BULLETIN (New Series) OF THE
AMERICAN MATHEMATICAL SOCIETY
Volume 41, Number 4, Pages 559–564
S 0273-0979(04)01028-6
Article electronically published on June 17, 2004

Nonlinear dynamics in physiology and medicine, A. Beuter, L. Glass, M. C. Mackey, and M. S. Titcombe (Editors), Interdisciplinary Applied Mathematics, vol. 25, Springer-Verlag, New York, 2003, xxvi+434 pp., $69.95, ISBN 0-387-00449-1

As long ago as 1620, no less a person than Francis Bacon extolled the virtues of interdisciplinary research. He wrote [1]:

> *The men of experiment are like the ant, they only collect and use; the reasoners resemble spiders, who make cobwebs out of their own substance. But the bee takes the middle course: it gathers its material from the flowers of the garden and field, but transforms and digests it by a power of its own. ... Therefore, from a closer and purer league between these two faculties, the experimental and the rational (such as has never been made), much may be hoped.*

For some hundreds of years, mathematicians followed his advice. The distinctions, not to say rivalries, between pure and applied mathematics that can be such an unfortunate feature of modern mathematics departments were of little significance to, for instance, Leonhard Euler, who in 1726 was offered a job in St. Petersburg teaching applications of mathematics and mechanics to physiology. (This is, alas, the sort of job that appears today only very rarely, if ever.) It is, of course, unnecesssary to point out yet again that scientists of old were people of broad education and interests, unlimited by more modern conceptions of specialty. However, despite this widely known fact, nowadays it is not always fully appreciated that mathematics and biology have been intertwined for well over 200 years and that the current high fashion for mathematical biology is nothing new, merely a reinvigoration of what people have been doing for a long time.

One of my favourite examples of early interactions between mathematics and medicine (although perhaps this is stretching things just a little) is Robert Recorde, a physician at the court of King Edward VI of England, but also a mathematical teacher of note and the first to use the modern "=" sign. In 1557 he published *The Whetstone of Witte*, in which he writes

> *...and to avoide the tediouse repetition of these woordes : is equalle to : I will sette as I doe often in woorke... , a paire of paralleles, or Gemowe [twin] lines of one lengthe, thus:* ═══════ *, bicause noe. 2. thynges, can be moare equalle.*

Indeed so. Another example that amuses me is the argument between Daniel Bernoulli (who, by the way, was Professor of Medicine at Basel for a time) and Jean-le-Rond D'Alembert over whether or not one should be vaccinated against smallpox. To address this question Bernoulli published in 1760 [2] one of the first mathematical models in biology, a simple compartmental model involving susceptible and immune populations. D'Alembert [3] didn't like his arguments a great deal, responding that (if I may be allowed to paraphrase) vaccination was all very well, but it only helps you to live a few more years at the end of your life, and, after all, you can't enjoy life then anyway, so what's the point? Although he may

2000 *Mathematics Subject Classification.* Primary 37N25; Secondary 92C30.

©2004 American Mathematical Society

have been the first well-documented case, D'Alembert certainly has not been the last mathematician to miss the biological point completely. Another early mathematically inclined physiologist was Otto Frank, of the Frank-Starling law, who in 1899 used a lovely model of the ejection pressure pulse to derive the blood flux out of the heart [4]. Similarly, Helmholtz was renowned, not just as a mathematician and physicist, but also as a physiologist; he was the first to measure the speed of the action potential [5], as well as formulating a theory of hearing [6] that is still valid today, at least for some amphibians.

In the last 100 years, examples of interactions between mathematics and biology have come at an ever-increasing rate; many of them are discussed in a wonderful introductory chapter in a recent book by Beuter, Glass, Mackey and Titcombe, about which I shall have more to say later. Huxley, originally trained in physics, mathematics and chemistry, gained a Nobel Prize in 1963 for his work with Hodgkin (who himself was encouraged while young to learn as much mathematics as he could) on the action potential of the squid giant axon; A.V. Hill, third wrangler in the Mathematical Tripos at Cambridge, gained a Nobel Prize in 1922 for his work on muscle; the physics background of Francis Crick is widely known — what is less well known is that Watson and Crick shared the 1962 Nobel Prize with the physicist Maurice Wilkins, who was, I kid you not, born in Pongaroa, New Zealand (I just had to mention that). More recently, Sakmann, whose initial passion for physics and biology led him into electrophysiology, shared the 1991 Nobel Prize in Physiology and Medicine with Neher, whose early interest in mathematics and physics led him into biophysics.

