What Is Mathematical Biology and How Useful Is It?

Avner Friedman

Recent years have witnessed unprecedented progress in the biosciences. Perhaps the most visible event is the completion of the Human Genome Project—the first step toward a molecular genetic understanding of the human organisms. Subsequent discovery of noncoding genes and deeper understanding of the genomic/proteomic machinery continue to advance biology at a revolutionary pace. Advances are reported continually in the fights against cancer and degenerative diseases of the brain, such as Alzheimer's, Parkinson's, and ALS, and in the management of health threats such as AIDS, insect disease vectors, and antibiotic resistance. Society is eager to see basic research quickly translated into longer and better quality of life through deeper understanding of disease mechanisms and better medical treatment. Accordingly, many topics from bioscience have been given high priority on the national agenda.

Behind the headlines lie astonishing advances in basic science and technology, including medical imaging, nanoscale bioengineering, and gene expression arrays. These technologies have rapidly generated massive sets of loosely structured data and enabled researchers to elucidate basic biomedical mechanisms and pathways. This explosion of experimental results has challenged researchers' abilities to synthesize the data and draw knowledge from them.

Thus the emergence of models and the existence of large data sets that require quantitative

analysis, coupled with strong public support for accelerated progress in the biosciences, presents a great opportunity for the mathematical sciences. To successfully exploit this opportunity will require mathematical scientists to learn the bioscientists' language so that they can understand the underlying biology clearly enough before they bring the power of mathematics to bear. While we can expect that established methods in mathematical sciences will be of immediate use, the quantitative analysis of fundamental problems in bioscience will undoubtedly require new ideas and new techniques. Indeed, when viewed over a long times cale, biological applications launched new fields within mathematics, for example, pattern formation in reaction-diffusion equations and combinatorial problems arising in sequence alignment. There already exist several mathematical bioscience research groups in departments of mathematics, statistics, computer science, and biology, as well as biostatistics centers in medical research facilities around the country. In addition, individual topics from mathematical biosciences have been featured in the programs of some of the existing mathematical institutes in the United States. Nevertheless, the current size of the mathematical biosciences community is relatively small compared with the demands of the biosciences. Therefore, there is a need to encourage an influx of mathematicians and statisticians into mathematical biosciences and to nurture a new generation of researchers more systematically than before.

These challenges have motivated us to found the Mathematical Biosciences Institute at Ohio State University as one of the NSF/DMS Mathematical Institutes. The Institute became operational in the autumn of 2002, and having served as its first

Avner Friedman is Distinguished University Professor and former director of the Mathematical Biosciences Institute at Ohio State University. His email address is `afriedman@mbi.osu.edu`.
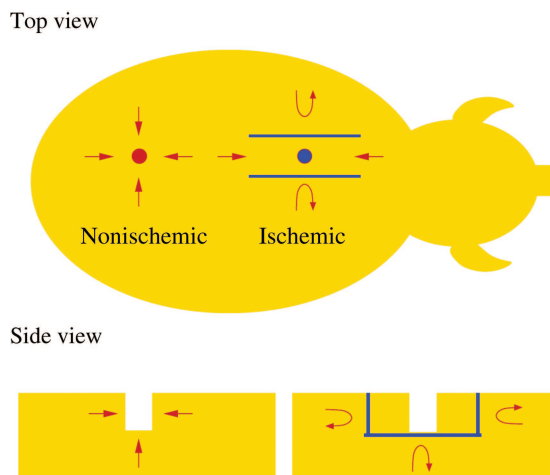
Top view

Side view

Figure 1. Schematic view of the wound environment developed by Roy et al. [18] (with permission from C. K. Sen). The blue segments represent circulation barriers created using a bipedicle flap, and the red arrows illustrate the blood circulation near the wound.

director, I witnessed firsthand the enthusiasm of thousands of our visitors, both mathematicians and biologists. In this article I would like to share with the mathematical community some of the knowledge I have gained as director and researcher in the MBI.

What Is Mathematical Biology?

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 [1]. Furthermore, since the human body has 10^{13} 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.

