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# 数理生物学懇談会
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***Japanese Association***
***for***
***Mathematical Biology***

## Obituary

# MASAHIKO HIGASHI - ECOLOGIST, MASTER WEAVER

August 11, 1954-March 27, 2000

Theoretical systems ecologist Masahiko Higashi was a weaver of human and ecological networks. He perished with four other ecologists in a tragic boating incident under treacherous wind and water conditions in the Sea of Cortez. At the time he was 45, survived by his wife of 19 years, Tomoko Nakamura, sons Torahiko Leonard (17) and Kazuhiko (11), daughter Sayuri (8), and his mother and father. His father is one of Japan's honored "national treasures" in recognition of his intricate designs in the art of bamboo basketry. The son's work showed the same refinement of artistry and style in another medium, mathematical ecology.

Masahiko - Higashi-san in the Japanese way - was Professor at Kyoto University's Center for Ecological Research at the time of his death. He was appointed Associate Professor in 1993, carrying with him the rank achieved that year at Ryukoku University after serving there as Lecturer since 1988. During 1986-88 he was a Fellow of the Japan Society for the Promotion of Science (J.S.P.S.), and from 1983-86 a Postdoctoral Fellow, then Research Associate, at the University of Georgia, Institute of Ecology (U.S.A.). He attained the Ph.D. in Systems and Computer Sciences and Applied Mathematics at S.U.N.Y.-Binghamton in 1983 (State University of New York, advisor: G.J. Klir), following an M.S. in Biophysics and Mathematical Biology from Kyoto University (advisor: E. Teramoto), and B.S. in Mathematics (advisor: M. Yamaguchi) and Biology (advisor, T. Miura). His joint background in biology and mathematics led him to original contributions in both areas.

Masahiko liked people and had a gift for bringing them together. He was a natural attractor for lively minds who circled him like moths at a flame. His humble and open nature, his easy confidence and intelligence in instructing others, were engaging. He always penetrated unknowns a little deeper and clearer than the next, but he never displayed any particular awareness of this. It was just a quiet fact among those who knew and worked with him. He had some endearing trademarks of expression. The circular motions of his writing hand and tapping of chalk against the chalk board as he explained the intricacies of something arcane - these must have been the same gene-given movements his master-weaver father used in plying his trails through the reeds of bamboo. And when he was receiving rather than giving understanding, he would acknowledge with quick affirmative bows of the head punctuated with a Japanese-inflected vocalization, "... hhaoh ... hhaoh ... hhaoh ...", that was his alone. Masahiko liked people, and people liked him.

He began building the personal and professional networks of his future as a graduate student at S.U.N.Y.-Binghamton shortly after his arrival in America in 1980. With budding awareness of ecology, and the importance of systems thinking to this field, Masahiko went to Binghamton to study systems science. From the outset he established himself as a brilliant student. He became interested in the emerging area of fuzzy set theory and the closely associated possibility theory, and decided to explore in his dissertation research the use of possibility theory for ecological modeling. This was contingent on solving a host of hard mathematical problems. In addressing these, he demonstrated his extraordinary mathematical background and talents for deep mathematical research. He was instrumental in making several seminal contributions to possibility theory and fuzzy set theory, which are recorded in eight mathematical papers published during 1982-85. For his dissertation (1983. A Systems Modelling Methodology: Probabilistic and Possibilistic Approaches. 299 pp.) he received at his graduation the highly

competitive 1984 S.U.N.Y. Distinguished Dissertation Award in Science, Mathematics and Engineering.

Following completion of his doctorate at Binghamton, Masahiko was attracted by his interests in mathematics, biology, and systems science to the University of Georgia program in systems ecology. He arrived there in 1983 with his wife and first son, newly born, and soon began interactions that would establish him as the central node in an international network of collaborators that in a few short years would touch five continents. He linked his new American colleagues with his academic family of origin - students of biophysics professor Ei Teramoto at Kyoto University. It was not long after Higashi left before two of these - Drs. H. Nakajima of Ritsumeikan University and K. Kawasaki of Doshisha University - made their way to Georgia also for extended periods of study.

As a Georgia postdoc and research associate, Higashi-san took a scientific turn to ecological network theory. He was there at a critical moment when a mathematical theory of environment was pointing to holistic determination - of parts by wholes - as the dominant mode of causality in connected nature (1989. Amer. Nat. 133, 288). He was able to confirm the basis for this - quantitative dominance of indirect effects in interactive networks - while building interactive relationships with an expanding family of ecosystem and population ecologists, empiricists and theoreticians, graduate students and professors. The mechanism was the summation of higher order, nonzero-sum terms of power series exceeding the values of direct, zero-sum interactions whose powers formed the series. The direct terms represented local energy or matter exchanges within ecological systems, and the series sums were totals (boundary, plus direct, plus indirect). The upshot was that ordinary local cause-and-effect carried by energy-matter transactions served mainly to establish, two components at a time, vast within- and across-scale interactive networks that, once in place and operating, shifted dominant causality from parts to the whole.

This was an elegant way to demonstrate the inherent wholeness of ecological organization, but it was mathematical and in its holism went against the favored grain of reductive empiricism. The mathematics made it theoretically clear that (and why) nature had to be unified by dominant indirect effects, but in an empirical science based mainly on the study of direct organism interactions, this was too heterodox for easy acceptance. The result has been generally ignored, its significance not seen or not well enough understood to become integrated into the fabric of conventional wisdom, though the term "indirect effects" is now appearing in empirical ecological literature with increasing frequency. Methodological intractability hinders real-world demonstration of what is so clear from theory, and in ecology empirical, not mathematical, proof is the standard.

Difficulties notwithstanding, the sureness and clarity of Masahiko's simple but incisive formulations, like the elementary knots and ties of his father's weavery, gave assurance that if the assumptions behind the mathematics were correct, dominant indirect effects will ultimately stand as an important basis for a new, more systemic, future ecology. His culminating papers in this area were with mathematician Hisao Nakajima - Indirect effects in ecological interaction networks I. the chain rule approach (1995. Math. Biosci. 130, 99), and II. the conjugate variable approach (1995. Math. Biosci. 130, 129). The titles make it clear why ecological acceptance will be slow in coming. Starting at Georgia, Higashi-san also contributed to a network revision of classical trophic dynamics - the study of energy and matter flows in food webs. After ecologist R.L. Lindeman's watershed paper introduced the subject in 1942, it became

established by mid-century as the basis of ecosystem ecology. Solar energy fixed by plants was transferred along food chains at low (±10 percent) efficiencies, giving rise to only three or four "trophic levels" (producers, herbivores, carnivores, top carnivores) before the original energy was effectively all dissipated. This became the textbook view that persists today. The result differs, however, when food chain abstractions are restored to their true form as woven webs with cycles.

Working in Kyoto with Georgia graduate student T.P. Burns, with whom a close friendship developed, the two partitioned food networks into two transfer modes inherent in their cyclic organization (1993, Ecol. Mod. 66, 1). In cycling, which is "mode 2", dissipation is a limit process reflected in the same kind of infinite series treated previously for indirect effects. In the limit, an indefinite number of trophic levels of tapering energy contents is generated as the energy and matter in biota - that is "food" - moves around the ecosystem, tending to become uniformly distributed in the process. Network unfolding (1989. J. theor. Biol. 140, 243) is the Higashi-Burns algorithm for transforming arbitrary food networks into isomorphic "macrochains" that differ from classic food chains in that their reciprocal constituents (organisms and trophic levels) are distributed, rather than discrete, in terms of their energy and matter contents. For example, the trophic composition of detritus is distributed because of many sources (anything that dies), hence so is that of detritivores and any subsequent organisms deriving sustenance from these. The features of energy cycling, extended energy supply, and homogenization of sources all conflict with the normative concepts still taught in contemporary textbooks. As history amply confirms, in science and other fields, established belief systems are hard to dislodge even in the face of new evidence. Once again, Higashi-san's contributions in an area difficult for non-mathematical minds to follow, have never received the attention they deserve. It may take a generation or more before the weight of accumulating errors prompts revisitation of the old trophic-dynamic ground, but when this happens due recognition of achievements made before their time is bound to occur.

When he returned to Kyoto after Georgia in 1986, the Higashi network continued to expand as he assumed new dimensions in scientific leadership. He conceived and promoted the first of two U.S.-Japan Cooperative Research Programs that brought the Teramoto laboratory and other Japanese researchers together with American ecologists from several institutions. He led a small group to Oak Ridge, Tennessee, which forged a long-lasting and productive link with Dr. D.L. DeAngelis and other ecologists at Oak Ridge National Laboratory. In 1986 he organized two symposia at the I.S.E.M. meeting (International Society for Ecological Modelling) in Syracuse, New York which led to a volume he coedited with Tom Burns (1991. Theoretical Studies of Ecosystems, The Network Perspective. Cambridge, 364 pp.). The second U.S.-Japan Cooperative Program, "Synthesis of Species Population Dynamics and Ecosystem Processes", culminated in a conference at the East-West Center in Honolulu in 1989 that brought together a diverse group of ecologists and fostered many interactions over several years. There were further meetings, for example, at Fukuoka, Japan and Racquette Lake in New York's Adirondack mountain wilderness.

Masahiko rejoined Kyoto University in 1993 (where he never actually relinquished his desk when he moved to Ryukoku five years earlier! – weaver holding the place for the thread to return) to assist with the development of a new Center for Ecological Research. Today this unit exists in a shining new modern facility in nearby Otsu. Efforts to establish the Center were to become a springboard for later development of a Japanese National Institute of Ecology. This effort continues today, and toward both the center and the national institute Masahiko

worked tirelessly during the remainder of his life. Reports are he was an indomitable force - of intellect, personality, compelling reason, and persuasion – for bringing these ends to fruition.

