
Conferences

AMS Short Courses

Lecture notes will be available to those who register for this course. Advance registration fees: \$80 (\$35/student/unemployed/emeritus; on-site registration fees: \$95 (\$45/student/unemployed/emeritus). Registration and housing information can be found in this issue of the *Notices*; see the section "Registering in Advance and Hotel Accommodations" in the announcement for the Meetings in New Orleans.

Mathematical Biology

New Orleans, Louisiana, January 8–9, 2001

This program is under the direction of James Sneyd, Massey University, New Zealand. Please refer to the Web site maintained by the organizer at <http://www.massey.ac.nz/~jsneyd/ams/> for the most current information.

Although mathematical biology is one of the fastest growing areas of applied mathematics, with tremendous vitality and energy, there are still substantial barriers to any mathematician wishing to enter the field. Firstly, research in mathematical biology is done along very different lines than is most other mathematical research, as it is judged entirely on the quality of the science, not on the complexity or elegance of the mathematics involved. Secondly, it requires a substantial investment in time to learn the biological vocabulary and facts and to establish collaborations with experimentalists.

Breaking down these barriers is to the benefit of all mathematicians, as the close involvement of mathematics in the biological sciences greatly enriches both disciplines. In addition (to raise more mercenary points), such interdisciplinary efforts tend to be highly regarded by funding agencies and academic administrations.

The goal of this proposed AMS short course will be to present a selected number of topics in mathematical biology to a mathematical audience. The talks will not be aimed at specialists in each field, but will be aimed at those in more theoretical areas, with the goal of stimulating their interest and showing them how best they could begin research in mathematical biology themselves. Each talk will include a brief historical overview of the field, a summary of the present uses of mathematics in the field, and a discussion of open problems where mathematicians could reasonably expect to be useful.

Because mathematical biology is such a huge field, ranging from studies of individual molecules such as DNA to the study of entire populations, it is simply not possible to provide an overview of the entire field in a single short

course. Instead, we shall cover only a relatively small number of topics. Four of the six talks will be organized around the theme of excitable cell modelling and its applications to neurophysiology and cell physiology. Of the remaining two talks, one will be on human genetics, while the other will be on models of HIV (or other viral) infection. Thus participants will be able to learn about a range of different types of mathematical models, but with an overall emphasis on biophysically based models.

Mathematical Aspects of Vision

Daniel Tranchina, New York University

Synopsis

The first stage of processing of visual information is the retina. It is a complex network, consisting of five major classes of neurons, which lines the back of the eye. The retina acts as a transducer which transforms the visual image into electrical signals sent to the brain via the optic nerve. Within the retina, information is encoded in an analog manner by the voltage difference across the membrane of each neuron.

At the output stage, the retinal ganglion cell level, the slowly and smoothly varying voltage signals are converted to electrical impulses which are transmitted to higher brain areas along several hundred thousand axons comprising the optic nerve.

The lateral geniculate nucleus (LGN) of the thalamus receives input from retinal ganglion cells and acts as a gateway for sensory information from the retina to the visual cortex. The LGN transforms its inputs to some extent and sends its output ("projects") to the primary visual cortex (V1). V1 projects to higher cortical areas, sends feedback to the LGN, and receives feedback from higher cortical areas.

One overarching goal of visual neuroscience is to understand the neurophysiological basis of visual perception. Many laboratory experiments along these lines involve recording the electrical responses of neurons to visual stimuli created by the experimenter and imaged onto the retina. One goal is to describe quantitatively the input-output properties of each neuron, that is, the relationship between stimulus and response. Another is to understand the underlying biophysical mechanisms.

It is easy to see how mathematics comes into play. The visual stimulus is described by a spectral density function, $f(x, y, t, \lambda)$, where x and y are coordinates in visual space, t is time, and λ is the wavelength of light. The response of a neuron $r(t)$ is a function of time, and it is a functional of $f(x, y, t, \lambda)$. Much of the difficulty in sensory physiology in general has to do with the fact that there is no general-purpose method to characterize the functional describing

the input-output properties of a neuron. In fact, there is not a single case in all of visual neuroscience where such a functional has been completely characterized. The greatest progress has been in the retina. Ideally, the functional would consist of a system of differential or differential-integral equations describing in detail the physical processes linking stimulus and response. Thus the problems of characterizing and understanding the neural basis of response properties are closely intertwined.

In general, retinal neurons are highly nonlinear devices. This is a consequence of the fact that the retina must encode information over an enormous dynamic range of input. The intensity of reflected sunlight on a bright, sunny beach is roughly ten orders of magnitude greater than the intensity of reflected starlight. The dynamic range of retinal output is only about two orders of magnitude as a consequence of various forms of neural noise. The retina deals with this mismatch problem through light adaptation, which adjusts response sensitivity according to the ambient level of illumination. I will describe an important stage of light adaptation in photoreceptors and explain it in the context of a mathematical model for phototransduction.