In order to develop a model, for instance in terms of a system of differential equations, the mathematician needs to determine a diagram of relationships among the biological variables and specify rate parameters. Typically some of these parameters are not found in the literature and need to be estimated. They are determined in an iterative process of simulations aimed at achieving good fit with the experimental data. This process may take many iterations. Hence it is crucial that each simulation does not take too much computational time. When the model simulations finally agree with experimental results, the model may be considered useful for suggesting new hypotheses that are biologically testable. It may suggest, for example, a particular therapy that is represented, in the model, in the form of an increase in one or several rate parameters.

"How useful is mathematical biology?" is a question with two parts: Does mathematics advance biology, and does biology inspire new mathematics? In what follows I shall give a few examples of research conducted at the Mathematical Biosciences Institute that illustrate how both disciplines, mathematics and biology, benefit from each other.

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. [18]. 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 Figure 1. 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, Xue et al. [19] developed a mathematical model 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.
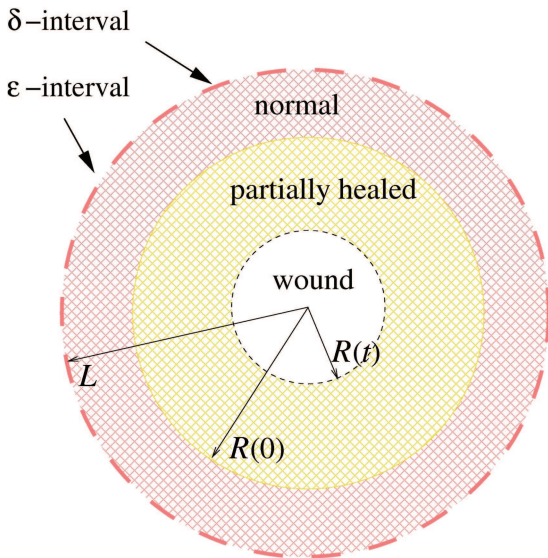
Figure 2 (from [19]). The open wound is the circular region $\{0 \leq r \leq R(t)\}$, the partially healed region is the annulus $\{R(t) \leq r \leq R(0)\}$, and the normal healthy tissue is $\{R(0) \leq r \leq L\}$.
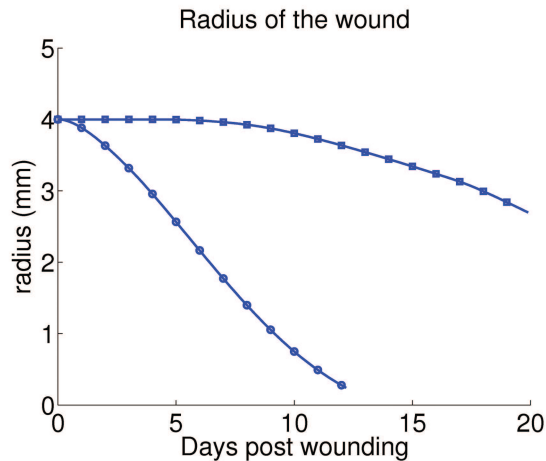

Figure 3 (from [19]). Radius of ischemic ($\alpha = 0.92$) and nonischemic wound ($\alpha = 0$) over a period of twenty days. The nonischemic wound closes after thirteen days, whereas the ischemic wound does not heal.

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. [19] assumed that the wound is circular, as shown in Figure 2, but that many small incisions of size δ are made at $r = L$ with adjacent incisions separated by distance ϵ. Taking $\delta, \epsilon \to 0$ in appropriate proportions and applying homogenization theory, they deduced that each boundary condition $u = u_s$ (for a solution of $\Delta u = f$) before the incisions changed into a boundary condition

$$(1 - \alpha)(u - u_s) + \alpha \frac{\partial u}{\partial r} = 0 \text{ at } r = L$$

