a mathematicalmodel that incorporates the main variables involved in the wound closure phase of the healing process, namely, several types of blood and tissue cells, chemical signals, and tissue density. The model was formulated in terms of a system of partial differential equations in a viscoelastic, partially healed domain where a portion of the boundary, namely the open wound's surface, is a free boundary unknown in advance. 852 [14]. The open wound is the circular region $\{0 \leq r \leq R(t)\}$, the partially healed region is the annulus $\{R(t) \leq r \leq R(0)\}$, and the normal healthy tissue is $\{R(0) \leq r \leq L\}$. However, each simulation of the free boundary problem in the 3-dimensional geometry takes too much time. The challenge then was how to simplify the geometry while still imposing conditions of ischemia. Xue et al. [14] assumed that the wound is circular, but that many small incisions of size δ are made at $r = L$ with adjacent incisions separated by distance ϱ. Taking $\delta, \varrho \rightarrow 0$ in appropriate proportions and applying homogenization theory, they deduced that each

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boundary condition u = us (for a solution of Δu = f) before the incisions changed into a boundary condition (1 − α)(u − us) + α ∂u ∂r = 0 at r = L after the incisions were made, where α is a measure of ischemia; α near 1 means extreme ischemia. Figure 3 shows simulations of the radii of the open ischemic and nonischemic wounds over a period of twenty days. The results are in tight agreement with the experimental results of Roy et al. [13]. The model is now going to be used as a tool to suggest biologically testable hypotheses for improved healing, thereby reducing the need for guesswork and time-consuming animal testing. Cancer-Inspired Free Boundary Problems The mathematical theory of free boundary problems has developed extensively over the last forty years, but the range of new applications has remained modest. Recently, histological changes in biology offered new [14]. Radius of ischemic (α = 0.92) and nonischemic wound (α = 0) over a period of twenty days. The nonischemic wound closes after thirteen days, whereas the ischemic wound does not heal. inspired new theories; examples occurred in tumor growth, wound healing, and developmental biology, to name a few. We shall consider here tumor models and describe a new class of free boundary problems related to symmetry-breaking bifurcations of a spherical tumor and its stability. Consider a tumor that occupies a region Ω(t), at time t, and assume that all the cells in Ω(t) are identical tumor cells and are uniformly distributed. Due to proliferation, the region Ω(t) will expand, but only as long as there is sufficient supply of nutrients σ. The concentration σ is assumed to satisfy a diffusion system σt − Δσ + σ = 0 in Ω(t), σ = 1 on ∂Ω(t), and the proliferation rate S is assumed to depend linearly on σ: S = μ(σ − σ) (μ > e 0, 0 < σ < e 1); roughly speaking, if σ >σe , the tumor expands, and if σ <σe , the tumor shrinks. By conservation of mass div v~ = S, where v~ is the velocity of cells within the tumor. Assuming Darcy's law v~ = −∇p, where p is the inner pressure, one gets −Δp = μ(σ − σ) e in Ω(t). We introduce a boundary condition σ = κ on ∂Ω(t) (κ = mean curvature), which represents the adhesive forces among cells at the boundary, and the continuity condition Vn = v~ · n~ = − ∂p ∂n on ∂Ω(t), where Vn is the velocity of the free boundary in the outward normal direction n~. August 2010 Notices of the AMS 853 Figure 4 (from [16]). Schematic of tissue flap. The top colored layer consists of dermis, epidermis, and subdermal plexus. The bottom layer represents fat tissue. The perforator artery and vein are located at the bottom of the flap. It is well known that for every σe there exists a μ- family of stationary radially symmetric solutions with radius R which depends only on σe : 1 R2 (R coth R − 1) = σe 3 , σ (r) = R sinh R sinh r r , p(r) = C − μσ (r) + μ 6 σ r e 2 , where C = 1 R + μ − μ 6 σ R e 2 . The radius R varies from 0 to ∞ when σe varies from 1 to 0. The stationary problem lends itself to questions naturally considered in bifurcation analysis, with μ as the bifurcation parameter. There exists a family of symmetry-breaking bifurcation branches of solutions originating at μ = μn(R) where 0 < μ2 < μ3 < · · · < μu < · · · , μ = μn + ϱ μn,1 + O(ϱ2), r = R + ϱ Yn,0(θ) + O(ϱ2) and where Yn,0(θ) is the spherical harmonic of order (n, 0). The spherical solution is asymptotically stable (as t → ∞) if μ < μ∗(R) and linearly unstable (as t → ∞) if μ > μ∗(R). Here μ∗(R) = μ2(R) if R > R, and μ∗(R) < μ2(R) if R < R, where R = 0.62207 . . . is a solution of a transcendental equation. In case R > R, the first bifurcation