Still, he never let the lure and demands of executive promotion eclipse his primary interest in discovery. No year passed without at least one English language publication, and usually several in his native tongue. On the international front he published in General Systems, IEEE Transactions, Nature, The American Naturalist, Evolution, Proceedings of the Royal Society, London, Journal of theoretical Biology, Mathematical Bioscience, and Ecological Modelling. He also edited a number of influential books and special journal issues in subjects ranging from ecological networks to biodiversity to termite biology. His final c.v. lists 37 papers in English in refereed journals, 13 in proceedings and non-refereed journals, and three edited books; he also published 21 papers in Japanese language publications, and about a dozen newspaper articles.

From his earliest days, Masahiko had an abiding interest in biodiversity and evolution. His return to Kyoto brought him into collaboration with T. Abe, H. Kawanabe, T. Ohgushi, and N. Yamamura, with whom he published on a variety of evolutionary topics. Of interest from these interactions is the "symbiosphere" concept, introduced many years before "biocomplexity" entered the contemporary lexicon, advancing the idea that ecological complexity promotes biodiversity. In his work with Takuye Abe, a world renowned termite expert who also perished in the Sea-of-Cortez accident, Higashi-san saw in these social organisms an experimentally tractable example of living evolutionary "complex adaptive systems" of the kind now receiving wide attention in complexity theory. As always-self-effacing Abe, his senior, said of him, "I am the boss, but he is the brains." Their work together in Kenya and Cameroon, and planned for Thailand and Australia, led to them dying together in Baja California. As said earlier, five continents they touched in the meantime.

Here is termite biologist David Bignell's final tribute to Higashi-san in the book, published posthumously, they edited together (T. Abe, D.E. Bignell, M. Higashi, eds. 2000. Termites: Evolution, Sociality, Symbiosis, Ecology. Kluwer, 466 pp.):

"A man of immense intellect, trained in both mathematics and biology and partly educated in the U.S.A., he was one of the ecological modernists who have swept all before them in the last decade with the modelling of ecosystem processes and evolutionary selection. Like other theoreticians, he worked broadly and did not confine himself to termites: rather he saw them as the ideal challenge for the mathematical biologist, who must seek to explain why they are universally eusocial within the context of detritivory, an obligate symbiosis with two or three other biotic kingdoms and diplo-diploid inheritance. The fruits of this enquiry can be seen in Chapter 8 of this volume: it explains [mathematically] how selection can favour sterile castes in the evolution of Isoptera even without the close relatedness between reproductives and workers seen in the social Hymenoptera. Another notable achievement was the demonstration (with Norio Yamamura [again mathematically]) of how conflicts could arise and then be resolved between relatives in animal societies. Unusually for ecologists, Higashi-san kept a tidy office. Perhaps this reflected the way he wanted to find neat mathematics to describe the complex natural world he saw: unquestionably his career and reputation were only just beginning to mature. A connoisseur of sake and sushi, and an expert on the history and culture of Kyoto, he hosted many visitors to his laboratory. A few days spent in his company at the Center for Ecological Research was always an education in itself."

And for those of us who experienced the richness of a few years pursuing the hard unknowns of systems science and ecology with this web-weaving son of a basket-maker, well, it can only be said that he gave us a standard to live by, both personal and professional. It is always tragic when promise ends abruptly and pointlessly in the full flower of life. Masahiko Higashi gave a push to the wheel of human progress that will continue as a legacy of quiet excellence into a long future. He is missed, for his ecology, his humanity, and the networks he wove joining both.

Thomas P. Burns
Oak Ridge, Tennessee, U.S.A.

George J. Klir
Binghamton, New York, U.S.A.

Bernard C. Patten
Athens, Georgia, U.S.A.

# PROGRAM OVERVIEW

ALL EVENTS ARE IN HAWAII NANILOA, EXCEPT ON MONDAY EVENING

IMPORTANT NOTE TO POSTER PRESENTERS:
SET YOUR POSTERS UP BETWEEN 12 AND 6 PM MONDAY
NUMBER OF YOUR ABSTRACT IN THE PROGRAM CORRESPONDS
TO THE NUMBER OF THE POSTER BOARD ASSIGNED TO YOU
TAKE YOUR POSTERS DOWN BEFORE 10 PM MONDAY

Sunday, July 15 PM - ARRIVAL DAY:
4 PM - 8 PM: Registration (Lobby)

Monday, July 16 AM:
7 AM - 4 PM: Registration (Lobby)
7 AM - 7:50 AM: Continental Breakfast (Crown Room)
8 AM - 8:15 AM: Opening Chant and Welcome (Crown Room):
Kumu Maile Canerio (Hawaii), Alex Mogilner (Davis) and Yasuhiro Takeuchi (Shizuoka)
8:15 AM - 9:15 AM: Plenary Talk (Crown Room):
George Oster (Berkeley)
The mysterious meanderings of Myxobacteria
9:15 AM - 9:40 AM: Break (Crown Room Lobby)
9:45 AM - 11:45 AM:
1) Minisymposium: Spatial Models in Ecology (Kilohana Room)
2) Minisymposium: Bioinformatics/Proteomics (SandalWood II Room)
3) Contributed session I: Cancer (Palm Room)

Monday, July 16 PM:
12 PM - 1:30 PM:
LUNCH (provided) and Special lecture by Okubo Prize Winner (Crown Room):
Simon Levin (Princeton)
Ecosystems as Complex Adaptive Systems
1:30 PM - 5:30 PM: Free Afternoon
4 PM - 5:45 PM: Board of Directors Meeting (SandalWood II Room)
6 PM - 7 PM: Plenary Talk (Hilo Hawaiian Hotel, Moku'ola Room):
Nanako Shigesada (Nara Women's University)
Modeling spatial spread of invading species
7 PM - 9:30 PM:
Poster Session / Opening Reception (Hilo Hawaiian Hotel, Moku'ola Rooms I & II)

Tuesday, July 17 AM:
7 AM - 7:50 AM: Continental Breakfast (Crown Room)
8 AM - 9 AM: Plenary Talk (Crown Room):
Charles Peskin (New York University)
A Secret of Life Revealed: Immersed Boundaries Everywhere!
9 AM - 9:20 AM: Break (Crown Room Lobby)
9:30 AM - 11:30 AM:
1) Minisymposium: Matrix Population Models I (Crown Room)
2) Minisymposium: Immunology (Kilohana Room)
3) Contributed session II: Physiology (Palm Room)

LUNCH - ON OWN (except for participants of a field trip)

Tuesday, July 17 PM:

NOON - 6:15 PM: Free Afternoon
12 PM - 5:30 PM: optional field trip (lunch provided)

6:45 PM - 7:45 PM: Plenary Talk (Crown Room):
Leslie Loew (University of Connecticut Health Center)
The Virtual Cell Project
7:45 PM - 7:55 PM: Break (Crown Room Lobby)
8 PM - 9:30 PM:
1) Minisymposium: Matrix Population Models II (Crown Room)
2) Contributed session III: Education (Palm Room)

3) Contributed session IV: Morphogenesis, Wound Healing and Tissues (Kilohana Room)

Wednesday , July 18 AM:
7 AM - 7:50 AM: Continental Breakfast (Crown Room)
8 AM - 9 AM: Plenary Talk (Crown Room):
Masayasu Mimura (Hiroshima)
Self-organized Patterns in Biological Systems
from Reaction-Diffusion Modelling Viewpoints
9 AM - 9:20 AM: Break (Crown Room Lobby)
9:30 AM - 11:30 AM:
1) Minisymposium: Mathematical Modeling in Medicine (Kilohana Room)
2) Contributed session V: Epidemiology (SandalWood II Room)
3) Contributed session VI: Population Dynamics and Evolution (Palm Room)

Wednesday, July 18 PM:
12 PM - 1:30 PM:
Contributed session VII: Cell and Molecular Biology (Crown Room, lunch provided)

1:30 - 5:30 PM: Free Afternoon
12 PM - 5:30 PM: optional field trip (lunch provided)

NOTE: if you do not participate in the contributed session VII,
or the optional field trip, then lunch is on own

6 PM - 7 PM: Open SMB/JAMB Business Meeting (Crown Room)
7 PM - 9 PM: Closing Hawaiian Dinner (Crown Room)

Thursday, July 19 AM:
7:30 AM - 8:20 AM: Continental Breakfast (Crown Room)
8:30 AM - 9:30 AM: Plenary Talk (Crown Room):
Yoh Iwasa (Kyushu University)
Pollen-Coupling of Forest Trees, Forming Synchronized and Periodic
Reproduction out of Chaos

9:30 AM - 9:35 AM: Closing Remarks and Thanks

9:35 AM - 9:45 AM: Break (Crown Room Lobby)

9:45 AM - 11:45 AM:
1) Minisymposium: Mathematical Neurophysiology (Palm Room)
2) Contributed session VIII: Disease / Immunology (Kilohana Room)
3) Contributed session IX: Spatially Explicit Models in Ecology (Crown Room)

DEPARTURE

## DETAILED SCIENTIFIC PROGRAM

**Monday, July 16 AM:**

**8 AM - 8:15 AM**: Welcome (Crown Room):
Alex Mogilner (Davis) and Yasuhiro Takeuchi (Shizuoka)

**8:15 AM - 9:15 AM**: Plenary Talk (Crown Room):
George Oster (Berkeley)
The mysterious meanderings of Myxobacteria

**9:15 AM - 9:40 AM**: Break (Crown Room Lobby)

**9:45 AM - 11:45 AM**:

**Minisymposium: Spatial Models in Ecology** (Kilohana Room)
(in Memory of the Late Professors Ei Teramoto and Masaya Yamaguti)
Chairs: Simon Levin (Princeton) and Toshiyuki Namba (Osaka)