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. [18]. 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 mathematical models and 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 $\Omega(t)$, at time t, and assume that all the cells in $\Omega(t)$ are identical tumor cells and are uniformly distributed. Due to proliferation, the region $\Omega(t)$ will expand, but only as long as there is sufficient supply of nutrients σ. The concentration σ is assumed to satisfy a diffusion system

$$\sigma_t - \Delta\sigma + \sigma = 0 \text{ in } \Omega(t), \ \sigma = 1 \text{ on } \partial\Omega(t),$$

and the proliferation rate S is assumed to depend linearly on σ:

$$S = \mu(\sigma - \tilde{\sigma}) \quad (\mu > 0, \ 0 < \tilde{\sigma} < 1);$$

roughly speaking, if $\sigma > \tilde{\sigma}$, the tumor expands, and if $\sigma < \tilde{\sigma}$, the tumor shrinks. By conservation of mass div $\vec{v} = S$, where $\vec{v}$ is the velocity of cells within the tumor. Assuming Darcy's law $\vec{v} = -\nabla p$, where p is the inner pressure, one gets

$$-\Delta p = \mu(\sigma - \tilde{\sigma}) \text{ in } \Omega(t).$$

We introduce a boundary condition

$$\sigma = \kappa \text{ on } \partial\Omega(t) \quad (\kappa = \text{mean curvature}),$$

which represents the adhesive forces among cells at the boundary, and the continuity condition

$$V_n = \vec{v} \cdot \vec{n} = -\frac{\partial p}{\partial n} \text{ on } \partial\Omega(t),$$

where V_n is the velocity of the free boundary in the outward normal direction $\vec{n}$.
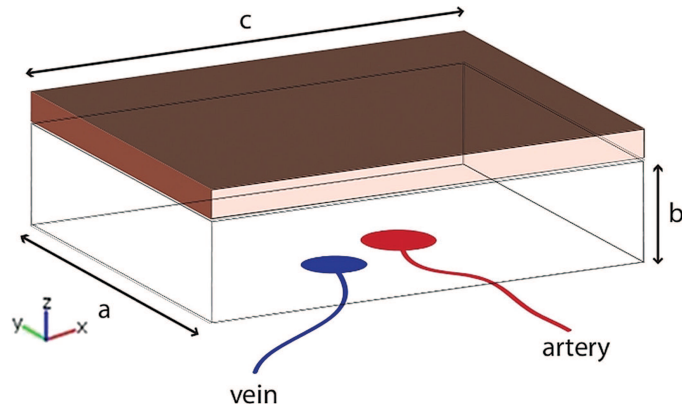
Figure 4 (from [16]). Schematic of tissue flap. The top colored layer consists of dermis, epidermis, and subdermal plexus. The bottom layer represents fat tissue. The perforator artery and vein are located at the bottom of the flap.

It is well known that for every $\tilde{\sigma}$ there exists a μ-family of stationary radially symmetric solutions with radius R which depends only on $\tilde{\sigma}$:

$$\frac{1}{R^2}(R \coth R - 1) = \frac{\tilde{\sigma}}{3}, \ \sigma(r) = \frac{R}{\sinh R} \frac{\sinh r}{r},$$

$$p(r) = C - \mu\sigma(r) + \frac{\mu}{6} \tilde{\sigma} r^2,$$

where $C = \frac{1}{R} + \mu - \frac{\mu}{6} \tilde{\sigma} R^2$. The radius R varies from 0 to ∞ when $\tilde{\sigma}$ varies from 1 to 0. The stationary problem lends itself to questions naturally considered in bifurcation analysis, with μ as the bifurcation parameter.

It was proved in [15], [6], and [7] that, given R, there exists a family of symmetry-breaking bifurcation branches of solutions originating at $\mu = \mu_n(R)$ where
$0 < \mu_2 < \mu_3 < \cdots < \mu_u < \cdots,$

$$\begin{aligned} \mu &= \mu_n + \epsilon \, \mu_{n,1} + O(\epsilon^2), \\ r &= R + \epsilon \, Y_{n,0}(\theta) + O(\epsilon^2) \end{aligned}$$

and where $Y_{n,0}(\theta)$ is the spherical harmonic of order $(n, 0)$. Furthermore ([7], [8]), the spherical solution is asymptotically stable (as $t \to \infty$) if $\mu < \mu_*(R)$ and linearly unstable (as $t \to \infty$) if $\mu > \mu_*(R)$. Here $\mu_*(R) = \mu_2(R)$ if $R > \overline{R}$, and $\mu_*(R) < \mu_2(R)$ if $R < \overline{R}$, where $\overline{R} = 0.62207\ldots$ is a solution of a transcendental equation. In case $R > \overline{R}$, the first bifurcation point μ_2 is transcritical, with one branch being linearly stable and the other branch unstable [13].

