Mathematical Biology Newsletter

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1990 SMB ANNUAL MEETING JULY 16-20, 1990, CHICAGO

The 1990 SMB Annual Meeting will be held in conjunction with the SIAM Annual Meeting. The program has been finalized, and listed below are those sessions which should be of particular interest to SMB Members.

Monday, July 16, 1990

10:30 am - 12:30 pm
CONTRIBUTED PRESENTATIONS, 3A/GOLD COAST ROOM
MATHEMATICAL BIOLOGY 1
Sponsored by SMB; Chair: Torcom Chorbajian, University of Northern Colorado

10:30 am. **Self-complicating Dynamics of Evolution.** Michael Conrad, Wayne State University.

For a population to evolve there must be a reasonable probability that genetic variation of the constituent organisms carries it from one adaptive peak to another. But in order to occupy an adaptive peak (to be fit) the organisms should not be overly unstable to phenotypic perturbations. May's complexity-stability theorem suggests that organisms that are complex in terms of numbers of components and interactions are more likely to meet the peak-climbing condition, but less likely to meet the stability condition. Systems that are characterized by a high degree of component redundancy and multiple weak interactions satisfy these conflicting pressures.

10:45 am. **Protein Evolution on Rugged Landscapes.** Catherine A. Macken, Stanford University; Alan S. Perelson, Los Alamos National Laboratory.

The rapid evolution of antibody molecules during an immune response enables the immune system to respond to a vast array of antigenic challenges. We develop and analyze a model of protein evolution in which the evolutionary process is viewed as hill climbing on a random fitness landscape. A large number of local optima exist in these landscapes. We compare statistics of walks to local optima with observations on mutation of antibody genes during an immune response. Such a hill climbing process may underlie the evolution of antibody molecules by somatic hypermutation.

11:00 am. **The DNA End-Replication Problem and Cellular Senescence.** Michael Z. Levy and Calvin B. Harley, McMaster University, Canada.

DNA polymerase requires a labile primer to initiate unidirectional 5'-3' synthesis. Thus, a gap of unreplicated bases would be present at the 5' end of each new strand unless special mechanisms circumvent this problem. After many generations, the 46 chromosomes of human cells would have a distribution of terminal (telomere) DNA lengths, the shortest of which could affect chromosome stability, gene function, and ultimately cell viability. We derived a relationship that predicts the fraction of cells having less than a critical number of deletions on any telomere at any generation. Allowing for variation in cell doubling time, we show that the critical number of deletions occurring in culture consistent with observed kinetics of cellular senescence is ≈25. This model is also in accord with data showing a linear decrease of ≈50 base pairs (bp) in telomere length per generation *in vitro.* Thus, the end-replication problem could explain the observed loss of telomeric DNA with cellular aging.

11:15 am. **Gene Regulation as a Problem in the Analysis of Mis-aligned Data.** Charles E. Lawrence and Andrew A. Reilly, Wadsworth Center for Laboratories & Research, New York State Department of Health, Albany.

The regulation of gene expression is largely effectuated by the binding of cellular constituents to multi-element "signal" sites on DNA/RNA sequences. We propose a method for the identification and characterization of these sites when the signal sequence, the locations of the sites, and the spacing of the elements are all unknown. The solution is cast as a specific example of a more general problem: parameter estimation for multivariate data in which the data indices have been permuted. It takes the form of a finite mixture with the special features that subpopulations share common parameters. An application to translation initiation sites illustrates the methods.

11:30 am. **New Methods of Calculating Biomolecular Conformation from Theoretical and Experimental Distance Constraints.** T. F. Havel, University of Michigan, Ann Arbor.

A recurring problem in molecular biophysics is to find all possible conformations (spatial structures) for a molecule such that the interatomic distances all lie within given lower and upper bounds. We describe a new package of computer programs that enables us to reliably solve this problem even for proteins and nucleic acids containing more than a thousand atoms. These programs implement a variety of recent mathematical developments from fields as diverse as algorithmic combinatorics, multidimensional scaling and nonlinear optimization. Some examples of their application to the determination of biomolecular structure from NMR data are also given.