Looking around applied mathematics today, we see that these traditional connections are alive and well; from genetics to ecology, applied mathematicians are playing an ever-increasing role in the biological sciences. Just as physics inspired a great deal of applied mathematics in the 19th century, there is no doubt that biology is one of the most dynamic areas in modern applied mathematics.

The tremendous vitality of mathematical physiology comes about because it serves, as it has in the past, as a meeting ground for people trained in different disciplines. Not only are many physiologists using advanced mathematical and numerical techniques, many mathematicians are applying their skills to the solution of physiological problems. An excellent example of the former is Charles Peskin, currently at New York University. Although his initial training was in medicine, his interest in the heart led to him learning fluid mechanics and numerical methods under Chorin. His subsequent work with David McQueen [7] is widely considered to be one of the most outstanding examples of mathematical physiology and fluid mechanics and has spawned a considerable industry based around the immersed boundary method. Another of my favourite current mathematical physiologists is John Rinzel [8], who worked for many years at the NIH. In the early 1970s he published papers with one of the most eminent electrophysiologists of the time (W. Rall) as well as with one of the eminent applied mathematicians of the day (J.B. Keller), went on to discover the beautifully elegant analysis of bursting oscillations so important in endocrine cells, and now works with experimental colleagues on a wide range of problems in neuroscience. Or take Jim Keener, whose mathematical studies of cardiac electrophysiology have inspired more than one generation of applied mathematicians, myself included. Or Nancy Kopell, the co-author of some of the most profound results in coupled oscillators, now working with experimentalists in neuroscience. The late, and much missed, Joel Keizer was originally a physical chemist, specialising in non-equilibrium thermodynamics, but later in life turned to biological modelling, constructing some of the most important models of bursting oscillations and calcium dynamics [9]; partly as a result of the efforts of Joel Keizer, in the study of calcium oscillations and waves the connections between experimentalist and theoretician are now close and commonplace. For a final example, let me point to the current work of Sakmann and Neher [10] on synapses, where we see an impressive combination of modeling and experiment in which both the mathematics and the physiology are crucial and nontrivial. In just about every area of physiology, from neurons to the kidney, from the retina to the cochlea, from the behaviour of single receptor proteins to the control of whole-body hormonal oscillations, mathematical methods have remained an integral part of modern physiology.

The ease with which mathematical methods may be used in physiology is due, in great part, to two complementary things. On the one hand, physiology has always been a highly quantitative science. Studies of ion channels and neurons, of kidney function or the circulatory system have always required a detailed knowledge of mathematics and physics, today no less than before, and the data obtained are, in general, highly reproducible. This means that models can be held to a high standard of accountability, necessitating sophisticated methods for their construction and analysis and providing a space for the mathematical modeller to work. On the other hand, the rise of the computer has allowed for the construction of ever more detailed models and the analysis of such models by people who may not have a rigorous mathematical training but who are expert in computational approaches and visualisation. As a result, nowadays a large part of the interaction between modellers and experimentalists takes place in the common domain of the simulation.

Having painted such a rosy picture of happy mathematicians and smiling experimentalists skipping hand-in-hand across a field of daffodils, I must address the obvious question. If, as I claim, there is such a rich history of mathematical biology and physiology, why then are there not mathematical physiologists in every math department? Why do tensions still exist between those mathematicians of a purer persuasion and those working at the experimental coal-face? Why is the current high fashion of mathematical biology often seen as something new and radical? Mathematical physiologists who concentrate on understanding and answering a scientific question rather than developing new mathematical techniques run the risk of being considered second-rate by their theorem-inclined colleagues, while those same colleagues understandably resent being considered elitist and irrelevant. The complete difference in philosophy between these two ends of the spectrum can make mutual understanding difficult. Only 15 years ago, one of the great leaders of mathematical biology in the 20th century, James Murray, likened mathematical biology to a camel train being annoyed by barking dogs but continuing nonetheless [11]. And let us not forget that mathematicians are not solely to blame; there have been few jobs for mathematicians in physiology departments in the last 30 years. Not to mention that one still hears, as I have heard so many times in the past: "Mathematical modelling? It's all garbage. Stay in your ivory tower and leave us real people alone." However, although I don't entirely understand why, I believe that these times are passing, if not gone already. Now we have a plethora of jobs for mathematical biologists across the world; we have grant money from the NIH and NSF targeted specifically to interdisciplinary research; we even have an NSF-funded institute, the Mathematical Biosciences Institute (http://www.mbi.osu.edu), devoted entirely to mathematical biology. I believe that the true value of mathematical biology is once again widely appreciated. The exact reasons for this change may escape me, but I appreciate the result.