The bifurcation results have been extended to the case where Darcy's law is replaced by the Stokes equation ([11], [12]); 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:

$$r = R + \Sigma \, Y_{n^*(R),0}(\theta) + O(\epsilon^2)$$

where $n^*(R) \to \infty$ if $R \to \infty$. 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 in [3], 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. [16] to determine the transport of oxygen in a rectangular flap with one perforating vessel, as shown in Figure 4. 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 $\theta_c(x)$, $\theta_a(x)$, and $\theta_v(x)$. Correspondingly, the model includes three transport/diffusion equations for the oxygen concentrations and two conservation laws for arterial and venous blood flow. Simulations
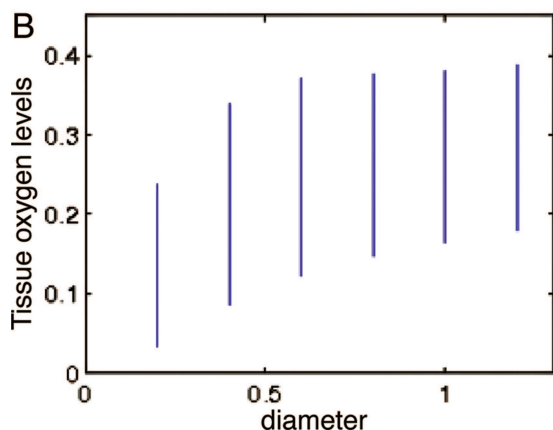
Figure 5 (from [16]). Range of oxygen concentration in the flap of dimension 4 cm x 2.5 cm x 1 cm with different arterial diameter ranging 0.2 cm to 1.2 cm.

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. [4] 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

$$\epsilon(\partial_t + v_i \partial_x)p_i$$
$$= \sum_{j=1}^{n} k_{ij}p_j \text{ for } 0 < x < \infty, \ t > 0, \ 1 \le i \le n,$$

where $k_{ij} \ge 0$ if $i \ne j$, $\sum_{i=1}^{n} k_{ij} = 0$ and $0 < \epsilon << 1$. Here $p_i(x,t)$ is the density of 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

$$p_m(x,t) = \lambda_m Q_m \left(\frac{x - vt}{\sqrt{\epsilon}}, t\right),$$

where λ_m is determined by the boundary conditions at $x = 0$ and v is a weighted average of the velocities v_i (v_i can be positive or negative), it was proved in [9] that

$$Q_m(s,t) \to Q(s,t) \text{ as } \epsilon \to 0,$$

where $Q(s,t)$ is the bounded solution of a parabolic system

$$(\partial_t - \sigma^2 \partial_s^2) Q(s,t) = 0, \ -\infty < s < \infty, t > 0,$$
$$Q(s,0) = \begin{cases} 1 & \text{if} \quad -\infty < s < 0 \\ q_0(s) & \text{if} \quad 0 < s < \infty; \end{cases}$$

$q_0(s)$ depends on the initial conditions of the p_i and σ^2 is a function of the k_{ij}.

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 [10].