**9:45** Intro: Toshiyuki Namba
**9:50** The legacy of Ei Teramoto: Toshiyuki Namba
**9:55** The legacy of Masaya Yamaguti: Yuzo Hosono
**10:00** Lecture by Yuzo Hosono
Propagation Speeds of Travelling Waves for Reaction-Diffusion Equations Arising in Population Dynamics
**10:25** Lecture by Michael Neubert
Advances in Invasion Theory
**10:50** Lecture by Simon Levin
Evolution of Dispersal
**11:15** Lecture by Toshiyuki Namba
Food Webs in a Patchy Environment
**11:40** Closing comments: Simon Levin

**Minisymposium: Bioinformatics/Proteomics** (SandalWood II Room)
Chair: Richard Goldstein (University of Michigan)

**9:45** Richard Goldstein
Modeling site substitutions during protein evolution
**10:25** Doron Lancet
Harvesting the genome: from gene arsenals to prebiotic evolution
**11:05** Andrej Bugrim
Architecture of biochemical networks, or: Why 30,000 genes is plenty

**Contributed session I: Cancer** (Palm Room)

**9:45** Catherine E Kelly
Inhibitory effects of macrophages in solid tumour growth
**10:00** Alexander R.A. Anderson
Mathematical Modelling of Angiogenesis: Predicting Drug Flow Through Vascular Networks
**10:15** Kristin R. Swanson
Can a Three-Dimensional Model for Brain Tumor Growth and Invasion Predict Clinical Behavior in Real Patients?
**10:30** L. G. de Pillis
Modeling Cancer Growth with a focus on Melanoma and Vaccine Treatment
**10:45** Brian M. Murphy
A Mathematical Model of White Blood Cell Engraftment Following Autologous Peripheral Blood Stem Cell Transplantation
**11:00** Karen Page
Cancer Dormancy
**11:15** Evans Afenya
Use of real time patient data to validate a model of the disseminated cancers
**11:30** MyungHo Kim
Application of Support Vector Machine to detect an association between a disease or trait and multiple SNP variations.

**Monday, July 16 PM:**

**12 PM - 1:30** PM:
LUNCH (provided) and Special lecture by Okubo Prize Winner (Crown Room):
Simon Levin (Princeton)
Ecosystems as Complex Adaptive Systems

**6 PM - 7 PM**: Plenary Talk (Hilo Hawaiian Hotel, Moku'ola Room):
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Modeling spatial spread of invading species

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**8 AM - 9 AM**: Plenary Talk (Crown Room):
Charles Peskin (New York University)
A Secret of Life Revealed: Immersed Boundaries Everywhere!

**9 AM - 9:20 AM**: Break (Crown Room Lobby)

**9:30 AM - 11:30 AM**:

**Minisymposium: Matrix Population Models I** (Crown Room)
Chairs: Hal Caswell (Woods Hole) and Takenori Takada (Hokkaido)

**9:30** Hal Caswell
Introduction to the symposium: matrix population models, theory and application
**10** Yuko Kaneko
A demographic analysis using a topographically combined matrix population model on a natural Japanese wingnut population along a riparian environmental gradient
**10:30** Jim Cushing
Lattice effects and complex dynamics
**11** Masami Fujiwara
New developments in parameter estimation for matrix population models

**Minisymposium: Immunology** (Kilohana Room)
Chair: Ramit Mehr (Bar-Ilan)

**9:30** Introduction (Ramit Mehr)
**9:35** Tim Manser
Revisiting Neo-Darwinian Models for Maturation of the B Cell Response: A New Definition of Fitness
**10:15** Ramit Mehr
Hypermutation and antigen-driven selection analyzed by measuring mutational lineage trees
**10:50** Jorge Carneiro
Self-tolerance: Lessons from mathematical modelling

**Contributed session II: Physiology** (Palm Room)

**9:30** Gen Kurosawa
Enzyme Kinetics in Circadian Clock Models
**9:45** Martin A. Bees
Bacterial Swarming and Rational Model Reduction
**10:00** John Ward
Investigating spatial factors in bacterial cell-cell signalling
**10:15** Eric Cytrynbaum
Stability of the traveling pulse and the restitution hypothesis
**10:30** Chung-Seon Yi
The Difference between ischemia and hypoxia a mathematical study concerning volume shifts and ionic concentration changes
**10:45** Ian M. P. Joseph
A Gastric Acid Secretion Model for the Study of *Helicobacter pylori* Colonization
**11:00** R. Miftakhov and J. Christensen
Towards a conceptual theory of gastrointestinal motility
**11:15** Harold Trease

Simulating the Mammalian Respiratory Tract Using NWGrid and NWPhys

**Tuesday, July 17 PM:**

**6:45 PM - 7:45 PM**: Plenary Talk (Crown Room):
Leslie Loew (University of Connecticut Health Center)
The Virtual Cell Project

**7:45 PM - 7:55 PM**: Break (Crown Room Lobby)

**8 PM - 9:30 PM:**

**Minisymposium: Matrix Population Models II** (Crown Room)

Chairs: Hal Caswell (Woods Hole) and Takenori Takada (Hokkaido)
**8** Takenori Takada and Hal Caswell
Perturbation analysis: the reliability of sensitivity and elasticity analyses and their interpretations
**8:30** Shripad Tuljapurkar
Stochastic elasticity: what and why
**9** Peter Kareiva
What happens when you use matrix models in the real world of conservation decision-making: can advances in mathematical insights keep the hounds of politics and lawsuits at bay?

**Contributed session III: Education** (Palm Room)

Chair: John R. Jungck (Beloit)
**8** John R. Jungck
Introduction
**8:10** George Oster
Berkeley Madonna$^{TM}$: A Powerful Tool for Modeling and Simulation
**8:30** Charles E. Smith
SOME RANDOM THOUGHTS ON STOCHASTIC MODELLING AS A GRADUATE COURSE
**8:50** Eric S. Marland
Incorporating a mathematician into biology, or something like that
**9:10** John R. Jungck
*in silico* DNA, RNA, Protein Sequence, and Structure Analysis: Theory and Practice

**Contributed session IV: Morphogenesis, Wound Healing and Tissues** (Kilohana Room)

**8:00** Hiroto Shoji
Stripe Pattern Formation Generated Reaction Diffusion with Anisotropy
**8:15** Sharon R. Lubkin
Force and Deformation on Branching Rudiments: Cleaving Between Hypotheses
**8:30** Philip K. Maini
Mathematical modelling of primitive streak dynamics
**8:45** Eamonn A. Gaffney
Investigating a Model of Angiogenesis
**9:00** John C. Dallon
A Mathematical Model of Transforming Growth Factor Beta and Extracellular Matrix Alignment in Dermal Wound Repair
**9:15** Eleanor Clark
Modelling the Differential Effects of Drugs on Cells in Tumour Spheroids

**Wednesday , July 18 AM:**

**8 AM - 9 AM**: Plenary Talk (Crown Room):
Masayasu Mimura (Hiroshima)
Self-organized Patterns in Biological Systems from Reaction-Diffusion Modelling Viewpoints

**9 AM - 9:20 AM**: Break (Crown Room Lobby)

**9:30 AM - 11:30 AM:**

**Minisymposium: Mathematical Modeling in Medicine** (Kilohana Room)
Chair: Lee Segel (Weizmann)

**9:30** Eliezer Shochat

On hematopoiesis and brain tumors: detailed mathematical representations of normal and malignant phenomena
**10:10** Larry Wein
Two Dynamic Control Problems in Medicine
**10:50** Jacques Demongeot
Modelling bio-medical knowledge: the example of minimal regulatory systems in biological modelling

**Contributed session V: Epidemiology** (SandalWood II Room)

**9:30** Chris Bauch
Reconciling the SEIR Model to Real-World Whooping Cough Dynamics
**9:45** Pejman Rohani
Comparative Nonlinear Dynamics of Sympatric Childhood Infections
**10:00** Baojun Song
Tuberculosis Control in the U.S.: astrategy to meet CDC's goal
**10:15** James Watmough
Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission
**10:30** David J.D. Earn
Spatial coherence in metapopulations
**10:45** Hiromi Seno
On Travelling Wave of Disease Infection with Diffusing Epidemic Vector
**11:00** Michael Boots
The evolution of virulence in spatially structured host populations
**11:15** Yasuhiro Takeuchi
Chemostat Models with Time Delays for Bacteria and Virulent Phage

**Contributed session VI: Population dynamics and Evolution** (Palm Room)

**9:30** Kevin Higgins
Metapopulation Extinction Caused by Mutation Accumulation
**9:45** Aaron A. King
Subtle temporal patterns in *Tribolium* population dynamics
**10:00** Roger M Nisbet
EFFECT OF HERBIVORE STOICHIOMETRY ON POPULATION STABILITY
**10:15** Fugo Takasu
A model of coevolution of egg appearance as a quantitative character in avian brood parasitism
**10:30** Natalia Komarova
Evolution of linguistic coherence
**10:45** Klaus Jaffe
Calculating the cost of altruism
**11:00** David J. T. Sumpter
Scramble and Contest: Understanding the Dynamics of Individual Based Models
**11:15** Suzanne Lenhart
Optimal Control of a Competitive System with Age-Structure

**Wednesday, July 18 PM:**

**12 PM - 1:30 PM:**

**Contributed session VII: Cell and Molecular Biology** (Crown Room, lunch provided)

**12:00** Rubem Mondaini
Minimal Surfaces as Internal Manifolds of Biomolecular Structures
**12:15** Ivan V. Maly
Diffusion Dynamics of Microtubules
**12:30** ANATOLY B. KOLOMEISKY
Description of motor protein motility using stochastic models
**12:45** Donald A. Drew
A MATHEMATICAL MODEL FOR ELONGATION OF A PEPTIDE CHAIN
**1:00** Nima Geffen
A SIMPLE GEOMETRIC MODEL FOR A SIMPLE UNICELLULAR ORGANISM
**1:15** Diana W. Verzi
A Conservation Model for Density of Actin-Polymers in the Crawling Cell