When I was an undergraduate student studying mathematics (of the purer sort), I got an old black book out of the library, a book called *Lectures on Nonlinear Differential Equation Models in Biology*, published in 1977 [12] by some guy Murray I'd never heard of. When I read that book I knew right then that is what I was going to do. I knew nothing at all about physiology or mathematics, or very much of anything really, but I decided this was for me. (As it happens, some two years later I applied to go to Oxford to do my doctorate with Murray. I have it on the very best authority that he looked at my application, thought to himself "Sneyd? That's a funny name" and threw it into the rubbish bin. Ah well.) Thus I know from personal experience that good books are crucial, that they can have a profound effect on students, and that without them to inspire the next generation, a field will wither and die.

Which (to get finally to the topic of this review, as promised earlier) is reason enough to welcome the recent book *Nonlinear Dynamics in Physiology and Medicine* [13], edited by Beuter, Glass, Mackey and Titcombe, four members of the Center for Nonlinear Dynamics, or CND. With six Canadian universities as participating members, spanning physiology, mathematics, neurology and physics departments, and with some of the best mathematical physiologists in the world, the CND stands out as one of the great international centres. Not only that, but the CND has also organised a number of summer schools (in 1996, 1997 and 2000) that have served as the training ground for many younger modellers. The book edited by Beuter et al. is a compilation of notes from these summer schools. It's partly a terse mathematics book (particularly the first few chapters on nonlinear dynamics) and partly a presentation of somewhat unconnected research questions (replication of blood cells, the pupil light reflex, reentry in excitable media, and muscular tremor), but it gives a clear picture of the mathematics that arises from the study of physiological dynamical systems (despite the title, there really isn't much on medicine). The application of nonlinear dynamics to physiology has a long and illustrious history, beginning with the work of Weiner, Rosenbluth, Van der Pol, Bonhoeffer and FitzHugh, with modern applications in neurophysiology, calcium dynamics, cardiac electrophysiology, and a host of other areas. Although the breadth of this book is considerably less than this — it really deals only with the work of people at the CND, with little attention to much else — it is well worth having just for that. As part of the Springer Interdisciplinary Applied Mathematics series [14] it joins a line of books that are leading the way in showing how mathematics can be usefully applied to biology and physiology.

Given the current drive to sequence genomes, it is easy to forget that knowing the alphabet does not mean we have deciphered the language. Mathematical models are crucial, not only for the initial steps of finding the gene sequences, but also for the subsequent study of how a genetic alphabet can organise and control a complex structured physiology. Thus, while we list each A, C, G and T, let us also remember the words of Francis Bacon exhorting us to be neither ant nor spider. Let us attempt to be neither busy collectors of data nor spinners of intellectual cobwebs, but instead let us digest from both flower and field, using mathematics and experiment jointly to advance our understanding of some of the most important scientific questions of our time.

References

[1] Francis Bacon (1620) Novum Organum, I, 95. Based on the standard translation of James Spedding, Robert Leslie Ellis, and Douglas Denon Heath in The Works (Vol. VIII), published in Boston by Taggard and Thompson in 1863. (Text given in http://www.constitution.org/bacon/nov_org.htm)

[2] Daniel Bernoulli (1766) Essai d'une nouvelle analyse de la mortalité causée par la petite Vérole, & des avantages de l'Inoculation pour la prévenir. Mémoires de Mathématique et de Physique, Académie Royale des Sciences. English translation entitled "An attempt at a new analysis of the mortality caused by smallpox and of the advantages of inoculation to prevent it" in: L. Bradley, Smallpox Inoculation: An Eighteenth Century Mathematical Controversy, Adult Education Department, Nottingham, 1971, p. 21. An excellent mathematical discussion of the controversy is given by K. Dietz and J.A.P. Heesterbeek, (2002) Daniel Bernoulli's epidemiological model revisited, Mathematical Biosciences, 180, 1–21.