11:45 am. **A Model of Autocrine/Paracrine Tumor Growth Control.** Seth Michelson, Syntex Research USA, Palo Alto; John T. Leith, Brown University.

A mathematical model describing autocrine and paracrine control of tumor growth has been developed. The model modifies the logistic equation of Verhulst, by using autocrine controls as modifiers of the Malthusian growth rate (r), and paracrine controls as modifiers of environmental factors (K). The control mechanisms are expressed in terms of "candidate" functions, based upon the dynamic distribution of TGF-alpha and TGF-beta in the local tumor environment.

Three paradigms of tissue growth have been modeled and simulated: normal tissue wound repair, unrestricted, unperturbed tumor growth, and tumor growth in a (radiation) damaged environment (the Tumor Bed Effect, TBE). Extensions to heterogeneous tumors, both with and without emergent subpopulations, and models of terminal differentiation are also discussed.

12:00 noon. **Modeling Growth Inhibitory/Stimulatory Factors in Cancerous/Normal Tissue.** John A. Adam, Old Dominion University.

Experimental evidence exists to support the idea that growth inhibitory and stimulatory factors (GF's) may be released by malignant cell lines. Typically, at low concentrations a GF does not affect cell mitotic rates, but at intermediate concentrations it can stimulate mitotic activity, and at still higher concentrations can severely inhibit such activity. In this presentation a number of basic mathematical approaches to describe this phenomenon will be discussed, and their limitations and advantages compared. In particular, features of a number of diffusion models will be examined in the light of recent experimental work.

12:15 pm. **Paradoxical "Cure" of a Dynamical "Disease".** C. D. Thron, Dartmouth Medical School

It is shown that in a sequence of metabolic reactions with constant input regulated by negative feedback from the end-product a "dynamical disease," *i.e.* instability, can be caused by a deficiency of end-product metabolizing enzyme, and "cured" by the seemingly paradoxical use of a competitive inhibitor of the deficient enzyme. Analysis of the Hurwitz determinant for one particular numerical example shows that most of the stabilizing effect of the competitive inhibitor is due to an increase in reaction order at the critical point (steady state), and not to increased heterogeneity of the time constants of the linearized system.

3:15 - 5:45 pm

CONTRIBUTED PRESENTATIONS 6A/GOLD COAST ROOM
MATHEMATICAL BIOLOGY 2
Sponsored by SMB; Chair: Michael Conrad, Wayne State University

3:15 pm. **A Neural Network for Color Constancy and Color Categorization.** Paul A. Dufort and Charles J. Lumsden, University of Toronto, Canada

We present a neurophysiologically plausible neural network model which instantiates color constancy and color categorization in a single unified framework. Previous models achieve similar effects but ignore the biological constraints. Color constancy in our model is achieved by a new application of the centre-surround opponency mechanisms which are common in the visual pathway. Color categorization emerges as a result of representing chromatic stimuli as vectors in a four-dimensional color space. A computer simulation of this model is subjected to the classic psychophysical tests which uncovered these phenomena, and its response matches the human results very closely.

3:30 pm. **Evolutionary Learning in Enzymatic Neurons with Internal Dynamics of Hopfield Circuits.** Qiang Gan, Yu Wei, Southeast University, P.R. China; Michael Conrad, Wayne State University

Intraneuronal dynamics plays an important role in the information processing of neural systems. Suitably complicated neuronal models with internal dynamics will likely provide an approach to un-fully interconnected neural networks. We introduce a new kind of enzymatic neuron consisting of read-out enzymes and internal dynamics of Hopfield circuits. In fact, the dynamics in Hopfield circuits are special cases of the reaction-diffusion processes, but the dynamical parameters are determined by energy functions. Based on the previous research of Gan et al. and Kirby et al., we develop an evolutionary learning algorithm with energy minimization as the criterion for best performance. The algorithm can be used to train a neural network to accomplish such tasks as optimization and robot navigation control.