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**7 PM - 9 PM**: Closing Hawaiian Dinner (Crown Room)

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Yoh Iwasa (Kyushu University)
Pollen-Coupling of Forest Trees, Forming Synchronized and Periodic Reproduction out of Chaos

**9:30 AM - 9:35 AM:** Closing Remarks and Thanks

**9:35 AM - 9:45 AM:** Break (Crown Room Lobby)

**9:45 AM - 11:45 AM:**

**Minisymposium: Mathematical Neurophysiology** (Palm Room)
Chair: Gerda de Vries (Alberta)

**9:45** Gerda de Vries, Introduction
**10:00** Christopher Del Negro
Periodic and quasiperiodic states in a motor pattern-generating neural network: experimental studies in the mammalian respiratory oscillator
**10:35** Yue-Xian Li
Synchronous phase-clustering states in networks of excitatory neurons with nonuniform coupling
**11:10** Richard Bertram
Intrinsic and Network Bursting in Pancreatic Beta-Cells

**Contributed session VIII: Disease / Immunology** (Kilohana Room)

**9:45** Karina Yusim
Using HIV-1 Sequences to Infer Historical Features of the AIDS Epidemic in the Democratic Republic of Congo
**10:00** Ying-Hen Hsieh
Estimating the number of HIV-infected individuals in Cuba
**10:15** Dominik Wodarz
Immunological memory and the control of HIV infection
**10:30** Yoram Louzoun
Endocytosis and Tolerance in B Cells
**10:45** Steven H. Kleinstein
Quantitative Simulation of Germinal Center Dynamics
**11:00** Erich R. Schmidt
Optimal Decision Making of Individual Cells: A Case Study of Affinity Maturation
**11:15** Emi Shudo
Inducible Defense against Pathogens and Parasites: Optimal Choice among Multiple Options
**11:30** David Schley
Slug Bio-Control Dynamics

**Contributed session IX: Spatially Explicit Models in Ecology** (Crown Room)

**9:45** Michael Doebeli
A new model for spatially structured populations
**10:00** Mark A. Lewis
How predation can slow, stop or reverse a prey invasion
**10:15** Dale R. Lockwood
The effects of dispersal on marine reserve design
**10:30** Robin E. Snyder
How population discreteness and demographic stochasticity can slow biological invasions
**10:45** Abdul-Aziz Yakubu
Dispersal and Intraspecific Competition in Discrete-time Patchy Environments
**11:00** Hideo Ezoe
Lotka-Volterra Competition Model in a Lattice Space
**11:15** Horst Malchow
Pattern Formation and Noise in Models of Plankton–Fish Dynamics in a Patchy Environment
**11:30** K Magnusson
Models of spawning and feeding migrations of pelagic fish species in the North-Atlantic

DEPARTURE

# Plenary Talks

## 1. The mysterious meanderings of Myxobacteria

**George Oster** *[1], **Oleg Igoshin**[1], **Alexander Mogilner**[2], **Dale Kaiser**[3]

[1]201 WELLMAN HALL, UNIVERSITY OF CALIFORNIA - BERKELEY
GOSTER@NATURE.BERKELEY.EDU
[2]UNIVERSITY OF CALIFORNIA - DAVIS, [3]STANFORD UNIVERSITY

The life cycle of myxobacteria resembles in many respects that of the well-studied slime mold Dictyostelium discoideum. When food is scarce, they aggregate into giant swarms which then coalesce into fruiting bodies containing the spores that will seed the next generation. During this aggregation they pass through a developmental stage called the 'ripple phase' characterized by elaborate patterns of waves that propagate over the colony surface. These waves generate the same kinds of patterns observed in Dictyostelium aggregations, including waves, bulls-eye and spiral patterns. However, myxobacterial patterns are unlike those in D. discoideum in several crucial respects: (i) they can persist for long periods in the absence of mass transport, (ii) colliding waves appear to 'pass through' one another, analogous to soliton waves in water, whereas D. discoideum waves, like those in chemical wave systems, annihilate one another when they meet. (iii) the spatial patterns in D. discoideum are organized by relaying diffusible morphogens, whereas myxobacteria communicate by direct cell contact only. Here we present a model for the wave patterns in myxobacteria that quantitatively explains most of their characteristics. Aside from the novel mechanism that generates these patterns, the model shows how the patterns can be used as a probe of the intercellular signal transduction mechanism, and may provide an alternate system for studying multicellular pattern formation based on direct cell contact rather than diffusible morphogens.

## 2. A Secret of Life Revealed: Immersed Boundaries Everywhere!

**Charles S. Peskin***

COURANT INSTITUTE OF MATHEMATICAL SCIENCES, NEW YORK UNIVERSITY
PESKIN@CIMS.NYU.EDU

Living systems are mostly water, but water is not alive. Life happens because of the stuff that is immersed in water. What that stuff is depends on the scale at which we look: it may be lipids, proteins, and nucleic acids, or it may be organelles, cells, or whole tissues and organs. In all cases, the stuff of life is elastic, and the mechanical problem of life is a hydroelastic problem. On the smaller of the scales mentioned above, however, there is the additional complication of thermal fluctuation (Brownian motion). This talk is about a computational scheme known as the Immersed Boundary (IB) method, which is designed for the computer simulation of hydroelastic systems. The IB methodology will be explained, including its extension to the case of thermal fluctuation, and it will be illustrated by computer animations showing the results of IB simulations of some large and small systems.

## 3. The Virtual Cell Project

**Les Loew***

CENTER FOR BIOMEDICAL IMAGING TECHNOLOGY UNIVERSITY OF CONNECTICUT HEALTH CENTER FARMINGTON, CT 06030-1507
LES@VOLT.UCHC.EDU

The Virtual Cell is a modular computational framework that permits construction of models, application of numerical solvers to perform simulations, and analysis of simulation results. An intuitive JAVA interface permits access via a web browser and includes options for database access, geometry definition (including directly from experimental images), specification of compartment topology, species definition and assignment, chemical reaction input, and computational mesh. This talk will describe the status of the project and will focus on several applications to cell biological problems. These include a comprehensive model of intracellular calcium dynamics and simple models of RNA trafficking.

## 4. Modeling spatial spread of invading species

**Nanako Shigesada*[1] and Kohkichi Kawasaki[2]**

[1]Dept. of Information and Computer Sciences, Nara Women's University, Kita-Uoya Nishi-machi, 630-8506, Nara, Japan
@ics.nara-wu.ac.jp
[2]Department of Knowledge Engineering and Computer Sciences, Doshisha University, Kyo-Tanabe 610-0321, Japan
@mail.doshisha.ac.jp

The range expansion of an invading species shows a variety of spatio-temporal patterns depending on how the dispersal and reproduction of the organisms proceed under the influence of life-history attributes, disturbance regime, and landscape structure. In particular, the dispersal process is crucial in determining the frontal pattern and its expanding speed. The dispersal often involves two modes, short-range dispersal and long-range dispersal. Short-range dispersal generally occurs through their own active movement such as walking, swimming or flying, while long-range dispersal is mediated by passive transport on wind, flowing water, or even artificial transportation facilities. Since long-range dispersal sparsely scatters the organisms, its large gain in distance is compromised by an increased risk of extinction due to demographic stochasticity, inbreeding depression or any other causes such as an Allee effect. Thus how to deal with the two dispersal processes is one of the major issues in modeling spatial spread of invading species. To this end, we introduce two different mathematical models, 1) Stratified diffusion model and 2) Integrodifference models.

In the stratified diffusion model, we focus on the patchy range pattern while disregarding the population density within each patch (Shigesada et al., 1995). Thus it somewhat resembles the idea employed in the metapopulation model. The invading species expands its range at a constant rate by short-distance dispersal and simultaneously produces long-distance dispersers, which create nuclei of new colonization at a certain probability. In this approach, the Allee effect is incorporated by assuming that successful colonization of a new satellite depends on how close its nearest colony is located. The integrodifference model is more mechanistic one that incorporates the population density in the range (Kot et al., 1996, etc.). The life cycle of organisms is assumed to consist of two phases, dispersal and reproduction. The spatial population density after a life cycle is given by a convoluted equation of a dispersal distance kernel and a growth function. The dispersal distance kernel consists of those for short- and long-distance dispersals with certain fractional weights.

By solving these models either analytically or numerically, we present some formulae for the rate of spread and explore how long-distance dispersal and reproduction interplay to accelerate the speed, or how the Allee effect or demographic stochasticity decelerates it. Finally these models are compared to each other and with other more general approaches.

## 5. Self-organized Patterns in Biological Systems from Reaction-Diffusion Modelling viewpoints

**Masayasu Mimura***

Department of Mathematical and Life Sciences, Institute for Nonlinear Sciences and Applied Mathematics, Graduate School of Science, Hiroshima University
mimura@math.sci.hiroshima-u.ac.jp

Regular and irregular spatio-temporal patterns have been observed in biological and chemical systems so far. Among them, a class of self-organized patterns have been described by reaction-diffusion (RD) systems. Numerical calculations reveal that RD systems generate a variety of complx patterns, even if the systems look so simple. The occurrence of such self-organized patterns arising in RD systems is originally stated by Turing who introduced the idea of "difusion-induced instablity" into the explanation of cell differentiation and morphogenesis in developmental biology. Since then, his idea have been found not only in biology but also in physics, chemistry, ecology and other scientific field. In my talk, I would like to focus myself on sef-organized growth and aggregation in biological systems and explain how these can be modelled by RD systems anddiscuss what kind of self-organized patterns are generated by using analytical and complementarily numerical methods.