[3] Jean-le-Rond d'Alembert (1761) Sur l'application du calcul des probabilités à l'inoculation de la petite vérole; In Opuscules Mathématiques, vol. 2; p. 26 ff, David, Paris.

[4] Otto Frank (1899) Die Grundform des Arteriellen Pulses, Zeitschrift für Biologie, 37: 483–526. A translation is given by K. Sagawa, R.K. Lie, and J. Schaefer (1990) J. Mol. Cell. Cardiol., 22, 253–277. Just as well, as I can't read German.

[5] H. Helmholtz (1850) Note sur la vitesse de propagation de l'agent nerveux dans les nerfs rachidiens. C. R. Acad. Sci. (Paris), 30: 204–206. A fascinating discussion of the history of electrophysiology is given by M. Piccolino (1998) Animal electricity and the birth of electrophysiology: The legacy of Luigi Galvani, Brain Research Bulletin, 46: 381–407.

[6] H. Helmholtz (1875) On the Sensations of Tone as a Physiological Basis for the Theory of Music, Longmans, Green and Co., London. I inherited a copy of this book from my grandfather, who was an accomplished violinist. I don't know how useful this book was for that, although I suspect not very.

[7] C.S. Peskin, D.M. McQueen (1995) A general method for the computer simulation of biological systems interacting with fluids. Symp. Soc. Exp. Biol. 49:265–76. C.S. Peskin (2002) The immersed boundary method, Acta Numerica 11:479–517. MR 2009378

[8] Rall W., Rinzel J. (1973) Branch input resistance and steady attenuation for input to one branch of a dendritic neuron model, Biophysical Journal, 13: 648–87. J. Rinzel, J.B. Keller (1973) Traveling wave solutions of a nerve conduction equation. Biophysical Journal, 13: 1313–37. Not many physiological modellers have had papers with the most eminent people on both sides of the fence, and in the same journal volume, no less.

[9] C. Fall, E. Marland, J. Wagner & J. Tyson (Eds.) (2002), Computational Cell Biology, Springer, New York, 2002. This book was begun by Joel Keizer, who died before he could complete it. It was finished by three of Keizer's students, and one of Keizer's long-time colleagues. A lot of the early material in the book is based on Keizer's research. MR 1911592 (2003j:92004)

[10] C.J. Meinrenken, J.G. Borst, B. Sakmann (2003) Local routes revisited: the space and time dependence of the Ca^{2+} signal for phasic transmitter release at the rat calyx of Held. Journal of Physiology, 547: 665–89. E. Neher (1998) Vesicle pools and Ca^{2+} microdomains: new tools for understanding their roles in neurotransmitter release. Neuron 20: 389–99. As it happens, a lot of the modeling of calcium in synapses has used some of Keizer's early work, particularly on the buffered diffusion equation.

[11] Well, OK, I haven't got a proper reference for this quote (which Murray adapted from an Arab proverb), but he did say it. I promise. He even wrote it somewhere, as he will admit when pressed.

[12] J.D. Murray (1977) Lectures on Nonlinear Differential Equation Models in Biology, Clarendon Press, Oxford. Mostly superseded by his more recent books and, sadly, out of print and difficult to find. A search on abebooks.com turns up only a single copy, for $136, with the lovely comment "The text is printed in a font resembling Courier." Quite so. His later books used real fonts, I believe.

[13] A. Beuter, L. Glass, M.C. Mackey, M.S. Titcombe (Eds.) (2003) Nonlinear Dynamics in Physiology and Medicine, Springer, New York, 2003. MR 2018243

[14] The Springer Interdisciplinary Applied Mathematics Series has published (or republished) some of the most important and best-known books in mathematical biology, including Mathematical Biology (Murray), Mathematical Physiology (Keener and Sneyd), The Geometry of

Biological Time (Winfree), Diffusion and Ecological Problems (Okubo and Levin), Branching Processes in Biology (Kimmel and Axelrod), Computational Cell Biology (edited by Fall et al.) and Molecular Modeling and Simulation; An Interdisciplinary Guide (Schlick). An impressive line-up by any standard, and Springer is to be commended. My bias is obvious, but my point valid nonetheless.

James Sneyd
University of Auckland
E-mail address: sneyd@math.auckland.ac.nz