3:45 pm. **Use of Recurrence Plots to Characterize Cardiac Interbeat Intervals**. M. Koebbe, G. Mayer-Kress, Univ. of California, Santa Cruz, and J. P. Zbilut, Rush Univ. and Hines VA, Chicago.

Recovering information about the periodic behavior of a non-stationary signal typically requires a large data set and extensive off-line analysis. Recently, Eckmann, Kamphorst and Ruelle proposed creating a "recurrence plot" to appreciate the dynamics of a time series. This method displays the evolution of the distances between n-dimensional reconstructed vectors in a square matrix. Geometrical properties of this picture provide complexity and local rate of divergence estimates. This method was applied to the heart-waves of four subjects with a history of congestive heart failure as they were administered normal saline.

4:00 pm. **Redundant Parameters and Degenerate Formulas in Models of Ion Channel Conductance**. Michael MacConaill, University of Ottawa, Canada.

The transmembrane ionic conductance relations described by Adrian (Progr.Biophys.Molec.Biol.,**19**:341, 1969) and others under the electro-diffusion paradigm have been reanalysed using the barrier function approach (MacConaill in Keeling and Benham (Eds), **Ion Transport**, p369, 1989). Seventeen initial models can be delineated using five basic formulas. These formulas may contain constant factors which become confounded with the permeability term of the conductance relation. The slope and curvature of experimentally derived barrier functions can determine the formula required to model it: parameter fitting will need standardized conventions for frames of reference. With the models derived from carrier processes, several sets of parameter values lead to collapse of a complex formula into one of the simpler forms. Thus some of the models proposed in the literature, or their equivalents under other paradigms, cannot be experimentally resolved.

4:15 pm. **Domain Decomposition to Solve for Acid-Base Balance in the Mammalian Kidney — Preliminary Report**. Raymond Mejia and Mark A. Knepper, NHLBI and NIDDK, National Institutes of Health.

Domain decomposition with parameter continuation has been used to solve differential equations that describe the renal concentrating mechanism [R. Mejia and J.L. Stephenson, Math. Biosci. 68:279—298 (1984)]. Differential algebraic equations that describe acid-base transport are now solved. Solute and fluid conservation, equations of motion, buffer balance and electroneutrality are described by:

$$\partial_t (AC) + \partial_x [F_v C - A(D\partial_x C + uC\partial_x \psi)] = -J + AS$$
$$\partial_t A + \partial_x F_v = -J_V$$
$$\partial_x P = -R_v F_v$$
$$pH = pK_B + \log(C_B - / C_{HB})$$
$$\langle z, C \rangle = -\langle z, J \rangle = 0$$

t is time, x distance, A cross-sectional area, F_v volume flow. Solute concentration is C, source S, flux J, and mobility u. ψ is electrical potential, P hydrostatic pressure, and R_v is resistance to flow. Subscripts B^- and HB designate the base and protonated forms of buffer pair B with dissociation constant K_B. **z** is the vector of valances for all species. An $O(\Delta x^4)$ accurate numerical scheme is demonstrated in a model with several buffers and many solutes.

4:30 pm. **Existence and Uniqueness Results for Flow of Solutes in a Nephron of the Kidney**. J.B. Garner, Mississippi State University

Boundary value problems which model multisolute flow in a nephron of the kidney are given. The model includes Bowman's space, the cortical interstitium, and the pelvis as well-stirred baths and represents the glomerulus, post-glomerulus capillary, and vas rectum as systems of flow tubes. The boundary value problems consist of large systems of differential and integral equations in the unknown solute concentrations, hydrostatic pressures, and volume flow rates. The implicit function theorem is used to obtain local existence and uniqueness results for these problems.

4:45 pm. **The Fractal Aspect of Stomach-Brain Interactions**. Berj L. Bardakjian and Jose Carlos Moraes, University of Toronto, Canada.