## 6. Pollen-Coupling of Forest Trees, Forming Synchronized and Periodic Reproduction out of Chaos

**Yoh Iwasa***

DEPARTMENT OF BIOLOGY, KYUSHU UNIVERSITY, JAPAN
YIWASSCB@MBOX.NC.KYUSHU-U.AC.JP

Trees in mature forests often show intermittent reproduction. Intensive flowering and seed production occur only once in several years, often synchronized over a long distance. We study a coupled map model for the dynamics of energy reserve of individuals, and show that trees become synchronized in reproduction when their fruit production is limited by the availability of outcross pollen. Without pollen limitation, the trees show independent chaotic fluctuation. With global pollen coupling, trees show various degree of reproductive synchronization. Lyapunov exponents are calculated analytically for perfectly synchronized forests, demonstrating that synchronized reproduction of trees can occur only if trees flower at low (but positive) levels in a significant fraction of years, resulting in small fruit sets due to the shortage of outcross pollen. We then study a coupled map lattice with local pollen exchange. Dynamic spatial covariance shows that a strong synchronization over the whole forest can develop from rather short range pollen exchange. We then examined the synchronization caused by common environmental fluctuation either in the annual productivity or the reproductive threshold level. Without pollen coupling, positive correlation between individuals are difficult to emerge even under environmental fluctuation correlated between individuals. Positive correlation can be maintained at high level only in the presence of both pollen coupling and correlated environmental fluctuation. We also discuss the reproductive synchronization between different species who share common pollinators, which is applicable to the synchronization in the tropical rain forest in Southeast-Asia.

## 7. Special Lecture by Okubo Prize Winner: Ecosystems as Complex Adaptive Systems

**Simon Levin***

DEPT. OF ECOLOGY AND EVOLUTIONARY BIOLOGY, PRINCETON UNIVERSITY
SIMON@ENO.PRINCETON.EDU

# Contributed Talks

## 1 Cancer

### 1. Inhibitory effects of macrophages in solid tumour growth

**Catherine E Kelly *, Helen M Byrne and Stephen M Cox**

DIVISION OF THEORETICAL MECHANICS, THE UNIVERSITY OF NOTTINGHAM, UK
ETXCEW@NOTTINGHAM.AC.UK

Macrophages are white blood cells that form part of the body's immune system. In cancer they may perform pro- and anti-tumour functions. For example, they lyse (destroy) tumour cells and also release angiogenic factors which promote the ingrowth of blood vessels into the tumour.

In this talk a mathematical model is presented that describes macrophage migration into a tumour-bearing tissue. A combination of analytical and numerical techniques is used to determine how the macrophage–tumour interactions depend on model parameters relating to macrophage activity. The model comprises normal, tumour and macrophage cells. The tumour cells have a proliferative advantage over normal cells and produce a chemoattractant under low oxygen tension (hypoxia), which stimulates macrophage migration into the tissue. The macrophages are assumed to have been engineered to have an increased rate of tumour cell lysis. In models such as the one described here, a mutation at the centre of the normal tissue induces a travelling wave of invading tumour cells. The macrophage cells may also infiltrate the tissue from a blood vessel as a travelling wave. Stability analysis and bifurcation theory can also be used to characterise possible solutions. The ultimate aim of such models is to manipulate the system, for example, by changing the rate of tumour cell lysis which can be experimently engineered, in order to predict an optimal regime for therapy.

### 2. Mathematical Modelling of Angiogenesis: Predicting Drug Flow Through Vascular Networks

**Alexander R.A. Anderson *, M.A.J. Chaplain**

DEPARTMENT OF MATHEMATICS, UNIVERSITY OF DUNDEE, DUNDEE DD1 4HN, UK
ANDERSON@MATHS.DUNDEE.AC.UK

The development of a primary (solid) tumour begins when a single, normal cell becomes a transformed cell through carcinogens, oncoviruses or radiation. This transformed cell differs from a normal cell in several ways, one of the most notable being its ability to proliferate uncontrollably. An individual transformed cell has the potential, through successive cell division and further mutation, to develop into a cluster (or nodule) of tumour cells. For any further development to occur the tumour must initiate angiogenesis. Angiogenesis, the formation of blood vessels from a pre-existing vasculature, is a process whereby capillary sprouts are formed in response to externally supplied chemical stimuli. The sprouts then grow and develop, driven initially by endothelial cell migration, and organise themselves into a dendritic structure. Subsequent cell proliferation near the sprout-tip permits further extension of the capillary and ultimately completes the process.

In this talk we initially generate theoretical capillary networks (which are morphologically similar to those networks observed in animal experiments) using the discrete mathematical model of Anderson and Chaplain. This discrete model describes the formation of a capillary sprout network in response to chemical stimuli (tumour angiogenic factors, TAF) supplied by a solid tumour and interactions with the extracellular matrix. We then examine flow through these structures. In order to achieve this we make use of flow modelling tools and techniques (Poiseuille flow through interconnected networks) from the field of petroleum engineering. The incorporation of fluid flow through the generated vascular networks has highlighted issues that may have applications in the study of nutrient supply to the tumour (blood/oxygen supply) and more importantly in the delivery of chemotherapeutic drugs to the tumour. We present results that clearly demonstrate the important roles played by tumour geometry and network connectedness (anastomosis density). Moreover, under certain conditions, an injected chemotherapy drug is seen to bypass the tumour altogether.

### 3. Can a Three-Dimensional Model for Brain Tumor Growth and Invasion Predict Clinical Behavior in Real Patients?

**Kristin R. Swanson *[,1], Ellsworth C. Alvord, Jr[2]**

[1] LABORATORY OF NEUROPATHOLOGY, UNIVERSITY OF WASHINGTON, 325-9TH AVENUE, HARBORVIEW MEDICAL CENTER, SEATTLE, WA
[2] DEPARTMENT OF APPLIED MATHEMATICS, UNIVERSITY OF WASHINGTON, SEATTLE, WA
SWANSON@AMATH.WASHINGTON.EDU

Gliomas are highly diffuse and invasive brain neoplasms accounting for about one half of all primary brain tumors. With increased detection capabilities in computerized tomography (CT) and magnetic resonance imaging (MRI), the last two decades have brought about earlier detection of these tumors. Despite this progress, the benefits of early treatment are scant. This failure is typically associated with the diffuse invasion of glioma tumor cells peripheral to the bulk mass not visible on MRI or CT imaging.

To investigate such observations, we have developed a mathematical model for glioma growth and diffusion written in words as:

Rate of change of glioma cell density =
Diffusion of glioma cells + Proliferation of glioma cells.

Equivalently, the model is written in mathematical terms as:

$$\frac{\partial c}{\partial t} = \nabla \cdot (D(\mathbf{x})\nabla c) + \rho c\left(1 - \frac{c}{K}\right) \tag{1}$$

where $c(\mathbf{x}, t)$ is the concentration of tumor cells at location $\mathbf{x}$ and time $t$. $D(\mathbf{x})$, a function of position $\mathbf{x}$ in the brain, is the diffusion coefficient defining the random motility of the glioma cells with $D(\mathbf{x}) = D_g, D_w$, constants for $\mathbf{x}$ in grey and white matter portions of the brain, respectively. There is a limiting local capacity of cells measured by $K$ while $\rho$ represents the net proliferation rate of the glioma cells at low densities.

Three-dimensional numerical simulations of the model system in the spatially heterogeneous virtual human brain (anatomically accurate to 1 cu mm) demonstrate the model's usefulness in establishing patterns of invasion for these tumors. We assume that the actual definition of the growth rate, $\rho$, and the diffusion coefficient, $D$, for each patient would define the real extent of the glioma at diagnosis, the extent of the glioma after each of the treatments, and, therefore, the effectiveness of each treatment in each individual patient. We will discuss some of our observations in this study.

## 4. Modeling Cancer Growth with a focus on Melanoma and Vaccine Treatment

**L. G. de Pillis * and A. E. Radunskaya**

HARVEY MUDD COLLEGE AND POMONA COLLEGE
DEPILLIS@HMC.EDU

We present a model of cancer tumor growth that includes drug therapy interactions and immunotherapy in a non-angiogenic tumor. Through optimal control with constraints, we have constructed mathematically optimal therapy protocols that we then compare with traditional periodic treatment. We have tailored this model to melanoma because preliminary experiments have shown melanoma to be particulary immunogenic. In this model we also include several types of immune cells and their response to the presence of the tumor. The clinical treatment of melanoma with therapeutic vaccines has already shown some promise. Therefore, we additionally include a simplified mathematical description of the system's response to cancer vaccine therapy.

## 5. A Mathematical Model of White Blood Cell Engraftment Following Autologous Peripheral Blood Stem Cell Transplantation

**Brian M. Murphy*, Stephen J. Merrill[1], Ann LeFever[2]**

* DEPARTMENT OF MICROBIOLOGY AND IMMUNOLOGY
UNIVERSITY OF MICHIGAN, ANN ARBOR, MI
[1] MARQUETTE UNIVERSITY, MILWAUKEE, WI
[2] ST. LUKE'S MEDICAL CENTER, MILWAUKEE, WI
BMMURPHY@PATHOGEN.MICRO.MED.UMICH.EDU

An available treatment for a number of high-risk or metastatic cancers is the use of high-dose chemotherapy followed by a transplant of a patient's own (autologous) peripheral blood stem cells (PBSCs). The success of a PBSC transplant, characterized by long-term disease-free survival or delayed time to relapse, depends on the patient's ability to *engraft*, or to generate a functioning, self-sustaining hematopoietic system with near-normal blood cell levels following transplant. In the case of breast cancer, clinical results of stem cell transplants are generally favorable, yet problems such as high relapse rates and delayed engraftment times still exist. Therefore, a better understanding of the mechanisms of hematopoietic reconstitution, and thus engraftment, may be of benefit. We developed a mathematical model of white blood cell (WBC) engraftment kinetics following high-dose chemotherapy and a PBSC transplant. The model is based on the architecture and microenvironment of bone marrow, which can be viewed as a redeveloping system following a PBSC transplant. The model includes this feature by assuming an initial autocatalytic process in the proliferation of granulocyte and lymphocyte precursors, possibly related to exogenous colony stimulating factors used as part of the transplant procedure. Model solutions identify surprising hyperbolic kinetics of WBC engraftment, allowing for a natural definition of time to engraftment (TTE). Based on the TTE, we create a control chart using Monte Carlo simulation to monitor the progress of a patient's engraftment and identify problems at early time points. This clinical tool is a significant improvement upon current post-transplant monitoring procedures.