One upshot of light adaptation is that the retina presents to the brain a signal which is much more closely related to the contrast in visual scenes rather than to absolute light levels. A fringe benefit from the mathematician's point of view is that neurons in the retina, before the retinal ganglion cell level, respond approximately linearly to physiological perturbations of light around a mean level. That is to say, their functionals are approximately linear when parametrized by the mean light level. I will explain how Fourier methods have exploited this linearity to characterize and model the first stages of visual information processing in the retina. The concept of the "receptive field" will be introduced, and the "spatiotemporal transfer function" and "spatiotemporal impulse response function" for quasi-linear neurons will be explained. Some particular examples will be derived and assembled into a model for the retinal ganglion cell. At the output stage of the retina, one can begin to see some of the neural basis for edge detection.

Neurons in the LGN behave much like the retinal ganglion cells that provide their input. However, at the level of V1, neurons start to become selective to stimulus "features". In particular, many neurons in V1 respond selectively to oriented contours passing through their receptive fields only over a narrow range of orientations. For example, some neurons respond best to vertical bars or edges, and the response magnitude when the contour is tilted by 20 degrees away from vertical. Across a population of cortical neurons all "preferred" orientations between zero and 180 degrees are represented. Neurons with like preferred orientation and nearby receptive field locations are organized into columns; a full set of such columns covering 180 degrees is called a hypercolumn. The sensitivity to stimulus orientation is a new response property not exhibited in earlier stages in the visual system. It is mediated in part through excitatory and inhibitory synaptic interactions among some cortical nonlinear models of orientation tuning. Progress in this area is hampered by an explosion in the number of neurons in the visual cortex

compared to the LGN or retina. Hence, new analytical and computational methods are needed for large-scale modeling of neuronal networks. I will describe some new approaches that borrow concepts and techniques from statistical mechanics.

Reading list

- [1] D. Q. NYKAMP and D. TRANCHINA, A population density approach that facilitates large-scale modeling of neural networks: Analysis and application to orientation tuning, *J. Comput. Neuroscience* **8** (2000), 19–50.
- [2] ROBERT W. RODIECK, *The First Steps in Seeing*, Sinauer Associates, Sunderland, MA, 1998.
- [3] M. SCHETZEN, *The Volterra and Wiener Theories of Nonlinear Systems*, Robert E. Kreiger Publishing Company, Malabar, FL, 1989.
- [4] BRIAN A. WANDELL, *Foundations of Vision*, Sinauer Associates, Sunderland, MA, 1995.

Application of Population Isolates in Gene Mapping

Kenneth Lange, UCLA

Synopsis

To map disease genes, geneticists conduct genome scans involving hundreds of genetic markers. Each marker represents a particular place (locus) on the human genome where there is substantial variation among individuals. The variants at each marker are called alleles. Genotyping, that is, the determination of the two alleles a person bears at each marker, is carried out on pedigrees of related individuals. Recombination reshuffles chromosomes and breaks up blocks of cotransmitted genes. To ensure that a pedigree contains information on a particular disease, at least one member of the pedigree should be affected by the disease. Given this selection criterion, the cosegregation of the marker alleles and the disease can be followed in each pedigree and the recombination fractions between particular markers and the disease locus estimated.

Haplotype mapping is an alternative to pedigree mapping. If enough genetic markers are typed in the vicinity of a disease locus and the number of disease mutations within a given population is small, then it is often possible to identify a unique haplotype signature for each mutation. These haplotype signatures are determined by their allelic backgrounds at nearby markers. Since the disease locus always resides in the conserved part of a signature, one can map the disease locus to the smallest region of overlap defined by the recombination events disrupting the various signatures. This method of mapping can be more powerful than mapping by pedigree methods, because it exploits fossil recombination events hundreds of years old and involves genotyping only affected children and possibly their parents.

In many studies geneticists have turned to population isolates such as the Amish or the entire populations of Iceland, Finland, or Costa Rica to map particular genes. Each isolate has its own particular list of rare, high-frequency genetic diseases. Some geneticists have questioned the value of population isolates as opposed to larger, outbred populations in mapping genes for common diseases. This

issue has great practical relevance as the biotechnology industry invests large sums in screening population isolates.

To resolve the practical issue of choosing a good study population, we need more realistic models that take into account population growth and the cotransmission of whole chromosome segments. This talk focuses on some relevant mathematical techniques that shed light on these complications. Time permitting, we will look at some of the following questions: How many mutations should one expect in a population of a given size? What is the impact of fast versus slow population growth? Is haplotype mapping apt to be more successful for dominant or recessive diseases? What combinations of fitness and mutation rate combine to provide the most favorable outcome? Can one quantify the comparative advantages of pedigree mapping and haplotype mapping? Both deterministic models based on difference equations and stochastic models based on branching processes, diffusion processes, and coalescent theory come into play.