The electrical control activity (ECA) in the stomach generally exhibits a regular rhythmic pattern. However, in response to neural stimuli, the ECA can exhibit strange behavior which causes disorders in gastric motility. The regular ECA in the stomach has been modelled by a population of coupled nonlinear oscillators. The aim of this study is to investigate the nature of the strange behavior of the ECA using animal and computer models. In animal studies, the fractal aspect of canine gastric ECA (before and during neural stimulation) was quantified using the correlation dimension "δ". Typically, δ (Mean ± SE) changed from 1.006 ± 0.064 to 1.425 ± 0.154 in response to neural stimuli. In computer studies, changing the amount of coupling between two gastric oscillators caused the rhythmic outputs to exhibit strange behavior; Nonoscillatory, periodic, quasiperiodic and chaotic modes were observed. In conclusion, stomach-brain interactions that may change the amount of coupling between gastric oscillators, produce temporal fractals of gastric ECA.

5:00 pm. **A Thermokinetic View of Cellular Ionic Transport**. Frances K. Skinner, Charles A. Ward, Berj L. Bardakjian, University of Toronto, Canada.

A common equation in electrophysiology is the Goldman-Hodgkin-Katz (GHK) current equation. It is derived from the Nernst-Planck equation by making several assumptions. Two of the assumptions are that equilibrium exists at the two interfaces (intracellular and extracellular sides) and that the partition coefficients at the two interfaces are the same. To investigate these assumptions, we use Statistical Rate Theory and obtain a generalization of the GHK current equation. This equation shows that it is possible to obtain a current reversal at a potential other than the Nernst potential by having different partition coefficients at the two interfaces. During dynamic events, this generalized GHK current equation considers nonequilibrium effects which are significant if the time to reach equilibrium exceeds the transit time of the particular species.

5:15 pm. **Demographic Equation for Populations of Circulating Lymphocytes**. Ferdinando Degan, Università di Padova, Italy; Luciano Frusi, ITIF Vendramin Calergi, Italy.

Advanced research on various kinds of blood pathologies may take advantage of availability of models for lymphocyte population kinetics. In our model we propose to distinguish between two populations of lymphocytes: the young ones, still resident in the follicle until completing maturation, and the circulating ones, which

have "migrated" from the resident population.

Equations describing the two populations are coupled through migration terms. The mortality rate m of the circulating population is independent of the age of the individual cells, while still depending on time. Equations proposed in /1/, /2/ can be specially adapted for dealing with such a situation, thus allowing one to build models adequate to various possible behaviors of mortality m.

/1/ F. Degan, L. Frusi. "Mathematical models of Neoplastic Cell Cultures". IMACS transactions-85 Modelling of Biomedical Systems (Eisenfeld, Witten editors), p.31.
/2/ F. Degan, L. Frusi. "A General Demographic Model for Populations of Proliphic Cells". IMACS-Biomedical Modelling-89 (Eisenfeld, Levine editors), p.3.

5:30 pm. **Simple Control Systems in Biochemical Reactions**. Somdatta Sinha, Centre for Cellular & Molecular Biology, India.

Biochemical reactions underlie cellular behaviour and these reactions are controlled by feedback processes, both negative and positive. Theoretical analyses of these processes allow prediction of new behaviour and modification of the existing process for improved performance. Detailed description of particular biochemical reactions render modelling difficult due to the complexity of the systems. We have analyzed behaviour of simple control systems, such as, single negative feedback, coupled dual negative feedback, and coupled negative and positive feedback processes, the kind that are observed in many genetic and metabolic processes in microbial cells.

These studies show that some of the simple networks exhibit complex behavioural pattern, such as, period bifurcations and chaos, on perturbation. A simple method of adaptive control can be used which allow the systems to return to original state after perturbations.

Tuesday, July 17, 1990

8:30 am. *Networks in Neurophysiology*, **Nancy Kopell**, Boston University.

9:15 am. *Wanted: Applied Mathematicians to Try the Fruit Fly Challenge*, **Garrett Odell**, University of Washington.