## 6. Cancer Dormancy

**Karen Page *, Jonathan W. Uhr**

INSTITUTE FOR ADVANCED STUDY, PRINCETON, NJ

In cancer the normal homeostatic processes which control the ratios of numbers of different cell types are upset. One clonal population grows and outcompetes all others. However, it has been known for some time that certain tumors may be induced to remain at the same size for an extended period. This new equilibrium in which the cancer cells coexist at constant levels relative to their normal counterparts is referred to as dormancy. The tumor neither regresses nor grows.

An example of the induction of dormancy is in murine B cell lymphomas. Vaccines against an idiotype present on the surface of only the cancerous cells or injections of antibodies against these idiotypes can arrest the growth of these tumors (*Uhr et al., 1997, Nature Medicine, 3, 505-509*). The tumors do not regress, but rather stay at a constant size (c. one million cells) for an extended period (up to two years). Within the population of cancer cells, most are in cell cycle arrest, but some proliferate. This proliferation is balanced by cell death. The antibodies negatively signal to the cells to induce either cell cycle arrest or apoptosis. Approximately three to five times as many cells are quiescent as in the absence of antibody.

So how does the negative signalling ensure that for each cell division there is exactly one death, so that the tumor remains at a fixed size, and what parameters determine the size of the tumor and the ratio of proliferating to quiescent cells? I will present models of tumor dormancy, in which the negative signalling of the antibody can prevent infinite growth of the tumors and attempt to relate the size of the tumor and the number of proliferating cells to the model parameters.

## 7. Use of real time patient data to validate a model of the disseminated cancers

**Evans Afenya***

DEPARTMENT OF MATHEMATICS, ELMHURST COLLEGE, 190 PROSPECT AVENUE, ELMHURST, IL 60126

EVANSA@ELMHURST.EDU

Real time data gathered on patients with cancer of the disseminated typeare presented and discussed. Investigations of the data reveal that certainspecific normal and abnormal cell types can be used to represent cell behaviorin the disseminated cancers. The data are used to validate a model of thedisseminated cancers by exploring agreements found between the data and theanalytical and simulation-based predictions of the model. Recent advances made in trials involving drugs directed against chronic myeloid leukemia buttress the importance of modeling the disseminated cancers and it is within this context that our investigations are reported.

## 8. Application of Support Vector Machine to detect an association between a disease or trait and multiple SNP variations.

**MyungHo Kim** *,

GENOMICS COLLABORATIVE INC. 99 ERIE STREET, CAMBRIDGE, MA 02139
MKIM@GENECOOP.COM

After the completion of human genome sequence was anounced, it is evident that interpretation of DNA sequences is immediate task to attack, and sequence analysis tools become in need for understanding their functions. In particular, which set of SNP(single nucleotide polymorphism) variations is related to a specific disease or trait is a fundamental question, since in the whole DNA sequence, it is known that people have different DNAs only at SNP locations, and moreover, the total SNPs are less than 5 millions. Therefore, finding an association between SNP variations and certain disease or trait is believed to be one of the essential steps not only for genetic researches but for drug design and discovery. In this paper, we are going to present a method of detecting whether there is an association between multiple SNP variations and a trait or disease. The method exploits the Support Vector Machine which has been attracting lots of attentions recently.

# 2 Physiology

## 1. Enzyme Kinetics in Circadian Clock Models

**Gen Kurosawa** *, **Atsushi Mochizuki and Yoh Iwasa**

DEPARTMENT OF BIOLOGY, FACULTY OF SCIENCES, KYUSHU UNIVERSITY
FUKUOKA 812-8581, JAPAN
KUROSAWA@BIO-MATH10.BIOLOGY.KYUSHU-U.AC.JP

We study simple models for circadian rhythm, and examine the condition in which the equilibrium is unstable, generating a sustained oscillation. In the models, a clock gene(s) is transcribed to produce mRNAs, which are translated to produce proteins, which suppress the transcription of the clock gene. We first prove with a Lyaponov function that two variable model is unable to generate a stable oscillation. If the proteins have to be modified before entering the nucleus possibly, sustained oscillation can occur. When all reactions except for the inhibition of transcription are of Michaelis-Menten type, the saturation of both degradation steps of mRNA and protein makes the oscillation more likely to occur. In contrast, the saturation in any of the reactions included in the feedback loop tends to suppress the oscillation. When all reactions except for inhibition of transcription are of a linear form, the cooperativity in inhibition of transcription or in the nuclear transportation is required to generate an oscillation. We discuss the implication of these results.

## 2. Bacterial Swarming and Rational Model Reduction

**Martin A. Bees** *

DEPARTMENT OF MATHEMATICS & STATISTICS, UNIVERSITY OF SURREY, U.K.
M.BEES@EIM.SURREY.AC.UK

Colonies of bacteria use a variety of techniques to proliferate on surfaces, subject to environmental conditions, whereby individuals co-operate and specialize to fulfil particular functions. Moreover, swarming colonies of several well known opportunistic human pathogens are able to rapidly colonize surfaces. However, the biological interactions and the physical processes involved in the expansion are, in general, poorly understood. A model of the swarming process and associated bacterial colony expansion will be described that incorporates both hydrodynamic and rigorously established biological processes. The model includes aspects of thin-film flow, variable suspension viscosity and co-ordinated cell differentiation. Simulations of the model are used to help validate the approach and also suggest the way forward for theoretical simplifications. Furthermore, a reduced model is proposed which is based on self-similar solutions of the governing equations. The solution space of the reduced model is explored. Additionally, biological experiments to determine expansion scaling laws are described and the results are contrasted with the theory.

## 3. Investigating spatial factors in bacterial cell-cell signalling

**John Ward[1]*, Julie Croft[2], John King[1], Adrian Koerber[1], Liz Sockett[2] and Paul Williams[3]**

[1]Division of Theoretical Mechanics, School of Mathematical Sciences, University of Nottingham, University Park, Nottingham, UK, NG72RD
[1] *john.ward@nottingham.ac.uk. [2]Division of Genetics, School of Clinical Laboratory Sciences, Queens Medical Centre, University of Nottingham, UK, NG72UH
[3]School of Pharmaceutical Sciences, University of Nottingham, University Park, Nottingham, UK, NG72RD
john.ward@nottingham.ac.uk

Over the last decade it has become increasingly apparent that many species of bacteria express a wide range of behaviours which are dependent on their population density. Such behaviours include the induction of bioluminescence, bacterial swarming and expression of virulence during infections (i.e releasing toxins and enzymes). The regulation of density dependent behaviour, often termed "quorum sensing", is achieved by the release and monitoring of cell-cell signal molecules (or quorum sensing molecules, QSMs), which build up in concentration as the population increases. In time these QSMs will accumalate to some threshold, reflecting a sufficiently high population density, at which certain genes are "switched on", whereby a significant portion of the bacteria population will, in concert, be observed to express the relevent behaviour.

In this talk, we focus mainly on the medically important pathogenic bacterium *Pseudomonas aeruginosa*, for which quorum sensing acts as a means of delaying attack on host tissues, following infection of an open wound or burn, as well as being a vital component in the maturation of biofilms, significant during infection of lungs of cystic fibrosis sufferers, for example. Two mathematical models are presented to model bacterial growth, productions of QSMs and up-regulation of cells in two different situations, namely 1) labatorial experiments (batch cultures) and 2) early biofilm development. For case 1) the system is well mixed and a system of ordinary differential equations result. The model for case 2), which consider loss of QSMs through diffusion away from the bacterial colony, result in a system of nonlinear, reaction-diffusion equations. Numerical solutions and analysis of the models will be described, comparing and contrasting the effects of quorum sensing in these different scenarios.

## 4. Stability of the traveling pulse and the restitution hypothesis

**Eric Cytrynbaum *, James P. Keener**

Department of Mathematics, University of Utah
eric@math.utah.edu

There has been much speculation about the importance of the slope of the restitution curve as a factor in the break-up of spiral waves. The restitution hypothesis claims that stability of a spiral wave relies on the slope of the restitution curve (dAPD/dDI) being less than 1. This hypothesis is the higher dimensional generalization of the stability result of Courtemanche, Keener and Glass (1996). In that paper, the authors show that the under the assumption that the back of the steady traveling pulse is a phase wave, the question of stability reduces to checking the slope of the restitution curve (dAPD/dDI). In this talk, we present a generalization of the result which assumes that the back of the traveling pulse is propagated (rather than a phase wave). Under this more physiological assumption, it can be shown that stability and the slope of the restitution curve are independent concepts. In particular, it is possible to have a stable pulse even if the slope of the restitution curve is greater than 1. Conversely, an unstable pulse can be associated with a restitution curve whose slope is less than 1.