Reading List

- [1] P. DONNELLY and S. TAVARÉ, Coalescents and genealogical structure under neutrality, *Ann. Rev. Genet.* **29** (1995), 401–421.
- [2] R. FAN and K. LANGE, Models for haplotype evolution in a non-stationary population, *Theoret. Pop. Bio.* **53** (1998), 184–198.
- [3] ———, Diffusion process calculations for mutant genes in nonstationary populations, *Statistics in Molecular Biology and Genetics* (edited by F. Seillier-Moiseiwitsch), Institute of Mathematical Statistics Lecture Notes-Monograph Series, vol. 33, The Institute of Mathematical Statistics and the American Mathematical Society, 1999, pp. 38–55.
- [4] J. F. C. KINGMAN, The coalescent, *Stochastic Proc. Appl.* **13** (1982), 235–248.
- [5] K. LANGE, *Mathematical and Statistical Methods for Genetic Analysis*, Springer-Verlag, New York, 1997.
- [6] K. LANGE and R. FAN, Branching process models for mutant genes in nonstationary populations, *Theoret. Pop. Bio.* **51** (1997), 118–133.

Arrhythmias by Dimension

J. P. Keener, University of Utah

Synopsis

Abnormalities of function of the cardiac conduction system are the cause of death of thousands of people every day. For that reason the study of cardiac arrhythmias is of great interest from a medical and scientific perspective. However, cardiac arrhythmias are also interesting for mathematical reasons, because the cardiac conduction system can be viewed as a dynamical system and the variety of its behaviors can be studied from the viewpoint of dynamical systems theory.

Strictly speaking, a cardiac arrhythmia is any departure of the heartbeat from strict periodicity. In that sense all living persons have arrhythmias. However, the arrhythmias of interest are those which have physiological consequences that would be considered abnormal.

There are (at least) three challenges presented by cardiac arrhythmias. The first is simply to identify the different arrhythmias and their mechanisms. The second is to understand the cause or origin of each arrhythmia, and the third is to determine how to control the arrhythmia so that

its harmful effects can be avoided. In this talk we will discuss only the first of these challenges, namely, a classification of arrhythmias. The classification we will give is based on spatial dimension and is therefore useful for mathematicians, but probably not for physicians.

Zero-dimensional arrhythmias are those involving single cells or small collections of cells. These have often been studied using simple caricatures of nonlinear oscillators or small systems of coupled or forced nonlinear oscillators (Glass and Mackey, 1988). An example of a zero-dimensional arrhythmia is SA nodal dysfunction or AV nodal conduction failure.

One-dimensional arrhythmias are characterized as such because their existence relies in some crucial way on a one-dimensional path of propagation. Arrhythmias of this type include the Bundle Branch Blocks and Wolff-Parkinson-White Syndrome. One-dimensional arrhythmias are the easiest of all arrhythmias to treat clinically. Their mathematical description typically involves diffusion reaction equations in one spatial dimension. Two-dimensional arrhythmias are associated with two-dimensional self-sustained waves of activity, such as occur during atrial flutter or fibrillation. Three-dimensional arrhythmias are self-sustained waves of electrical activity that occur in the ventricles. The simplest of these, monomorphic tachycardia, is probably a scrollwave (Winfree, 1987). However, ventricular fibrillation certainly has a more complicated structure and behavior.

It should be noted that there is currently no known method of treatment to eliminate the two- and three-dimensional arrhythmias other than by application of a large electrical current.

The mathematical study of the two- and three-dimensional arrhythmias is complicated by the fact that cardiac tissue is an anisotropic, inhomogeneous, irregularly shaped bidomain (Keener and Sneyd, 1998). At this point our understanding of these waves comes almost entirely from numerical simulations.

Reading List

- [1] L. GLASS and M. C. MACKAY, *From Clocks to Chaos: The Rhythms of Life*, Princeton University Press, Princeton, NJ, 1988.
- [2] J. KEENER and J. SNEYD, *Mathematical Physiology*, Springer-Verlag, New York, 1998.
- [3] A. T. WINFREE, *When Time Breaks Down*, Princeton University Press, Princeton, NJ, 1987.

Calcium Excitability: The Dynamics of Calcium Homeostasis

James Sneyd, Massey University, New Zealand

Synopsis

In some of the other talks we have seen how active control of the membrane potential leads to complicated dynamical behavior and how cells can thus use their membrane potential as an intercellular signalling mechanism. Such electrical communication underlies all neurophysiological systems.