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. [5] to address this question. Based on the biomedical literature, a diagram of interactions between various cell types, cytokines, and the bacteria was developed, as shown in Figure 6. Based on the diagram, a system of ordinary differential equations was set up, with parameters taken from
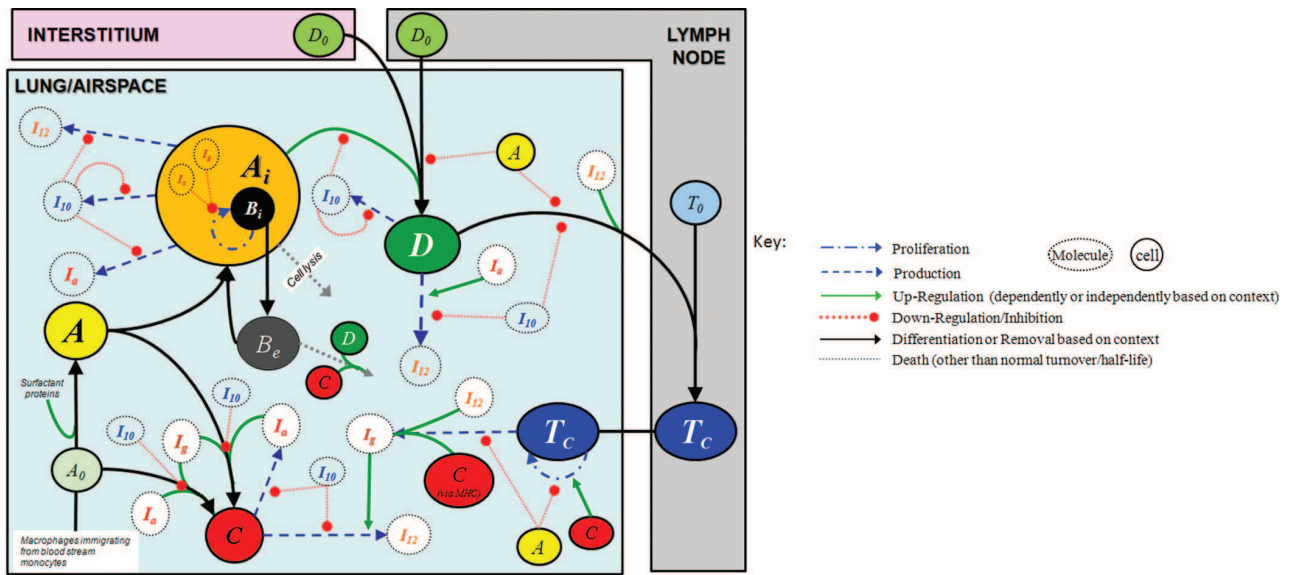
Figure 6 (from [5]). Diagram of interactions between various cell types and cytokines. Bacteria is found both in alveolar macrophages (A_i) and externally.

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 10^4 bacteria per cm^3 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 (x_1) and GATA-3 (x_2) within the cell. A T cell will differentiate into TH1 (TH2) if x_1 is high (low) and x_2 is low (high). A mathematical model was developed by Yates et al. [20] (see also [1]). Accordingly, the x_i evolve by a

dynamical system

$$\frac{dx_i}{dt} = f_i(x_1, x_2, S_i(t)) \quad (i = 1, 2),$$

where $S_i(t)$ is a signal of the form

$$S_i(t) = \frac{C_i(t) + \iint x_i \phi(x_1, x_2, t) dx_1 dx_2}{\iint \phi(x_1, x_2, t) dx_1 dx_2},$$

$C_i(t)$ is an external signal (e.g., an infection) and $\phi(x_1, x_2, t)$ is the density of cells with concentration (x_1, x_2) at time t. The function ϕ satisfies a conservation law

$$\frac{\partial \phi}{\partial t} + \sum_{i=1}^{2} \frac{\partial}{\partial x_i}(f_i \phi) = g\phi,$$

where g is a growth rate, and the f_i above have the specific form

$$f_i(x_1, x_2, S_i(t))$$
$$= -\mu\, x_i + \left(\alpha_i\, \frac{x_i^n}{k_i^n + x_i^n} + \sigma_i\, \frac{S_i}{\rho_i + S_i} \right)$$
$$\cdot \frac{1}{1 + x_j/\gamma_j} + \beta_i,$$

where $(i, j) = (1, 2)$ and $(i, j) = (2, 1)$.