## 5. The Difference between ischemia and hypoxia a mathematical study concerning volume shifts and ionic concentration changes

**Chung-Seon Yi *, Aaron Fogelson, James Keener, Charles Keener**

University of Utah
yi@math.utah.edu

When the cell is deprived of oxygen due to blockage of the arterial side of the capillary that provides blood to the cell, which is called ischemia. This results in oxygen deprivation which termed hypoxia. We develop a mathematical model with which to examine the different effects of ischemia and hypoxia on intra- and extracellular volume and extracellular ionic concentrations. We find that these quantities do not change much during 40 minutes of hypoxia, while with ischemia there is a noticeable change, rapid increase in extracellular potassium after 10 minutes onset of ischemia from 5.4 mM upto 40-50 mM and slower rise up to 75 mM, qualitative agreement with experimental data. We conclude that the reason why extracellular potassium in ischemia accumulates rapidly in the first phase is due to the nonlinearity of sodium channel. Cell volume and extracellular volume are similar to experiment data.

6.

## A Gastric Acid Secretion Model for the Study of *Helicobacter pylori* Colonization

**Ian M. P. Joseph*, Denise Kirschner**

DEPARTMENT OF MICROBIOLOGY AND IMMUNOLOGY
UNIVERSITY OF MICHIGAN, ANN ARBOR, MI
IJOSEPH@UMICH.EDU

Interspecies physiological and behavioral differences complicate the development of ideal animal models for the study of specific pathologies elicited by microorganisms. This lack of ideal animal models has hampered research into the hypothesis that *H. pylori* modulate acid secretion so as to favor their persistence. This has motivated us to develop a virtual human model of gastric acid secretion. This mathematical model captures the salient characteristics of acid secretion and its regulation. Food provides a driving force by triggering neural activity in both central and enteric nervous systems. This neural activity then results in a cascade of events characterized first by the release of gastrin, a critical stimulatory hormone, from gastrin (G) cells. Gastrin then elicits the release of a potent acid stimulator, histamine, by enterochromaffin-like cells (ECL). Together gastrin and histamine as well as acetylcholine, a neurotransmitter, provide positive stimulation for the secretion of acid by parietal cells. The secretion of somatostatin, from somatostatin secreting (D) cells, completes the feedback loop. The outcome is the maintenance of steady state pH (homeostasis). To validate our model, we compared the results of our numerical simulations with data gathered from literature. The model simulations are closely comparable to experimentally obtained data. In addition, we have performed various virtual hormonal and cell deletion studies so as to further validate our model. The virtual human gastric acid secretion model is a powerful tool for studying the significance of somatostatin secreted in different regions of the stomach as well as to now explore *H. pylori*. Similar experiments are presently impossible to perform both *in vivo* and *in vitro*. We also identify key parameters that may be potential targets in the therapy of many gastric ailments.

## 7. Towards a conceptual theory of gastrointestinal motility

**R. Miftakhov and J. Christensen**

UNIVERSITY OF IOWA HOSPITALS AND CLINCS, IOWA CITY, IA 52242, USA
JAMES-CHRISTENSEN@UIOWA.EDU

Our understanding of the means by which the gastrointestinal neuromuscular apparatus generates the great variety of patterns of motion that it exhibits remains poor, despite considerable recent advances in knowledge of its morphology, electrophysiology, neurophysiology, neuropharmacology, and biomechanics. Biological investigations in the past half-century have used a largely reductionist approach to analyze the organization of the neuromuscular mechanism at cellular and molecular levels, leaving unstudied the integration of the operations of the component processes through electromechanical, chemoelectrical and electrochemical coupling. A unified theory of gastrointestinal intestinal motility should rest on a framework of the established conceptual principles of solid mechanics, fluid mechanics, artificial neural networks, and mathematical science. Until such a theory has been developed and demonstrated to predict motor behaviors adequately, our understanding of how the gut regulates the flow of its contents in normal and disease states will remain fragmentary and semiquantitative, with correspondingly limited clinical applicability. In our mathematical model of intestinal motility, the gut is modelled as a continuum of spatio-temporally arranged functional units, controlled by a planar network of sensory and motor neurones linked through excitatory/inhibitory synapses. Electrochemical and chemoelectrical coupling includes the detailed biochemical pathways of synthesis, storage, release and degradation of a number of neurotransmitters as well the dynamics of the receptor complexes of the effector subsystem. Electromechanical interaction comprises a population of ionic channels that are responsible for the myoelectrical activity. We can (i) make quantitative statements about enteric nervous system function under various conditions, (ii) describe the dynamics of the stress-strain distribution along the gut wall during the peristaltic reaction, not as a result of prescribed motion but as a result of the electromechanical coupling that occurs at the smooth muscle level, and (iii) follow the dynamics of flow patterns even in the early stages of motor activity This is the first approach to the description of motor activity in the gut that uses working hypotheses from established principles of relevant physical sciences. It can serve as a template for the further development of a theory of gastrointestinal motility

## 8. Simulating the Mammalian Respiratory Tract Using NWGrid and NWPhys

**Harold Trease(1) *, Richard Corley(1), Chuck Timchalk(1), Kevin Minard(1), Donald Rommereim(1), David Dixon(1), Julie Kimbell(2), and Bahman Asgharian(2)**

(1) PACIFIC NORTHWEST NATIONAL LABORATORY, (2) CHEMICAL INDUSTRY INSTITUTE OF TOXICOLOGY
HET@PNL.GOV

We have developed computational models in order to perform parallel, numerical simulations of the fluid dynamics, material response, and particle flows in the upper respiratory tract (URT) and lower respiratory tract (LRT) for humans and rats. This work has been done by using the NWGrid and NWPhys computer codes. There are five key steps associated with applying our simulation models to respiratory system modeling: 1) Data acquisition, 2) Geometry generation, 3) Mesh generation, 4) Problem execution, and 5) Data analysis and results phase. We will present in detail the numerical models used in steps 3 and 4. We will present results for steps 1, 2 and 5 for completeness. Mesh generation is the transformation of geometry into a discrete computational mesh, where the problem geometry is tessellated by a set of elements that completely and uniquely span the region of space of interest. The mesh generation system that we use is called NWGrid. The process of generating hybrid meshe! s within NWGrid is a semi-automated process using recursive, hierarchical, parallel Adaptive Mesh Refinement (AMR) algorithms. The result of the mesh generation process is a 'restart file', which serves as the input for our simulation code, NWPhys. NWPhys is a parallel, unstructured, hybrid, multi-dimensional adaptive computer code that allows simulation of computational fluid dynamics, continuum mechanics, diffusion, radiation transport, and particle transport within a coupled Framework design. This paper describes several examples of geometry and grid generation for the URT and LRT in humans and rats along with examples of computational physics calculations including fluid dynamics, continuum mechanics, reaction-diffusion, and discrete particle transport.

# 3 Education

## 1. Berkeley Madonna$^{TM}$: A Powerful Tool for Modeling and Simulation

**George Oster *, Robert Macey and Tim Zahnley**

UNIVERSITY OF CALIFORNIA BERKELEY, CA 94720-3112
URL: <HTTP://WWW.BERKELEYMADONNA.COM>

Berkeley Madonna$^{TM}$ is a fast, easy, general purpose differential equation solver that we have used to teach biological simulation at Berkeley for nearly 10 years. Students learn how to design and run complex, interactive models in many areas, including biochemistry, cell biology, physiology, population dynamics and epidemiology. These models are formulated as sets of ordinary differential or difference equations, both initial and boundary value problems. In addition, Berkeley Madonna$^{TM}$ can generate stochastic solutions based on discrete event actions using conveyors, ovens, and queues. Vector processing, and a lightning fast stiff solver allow very complex models to be run and investigated using automatic parameter plots and parameter sliders. We have designed a visual interface that allows users to construct compartment models using drag-and-drop icons to 'wire up' a complex system, while Berkeley Madonna$^{TM}$ automatically constructs the corresponding equations in a separate window. Specialized modules allow users to simulate chemical reactions by simply typing the reaction in conventional chemical notation, import data and fit to your model, compute Fourier transforms, find roots, solve implicit equations, and much more. In addition to developing a simple, fast program for obtaining numerical solutions, we have devoted our attention to providing easy methods to display and analyze the results. These implementations will be illustrated with examples drawn from our classroom experience and research problems. A trial version of Berkeley Madonna$^{TM}$ can be downloaded from ¡http://www.berkeleymadonna.com¿. Development of Berkeley Madonna has been supported in part by grants from NIH (1R43RR10812-01A1) and NSF (DBI-9601458).

## 2. SOME RANDOM THOUGHTS ON STOCHASTIC MODELLING AS A GRADUATE COURSE

**Charles E. Smith *, Tim Elston**

BIOMATH GRADUATE PROGRAM, NORTH CAROLINA STATE UNIVERSITY, RALEIGH, NC 27695-8203
BMASMITH@UNITY.NCSU.EDU, ELSTON@UNITY.NCSU.EDU

We are starting to develop a website for our stochastic modeling course and are seeking your favorite examples to cover a variety of application areas. We hope eventually it will become a resource for the biomath community at large. A diverse background of the students in terms of probability and introductory stochastic processes, as well as in their research area have made this course a challenge at times. In the past, a methods book on stochastic differential equations or a more physics approach such as Gardiner's "Handbook of Stochastic Methods" provided some general tools that the students used in doing a term project in their area of interest. We are trying to incorporate examples from xpp, auto, Maple and Matlab that allows a follow-up to what they have seen in their previous three biomath courses. We will illustrate a few examples of using phase plane analysis to distinguish between additive vs multiplicative noise, a minimum function in disguise as a branched neuron, or receptor signaling, molecular motor modelling, and stochastic resonance. Another theme in the course is that noise can have roles besides just a smearing out or perturbing of the mean behaviour. For example, noise can also smooth out thresholds and facilitate changing domains of attraction.