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point μ2 is transcritical, with one branch being linearly stable and the other branch unstable .The bifurcation results have been extended to the case where Darcy's law is replaced by the Stokes equation ,this models a tumor developing in fluid-like tissue, for instance, in the mammary gland or in the brain. However, in this case the first bifurcation branch has a boundary with many fingers: r = R + Σ Yn∗(R),0(θ) + O(ϱ2) where n ∗(R) → ∞ if R → ∞. The biological interpretation is that when a spherical tumor in fluid-like tissue becomes unstable, it develops many fingers; hence it incurs a higher risk of metastasis. Tumor models with several types of cells (proliferating, quiescent, dead) were analyzed mathematically but the existence of spherical stationary solutions and their bifurcation and stability remain mostly open problems. Surgical Tissue Transfer Reconstructive microsurgery is a clinical technique used to transfer large amounts of a patient's tissue from one location to another in order to restore physical deformities caused by trauma, tumor, or congenital abnormalities. The trend in this field is to transfer tissue using increasingly smaller blood vessels, which decreases problems associated with tissue harvest but increases the possibility that blood supply to the transferred tissue may not be adequate for healing. Surgical flaps are currently designed based on blood supply from a single vessel. However, there is no objective method to assist the surgeon in deciding how large a flap can be transferred given the diameter of the perforating vessel. If the surgical flap is too large, some portion may develop ischemia and die, requiring another surgery. A mathematical model was developed by Matzavinos et al. [15] to determine the transport of oxygen in a rectangular flap with one perforating vessel,. The model is based on a multiphase approach, which assumes that the flap consists of tissue cells, arterial blood cells, and venous blood cells of volume fractions θc (x), θa(x), and θv (x). Correspondingly, the model includes three transport/diffusion equations for the oxygen concentrations and two conservation laws for arterial and venous blood flow. Range of oxygen concentration in the flap of dimension 4 cm x 2.5 cm x 1 cm with different arterial diameter ranging 0.2 cm to 1.2 cm. of the model show which flap will survive the transfer after four hours and which will develop necrosis. An example is shown in Figure 5 for a flap of dimensions 4 cm x 2.5 cm x 1 cm with different arterial diameter ranging from 0.2 cm to 1.2 cm. Each vertical segment represents the range of oxygen level in the flap; when the level is below 0.15 (which is 15% of the oxygen level in healthy tissue), the flap will develop necrosis. In order to develop the model into a predictive tool that could be used by surgeons, experiments with animal models will be needed to determine more carefully the parameters in the differential equations and, more importantly, to address, in the model, the issue of heterogeneity of the vasculature in the tissue. Reaction-Diffusion-Hyperbolic Systems in Neurofilament Transport in Axon Most axonal proteins are synthesized in the nerve cell body and are transported along axons by mechanisms of axonal transport. A mathematical model was developed by Craciun et al. [16] that determines the profile and velocity of the population of transported proteins, as observed in vivo and in vitro experiments. The model is described by a hyperbolic system of equations ϱ(∂t + vi∂x)pi = Xn j=1 kijpj for 0 < x < ∞, t > 0, 1 ≤ i ≤ n, where kij ≥ 0 if i ≠ j, Pn i=1 kij = 0 and 0 < ϱ << 1. Here pi(x, t) is the density of