It was proved by Friedman et al. [14] that, as $t \to \infty$, the function $\phi(x_1, x_2, t)$ 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

the (x_1, x_2)-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 more true 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. Two workshops held at the MBI in the autumn of 2008 and two held in the autumn of 2009 provide many examples of research on the mathematical-biological interface: "Multiscale problems in thrombosis development", "Biochemical reaction networks", "Computational modeling of blood flow", and "Topology and tomography of medical data" are just a few of the titles presented in these workshops. Viewing the present trends in mathematical biology, I believe that the coming decade will demonstrate very clearly that mathematics is the future frontier of biology and biology is the future frontier of mathematics.

References

[1] B. D. Aguda and A. Friedman, *Models of Cellular Regulation*, Oxford University Press, 2008.

[2] X. Chen, S. Cui, and A. Friedman, A hyperbolic free boundary problem modeling tumor growth: Asymptotic behavior, *Trans. AMS* **357** (2005), 4771–4804.

[3] X. Chen and A. Friedman, A free boundary problem for an elliptic-hyperbolic system: An application to tumor growth, *SIAM J. Math. Anal.* **35** (2003), 974–986.

[4] G. Craciun, A. Brown, and A. Friedman, A dynamical system model of neurofilament transport in axons, *J. Theor. Biology* **237** (2005), 316–322.

[5] J. Day, A. Friedman, and L. S. Schlesinger, Modeling the immune response rheostat of macrophages in the lung in response to infection, *PNAS* **106** (2009), 11246–11251.

[6] M. Fontelus and A. Friedman, Symmetry-breaking bifurcations of free boundary problems in three dimensions, *Asymptotic Analysis* **35** (2003), 187–206.

[7] A. Friedman and B. Hu, Bifurcation from stability to instability for a free boundary problem arising in a tumor model, *Archive Rat. Mech. and Anal.* **180** (2006), 293–330.

[8] ———, Asymptotic stability for a free boundary problem arising in tumor model, *J. Diff. Eqs.* **227** (2006), 598–639.

[9] ———, Uniform convergence for approximate traveling waves in reaction-hyperbolic systems, *Indiana Univ. Math. J.* **56** (2007), 2133–2158.

[10] ———, Uniform convergence for approximate traveling waves in linear reaction-diffusion-hyperbolic systems, *Arch. Rat. Mech. Anal.* **186** (2007), 251–274.

[11] ———, Bifurcation for a free boundary problem modeling tumor growth by Stokes equation, *SIAM J. Math. Anal.* **39** (2007), 174–194.

[12] ———, Bifurcation from stability to instability for a free boundary problem modeling tumor growth by Stokes equation, *J. Math. Anal. Appl.* **327** (2007), 643–664.

[13] ———, Stability and instability of Liapunov-Schmidt and Hopf bifurcation for a free boundary problem arising in a tumor model, *Trans. AMS* **360** (2008), 5291–5342.

[14] A. Friedman, C. Y. Kao, and C. W. Shih, Asymptotic phases in cell differentiation model, *J. Diff. Eqs.* (2009).

[15] A. Friedman and F. Reitch, Symmetry-reactive bifurcation of analytic solutions to free boundary problems: An application to a model of tumor growth, *Trans. AMS* **353** (2001), 1587–1634.

[16] A. Matzavinos, C. Y. Kao, J. Edward, F. Green, A. Sutradhar, M. Miller, and A. Friedman, Modeling oxygen transport in surgical tissue transfer, *PNAS* **106** (2009), 12091–12096.

[17] M. C. Reed, S. Venakides, and J. J. Blum, Approximate traveling waves in linear reaction-hyperbolic equations, *SIAM J. Appl. Math.* **50** (1990), 167–180.

[18] S. Roy, G. Gordillo, V. Bergdall, J. Green, C. B. Marsh, L. J. Gould, and C. K. Sen, Characterization of a pre-clinical model of chronic ischemic wound, *Physiol. Genomics* **37** (2009), 211–224.

[19] C. Xue, A. Friedman, and C. K. Sen, A mathematical model of ischemic cutaneous wounds, *PNAS* **106** (2009), 16782–16787.

[20] A. Yates, R. Callard, and J. Stark, Combining cytokine signaling with T-bet and GATA-3 regulations in TH1 and TH2 differentiation: A model for cellular decision making, *J. Theor. Biology* **231** (2004), 181–196.