What is not so well known is the fact that calcium plays a similar role, both within single cells and between multiple cells. Thus, the study of the dynamic properties

of calcium shows many mathematical similarities with models based on electrical excitability, but the physiological mechanisms are quite distinct.

In response to agonists such as hormones or neurotransmitters, a wide variety of cell types exhibit oscillations in the concentration of intracellular free calcium ions. In larger cells these oscillations often take the form of periodic intracellular waves, and such waves are commonly seen travelling from cell to cell, forming an intercellular calcium wave. The exact physiological function of these calcium waves and oscillations is not completely clear in any cell type. Nevertheless, they are believed to be one important mechanism whereby cells can control their behavior and coordinate with their neighbors. For instance, in response to mechanical stimulation of a single cell, ciliated tracheal epithelial cells respond with an intercellular calcium wave that originates at the stimulated cell and travels to tens, or even hundreds, of other cells in the culture. Since an increase in intracellular calcium concentration stimulates the beating of the cilia, this intercellular calcium wave serves to coordinate the ciliary activity of large numbers of cells, thus increasing the efficiency of mucus transport in the trachea. In other cell types the frequency of calcium oscillations has been shown to control gene expression, hormone secretion, cell differentiation, and other crucial cellular functions. The study of these calcium oscillations and waves is thus one of great physiological interest.

Not only is the study of calcium oscillations and waves important from the physiological point of view, the mathematics involved is nontrivial and interesting. Most models of calcium waves are of the excitable reaction-diffusion type, and, as yet, very little is known about the properties of travelling wave solutions in these highly nonlinear systems. The existence and importance of calcium buffers and intercellular boundaries add additional complications to what is already a difficult problem.

In my talk I shall present a brief history of models of calcium waves and oscillations, from the early model of Goldbeter, Dupont and Berridge in 1990 to more recent detailed models (for instance, LeBeau et al., 1999). I shall then discuss how the modelling work has answered (at least partially) specific physiological questions and thus shall show how mathematicians and experimentalists can combine effectively to address problems that would not be soluble by either working independently. I shall end by discussing some of the mathematical questions raised by this modelling work and by presenting a number of open problems.

Reading List

- [1] M. J. BERRIDGE, Elementary and global aspects of calcium signalling, *J. Physiol.* **499** (1997), 291–306.
- [2] G. W. DE YOUNG and J. KEIZER, A single pool IP₃-receptor based model for agonist stimulated Ca²⁺ oscillations, *Proc. Nat. Acad. Sci. USA* **89** (1992), 9895–9899.
- [3] A. GOLDBETER, *Biochemical Oscillations and Cellular Rhythms: The Molecular Bases of Periodic and Chaotic Behaviour*, Cambridge University Press, Cambridge, UK, 1996.
- [4] A. GOLDBETER, G. DUPONT, and M. J. BERRIDGE, Minimal model for signal-induced Ca²⁺ oscillations and for their frequency

encoding through protein phosphorylation, *Proc. Nat. Acad. Sci. USA* **87** (1990), 1461–1465.

- [5] J. P. KEENER and J. SNEYD, *Mathematical Physiology*, Springer-Verlag, New York, 1998.
- [6] A. P. LEBEAU, D. I. YULE, G. E. GROBLEWSKI, and J. SNEYD, Agonist-dependent phosphorylation of the inositol 1,4,5-trisphosphate receptor: A possible mechanism for agonist-specific calcium oscillations in pancreatic acinar cells, *J. Gen. Physiol.* **113** (1999), 851–871.
- [7] J. SNEYD, J. KEIZER, and M. J. SANDERSON, Mechanisms of calcium oscillations and waves: A quantitative analysis, *FASEB J.* **9** (1995), 1463–1472.
- [8] J. SNEYD, B. WETTON, A. C. CHARLES, and M. J. SANDERSON, Intercellular calcium waves mediated by diffusion of inositol trisphosphate: A two-dimensional model, *Amer. J. Physiology (Cell Physiology)* **268** (1995), C1537–C1545.
- [9] A. P. THOMAS, G. S. J. BIRD, G. HAJNOCZKY, L. D. ROBB-GASPERS, and J. W. J. PUTNEY, Spatial and temporal aspects of cellular calcium signaling, *FASEB J.* **10** (1996), 1505–1517.

Modeling Viral Infection

Alan Perelson, Los Alamos

Synopsis

I will review mathematical models of the dynamics of viral infection with infected individuals. The review will focus on models of HIV infection, comparison with experiments, and identification of important biological parameters. By analyzing experiments in which drugs or other means have been used to perturb the infection process, four different time scales have been identified. Similar techniques have been applied to other viral infections, such as hepatitis B and hepatitis C virus, and will be mentioned.

Title to be announced

David Terman