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cargo in one of n states (moving forward along a track, moving backward, resting, off track, etc.) and x is the distance from the cell body. Setting pm(x, t) = λmQm x – vt √ ϱ , t , where λm is determined by the boundary conditions at x = 0 and v is a weighted average of the velocities vi (vi can be positive or negative), it was proved in [9] that Qm(s, t) → Q(s, t) as ϱ → 0, where Q(s, t) is the bounded solution of a parabolic system (∂t – σ 2 ∂ 2 s) Q(s, t) = 0, −∞ < s < ∞, t > 0, Q(s, 0) = (1 if −∞ < s < 0 q0(s) if 0 < s < ∞; q0(s) depends on the initial conditions of the pi and σ2 is a function of the kij . This result, which was inspired by formal calculations in Reed et al. [17], shows that the cargo moves as an approximate wave: its velocity is fixed, but its profile decreases. The above result was extended to include cargo moving in multitracks.The Lung Response to Infection The lung environment is specialized to reorganize and eliminate most invaders without causing excessive inflammation. However, this highly regulated inflammatory strategy can be detrimental to the host when a prompt, strong inflammatory response is needed to effectively eradicate pathogens. Such is the case, for instance, in the early stages of infection with Mycobacterium tuberculosis (Mtb). The alveolar macrophages, which play a large role in the innate immune system in the lung, are unable to win the fight against the bacteria all by themselves. With the aid of another family of cells of the immune system, the dendritic cells, they communicate to the lymph nodes the need to activate a more inflammatory brand of macrophages, called classically activated macrophages (CAMs), and move them to the lung. It takes approximately two months before the CAMs become the dominant population of macrophages in the lung, i.e., before the number of CAM cells exceeds the number of alveolar macrophages; we call this time the "switching time". Considering that 5-10% of the world population develops clinical symptoms of tuberculosis, it is clearly important to investigate how to shorten the switching time. A mathematical model was developed by Day et al. [18] to address this question. Bacteria is found both in alveolar macrophages (Ai) and externally. the literature, or estimated using sensitivity analysis. The model simulations predict a switching time of fifty days and residual bacterial load, after recovery from the infection, of 104 bacteria per cm3 in the lung; these numbers are in agreement with the biomedical literature. The model was used to determine the effect of therapeutic drugs, such as IFN-γ, on shortening the switching time and, as a consequence, reducing the maximum bacterial load during the early weeks of infection and the residual bacterial load after host recovery. Modeling the immune rheostat of macrophages in the lung in response to infection is not restricted to infection with tuberculosis. Indeed, the same ideas of reducing the switching time can be applied to other airborne infections. However, for some infections it is desirable to slow down the activation of highly proinflammatory immune response. This is the case, for instance, in an infection such as anthrax, in which the immediate highly toxic immune response overwhelms the infected host and may result in sepsis shock. Cell Differentiation A T cell is a type of blood cell that is a key component of the immune system. T cells differentiate into either TH1 or TH2 cells that have different functions. The decision to which cell type to differentiate depends on the concentration of transcription factors T-bet (x1) and GATA-3 (x2) within the

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cell. A T cell will differentiate into TH1 (TH2) if x1 is high (low) and x2 is low (high). A mathematical model was developed by Yates et al. [20] (see also [1]). Accordingly, the xi evolve by a dynamical system dxi dt = fi(x1, x2, Si(t)) (i = 1, 2), where Si(t) is a signal of the form Si(t) = Ci(t) + RR xiφ(x1, x2, t)dx1dx2 RR φ(x1, x2, t)dx1dx2 , Ci(t) is an external signal (e.g., an infection) and φ(x1, x2, t) is the density of cells with concentration (x1, x2) at time t. The function φ satisfies a conservation law ∂φ ∂t + X2 i=1 ∂ ∂xi (fiφ) = gφ, where g is a growth rate, and the fi above have the specific form fi(x1, x2, Si(t)) = −μ xi + αi x n i k n i + x n i + σi Si ρi + Si ! · 1 1 + xj/γj + βi , where (i, j) = (1, 2) and (i, j) = (2, 1). It was proved by Friedman et al. [14] that, as t → ∞, the function φ(x1, x2, t) tends to 1-peak Dirac measure, 2-peak Dirac measures, or 4-peak Dirac measures, depending on the parameters of the dynamical system. The idea motivating the proof is to use a nested adaptive sequence of domains that enclose the trajectories of the dynamical system as time increases and then prove that the nested sequence converges to one, two, or four points. The location of each peak in 856 Notices of the AMS Volume 57, Number 7 the (x1, x2)-plane determines whether it represents TH1 or TH2 cells. The same idea can be applied, in principle, to other dynamical systems with nonlocal coefficients.

Conclusion Historically, science and technology have been a driving force for new mathematical theories. The great alliance between the physical and the mathematical sciences is recognized universally: both disciplines thrived by supporting each other. The renowned educator, John Dewey, wrote in his 1901 book The Child and Society that “We do not have a series of stratified earths, one of which is mathematical, another physical, etc. We should not be able to live very long in any one taken by itself. We live in a world where all sides are bound together; all studies grow out of relations in the one great common world.” What John Dewey wrote in 1901 is even truer today, especially in mathematical biology. The few examples in this article illustrate this point. But beyond these examples, there are substantial areas of biology that have advanced by mathematics, such as computational neuroscience, population dynamics, ecology, spread of disease, and phylogenomics. There is also a series of mathematical studies launched by biological applications, such as in reaction-diffusion equations, pattern formation, stochastic differential equations, numerical methods of PDEs, and hybrid methods connecting discrete to continuous models.

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