10:30 am - 12:30 pm. **Minisymposium, Columbus A**
Spatio-Temporal Patterns in Neural Systems. This minisymposium will focus on topics connected with dynamic behavior and pattern formation in neurophysiology, cellular interactions, and neural networks. The speakers will describe theoretical approaches to neural networks with refractory states, the complex behavior of model neural systems in which recurrent inhibitory loops and mixed feedback are present, models of cellular and neuralinteractions in which competition for dominance leads to pattern selection, and models for oscillations in populations of pancreatic cells, close relatives of nerve cells. This minisymposium will complement an invited lecture by N. Kopell (Networks in Neurophysiology). After the formal presentations, a forum for discussion of current mathematical techniques, models, and their application to the study of both theoretical and experimental neural systems will be provided.
Organizers: **Leah Edelstein-Keshet**, University of British Columbia, Canada, and **G.B. Ermentrout**, University of Pittsburgh.
Dynamical Pattern Formation in Neural Networks, **Jack Cowan**, University of Chicago.
Delayed Mixed Feedback and the Complexity of Neural Dynamics, **John Milton** and **Michael C. Mackey**, McGill University, Canada.
Competition for Dominance in Cellular and Neural Networks, **G. Bard Ermentrout**, University of Pittsburgh and **L. Edelstein-Keshet**, University of British Columbia, Canada.
Theoretical Models for Synchronization of Electrical Oscillations in the Pancreatic Islet, **Cynthia L. Stokes, Arthur Sherman,** and **John Rinzel**, National Institutes of Health.

12:30-2:00 pm. **SMB Board of Directors Meeting**.

3:15-5:15 pm. **Minisymposium, Columbus C**
The Geometry and Topology of DNA. Sponsored by SMB.
The DNA of a living organism is a complex thread-like object which experiences interesting and nontrivial geometric and topological changes during vital cellular life processes. During the last decade, molecular biologists have developed techniques which use differential geometry and knot theory in the analysis of experiments on circular DNA. The aim of these experiments is to understand and quantize spatial molecular conformation and DNA enzyme mechanism. This new and perhaps unexpected interplay between experimental molecular biology and "pure" mathematics will be the subject of this minisymposium.
Organizer: **De Witt L. Sumners**, Florida State University
The Biological Implications of DNA Topology, **Nicholas R. Cozzarelli**, University of California, Berkeley
The Topology of DNA Recombination, (to be presented by organizer)
The Geometry of Supercoiled DNA, **James H. White**, University of California, Los Angeles
Topological Quantum Field Theory and DNA Topology, **Louis H. Kauffman**, University of Illinois, Chicago

3:15 - 5:15 pm. **Minisymposium, Grand Ballroom South.**
Nonlinear Patterns and Dynamical Behavior of Biological Reaction-Diffusion Systems. With the increasing use of mathematical analysis in the life sciences, the application of reaction-diffusion equations to biological processes has become of interest to phenomenological modelers. Developmental biology and population ecology have proven themselves to be especially fruitful ground for such an endeavor. The minisymposium speakers will concentrate on specific model systems in these two areas and present analysis of their dynamical behavior by a variety of analytical and numerical techniques. Emphasis will be given to pattern formation when diffusion is present or the possibility of deterministic chaos in its absence.
Organizer: **David J. Wollkind**, Washington State University.
A Cascading Development Model for Amphibian Embryos, **Kemble R. Yates**, Southern Oregon State College.
Complex Spatial Patterns from Tissue Interactions, **Valipuram S. Manoranjan**, University of Surrey, U.K.
Qualitative Analysis of a Parametrically-Forced Temperature-Dependent Model of a Mite Predator-Prey Interaction, **John B. Collings**, Washington State University.
Diffusive versus Morphological Instability: Analogous Ecological and Solidification Nonlinear Pattern Regulation, (to be presented by organizer)

5:30-6:30+ pm. **SMB Mixer and Business Meeting**

Wednesday, July 18, 1990

11:30 am. *Application of Dynamic Programming to Problems of Optimal Habitat Choice and Optimal Timing of Metamorphosis*, **Donald A. Ludwig**, University of British Columbia, Canada.

12:30 - 2:00 pm. **SMB Board of Directors Meeting**

3:15-5:15 pm. **Minisymposium, Columbus C**
Algorithms for DNA Sequence Matching and Analysis. Sponsored by SMB. This session focuses on new algorithms for use in DNA sequence and analysis. The problems solved by these algorithms have recently taken on new importance with the start of the Human Genome Project and the enormous amount of partial and complete DNA sequence and map information that is expected to be generated in the near future. Most algorithms in this problem domain have been based on fairly straightforward dynamic programming. With increasing amounts of data, and increasing sequence and pattern lengths, much more attention to time and space efficiency will be needed. The talks in this session all address this issue for different specific problems in DNA analysis. Talks show how to speedup dynamic programming for particular problems, or how to avoid dynamic programming entirely for problems where dynamic programming has previously been the method of choice in DNA algorithms.
Organizer: **Daniel Gusfield**, University of California, Davis
An Overview of Old and New Approaches to DNA Sequence Analysis (to be presented by organizer)
Analysis of Restriction Maps, **Webb Miller**, Pennsylvania State University, University Park
Sparse Dynamic Programming, **Raffaele Giancarlo**, Columbia University
Sublinear Algorithm for Similarity Searching, **Gene Myers**, University of Arizona

3:15 - 5:00 pm. **Contributed Presentations, Columbus G.**
Mathematical Models in Population Dynamics and Physiology.
Juvenile Dispersal, Limited Breeding Sites, and Metapopulation Dynamics in a Class of BIDE Models. **Gregory J. Davis** and **Robert W. Howe**, University of Wisconsin, Green Bay
Stimulation of Epidemics for Diseases Which May Cause Immunity in Age Structured Populations. **Fabio A. Milner**, Ila Universita de Roma, Italy.
A Nonlinear Poroelastic Model of Flow and Deformation in the Pulmonary Interstitium. **Jeffrey R. Sachs, James B. Grotberg** and **Matthew R. Glucksberg**, Northwestern University.
A Three Dimensional, Hexagonal Lattice Theory of Muscular Mechanics, **Theodore S. Feit**, Burbank Imaging, Burbank, CA.
Geometric Analysis of the Carpal Complex, **Deborah P. Levinson**, University of South Florida.
Threshold Behavior and Propagation for a Differential-Difference System, **Wei-zheng Gao**, State University of New York, Buffalo.
Canonical Pharmacokinetic Compartment Modeling, **Patrick D. McCray**, Searle Research and Development, Skokie, IL.

Thursday, July 18, 1990

10:30 am - 12:30 pm. **Minisymposium, Columbus G.**
Moving Ions Through Channels in Biological Membranes. Sponsored by SMB. Membranes surround and define biological cells by restricting movement of the cell's components. But some ions must cross membranes if cells are to receive and transmit chemical energy, or communicate with neighbors. Many of these ions cross membranes in aqueous channels made from proteins. These ionic channels (as they are called) control biological functions such as signalling in the nervous system, energy transduction in sensory cells, coordination of muscle contraction, pumping of the heart, secretion of salt and fluids in kidneys, transport in epithelial cells. Thus, the mechanisms by which channels control the movement of ions are significant. One mechanism is electrodiffusion, described by the Nernst-Planck and Poisson partial differential equations and boundary conditions used to study transport in semiconductors, ceramics, solid, and liquid electrolyte solutions. Speakers will derive, analyze, solve, and apply such equations in this context of channel permeation.
Organizer: **Robert S. Eisenberg**, Rush Presbyterian-St. Lukes Medical Center.
Ionic Channels in Biological Cells (to be presented by organizer)
Flow of Ions Through Narrow Membrane Channels, **Victor Barcilon**, University of Chicago, and Rush Medical College
Boundary Conditions for the Diffusion of Ions Through Cell Membrane Channels, **Peter Gates, K. E. Cooper, and J. L. Rae**, Mayo Medical School
Langevin Studies of Ion Motion in Framework Electrolytes, **Mark Ratner**, Rush Medical College, and Northwestern University; and **Abraham Nitzan**, Tel Aviv University, Israel

EXHIBITORS

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