### 3. Incorporating a mathematician into biology, or something like that

**Eric S. Marland** *

DEPARTMENT OF MATHEMATICS, APPALACHIAN STATE UNIVERSITY, BOONE, NC 28608
MARLAND@PM.APPSTATE.EDU

We are beginning to change the relationship between the departments of mathematics and biology here at Appalachian State University. We have interested faculty members in both departments and have students who are capable. The process of integrating more mathematics into the biology curriculum still has a number of speed bumps that need to be addressed. Among the many such difficulties, one striking one is the lack of mathematical confidence of the biology faculty members themselves. We believe the our approach minimizes the largest speed bumps and will foster better communication between the departments. Since we are in the early stages of our efforts, we hope to get feedback on our somewhat grandiose plans.

### 4. *in silico* DNA, RNA, Protein Sequence, and Structure Analysis: Theory and Practice

**John R. Jungck** *, **Stephen J. Everse**

*DEPARTMENT OF BIOLOGY, BELOIT COLLEGE, BELOIT, WI 53511 AND DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF MEDICINE, UNIVERSITY OF VERMONT, BURLINGTON, VERMONT 05405-0068
JUNGCK@BELOIT.EDU, SJE@BLOOD.UVM.EDU

"In silico DNA, RNA, Protein Sequence, and Structure Analysis: Theory and Practice" is the title of week-long workshops that we have offered for over one hundred faculty in Thailand over the past four years. In addition, we have offered numerous three-day workshops around the U.S. for faculty to introduce them to computational molecular biology and molecular bioinformatics. Our intensive workshops emphasize both theoretical and empirical aspects of computational analyses of DNA, RNA, protein sequences, and structures. They are intended for molecular biologists, biotechnologists, geneticists, biochemists, biophysicists, and others who need to be able to download and utilize DNA, RNA, protein sequences, and structures in their own personal research and/or teaching. No prior experience in utilizing computational molecular biology packages or world wide web tools and data bases are expected. In addition to extensive time for learning how to use the software tools and databases, we introduce mathematics that should be accessible to anyone with a professional education in molecular biology. Topics include graph theory, coding and information theory, phylogenetic tree construction, multiple sequence alignment, topology of DNA, group theory and X-ray crystallography, computational geometry, and a variety of topics in discrete mathematics. The opportunities and challenges of introducing faculty without much mathematics to the beauty, power, and limitations of bioinformatics will be shared.

## 4 Morphogenesis, Wound Healing and Tissues

### 1. Stripe Pattern Formation Generated Reaction Diffusion with Anisotropy

**Hiroto Shoji**[*†], **Atsushi Mochizuki**[†], **Yoh Iwasa**[†] &
**Shigeru Kondo**[††]

†Dept. Biol., Kyushu Univ
†† Fac. Integrated Arts & Sci., Tokushima Univ.,
shoji@bio-math10.biology.kyushu-u.ac.jp

The stripe patterns observed on tropical fishes skin have been explained by applying reaction-diffusion (RD) model proposed by Turing (1952), a system of reacting and diffusing two substances (activator and inhibitor) could spontaneously evolve to spatially heterogeneous pattern. However, the classical RD model can't explaine the fact that most of the fish stripe are either parallel or perpendicular to the body axis, where the direction depends on the species. In this presentation, we study the RD model including anisotropic diffusion to explain specificity of the direction of the fish stripe.

Based on the fact that each scale comes out to the direction of the body axis in fish skin, we can expect that diffusion speed is different between parallel and perpendicular to the body axis caused by the structural difference in epidermis. The model is the following:

$$\begin{aligned} \partial u/\partial t &= \nabla(D_u(\theta)(\nabla u)) + \gamma f(u,v), \\ \partial v/\partial t &= d\nabla(D_v(\theta)(\nabla v)) + \gamma g(u,v). \end{aligned}$$

The diffusion coefficient is $D_\sigma(\theta) = 1/\sqrt{1-\delta_\sigma \cos(2(\theta-\psi))}$, where $\theta$ indicates the direction of the gradient of the variable, and $\psi$ indicate the specific direction to which the substance diffuse faster. The parameter $\delta_\sigma$ is the degree of anisotropy.

The direction of stripe was depeneds only on the relative magunitude between the anisotropy of activator ($\delta_u$) and that of inhibitor ($\delta_v$). If the anisotropy is almost the same between the two substances ($\delta_u \cong \delta_v$), the direction of the obtained pattern is random. If $\delta_u > \delta_v$, the direction of stripe is likely to be parallel to the diffusive direction. In contrast, if $\delta_u < \delta_v$, the direction of stripe is likely to be perpendicular to the diffusive direction. This result does not depend neither other parameter value nor the form of the reaction term.

We studied the effects of anisotropic diffusion more in detail.

## 2. Force and Deformation on Branching Rudiments: Cleaving Between Hypotheses

**Sharon R. Lubkin** *

North Carolina State University
lubkin@eos.ncsu.edu

Branching development occurs in many organs such as the salivary gland, lung, and kidney. We have developed several alternative mechanical models of the tissue deformations of such branching development, in terms of a free-boundary problem (interface propagation). We present a simple two-fluid model with active interface, which offers a quantitative interpretation of the relative magnitude of the forces hypothesized to cleft a developing salivary gland rudiment.

## 3. Mathematical modelling of primitive streak dynamics

**Philip K. Maini***

Centre for Mathematical Biology, Mathematical Institute, 24-29 St Giles', Oxford OX1 3LB, UK
maini@maths.ox.ac.uk

The formation of the primitive streak in early embryonic development marks the beginning of gastrulation, during which the blastoderm is transformed into distinct tissue types. Initiation of the primitive streak provides a well-studied example of a pattern-forming event that displays a striking capacity for regulation. The mechanisms underlying the regulative properties are, however, poorly understood and are not easily accounted for by traditional models of pattern formation, such as reaction diffusion models. Recently, we proposed [1] a new activator-inhibitor model for streak initiation. It is shown that this model is consistent with experimental observations, both in its pattern-forming properties and in its ability to form these patterns on the correct timescales for biologically realistic parameter values. A key component of the model is a travelling wave of inhibition. A mathematical analysis of the speed of such waves in both diffusive and juxtacrine relay systems is presented, and the model is used to make testable predictions. By varying parameters of the model two very different types of

patterning can be obtained, suggesting that our model may be applicable to other processes in addition to streak initiation.

The primitive streak itself shows intriguing spatio-temporal patterning with cells initially moving out across the blastoderm (progression) followed by a period of reverse movement (regression). To date, little is known concerning the mechanisms controlling either progression or regression. A simple chemotactic-cell model is presented [2] which is capable of capturing the principal features connected with progression and regression of the primitive streak. In particular, it is demonstrated that this model is capable of capturing several experimental results and a number of experimental tests which may serve to illuminate the mechanisms are indicated.

References:

[1] K.M. Page, P.K. Maini, N.A.M. Monk, C.D. Stern, A model of primitive streak initiation in the chick embryo, *J. theor. Biol.*, **208**, 419-438 (2001)

[2] K.J. Painter, P.K. Maini and H.G. Othmer, A chemotactic model for the advance and retreat of the primitive streak in avian development, *Bull. Math. Biol.*, **62**, 501-525 (2000)

## 4. Investigating a Model of Angiogenesis

**Eamonn A. Gaffney*, Philip K. Maini, Frank Arnold**

SCHOOL OF MATHEMATICS & STATISTICS,
UNIVERSITY OF BIRMINGHAM, U.K;
CENTRE FOR MATHEMATICAL BIOLOGY,
UNIVERSITY OF OXFORD, U.K;
JOHN RADCLIFFE HOSPITAL, OXFORD, U.K.
EAG@FOR.MAT.BHAM.AC.UK

A simple model of wound healing angiogenesis is presented, and investigated. The model captures all qualitative features of the wound healing angiogenic response, such as the propagation of a structural unit into the wound centre. A detailed perturbative study is pursued, and is shown to accurately predict all features of the model. This enables one to show that the level of the angiogenic response predicted by the model is governed to a good approximation by a small number of parameter groupings. Further investigations are pursued relating to how one should select between potentially optimal means of stimulating cell proliferation in order to increase the level of the angiogenic response.

## 5. A Mathematical Model of Transforming Growth Factor Beta and Extracellular Matrix Alignment in Dermal Wound Repair

**John C. Dallon *, Jonathan A. Sherratt and Philip K. Maini**

DEPARTMENT OF MATH EMATICS, BRIGHAM YOUNG UNIVERSITY

In order to understand the anti-scarring properties of TGF-beta, we study each of its individual effects on the wound process, how they interact and eventually result in less scarring. To this end, we have developed a mathematical model of alignment in wound healing which incorporates some of the effects of TGF-beta. In this model we focus on the interactions between fibroblasts and the extracellular matrix. We allow for time varying concentration of TGF-beta which can alter the motility, proliferation and collagen production of the fibroblasts. We find that although these properties of the fibroblasts can affect matrix alignment they seem to be of minor importance and cannot explain the anti-scarring properties of TGF-beta. However, we find that by changing fibroblast reorientation rates, consistent with experimental evidence, the alignment of the regenerated tissue can be significantly altered and thus explain the influence of TGF-beta on scarring.

## 6. Modelling the Differential Effects of Drugs on Cells in Tumour Spheroids

**Eleanor Clark *, John King, Helen Byrne**

DIVISION OF THEORETICAL MECHANICS, NOTTINGHAM, UK

A wide variety of chemotherapeutic drugs are used in the treatment of cancer. Whilst most drugs are designed to target rapidly proliferating cells (*e.g.* Cyclophosphamide), some, for example Mitomycin C, are more effective in an oxygen-deficient (or hypoxic) environment such as that commonly found in many solid tumours. We present a mathematical model of solid tumour growth which can be used to compare its response to these two types of drug. The model is formulated as a system of partial differential equations in which the processes of cell proliferation and death, together with an assumption of incompressibility, cause cell movement and so establish a velocity field within the tumour. Through a combination of numerical and asymptotic techniques we investigate the way in which the tumour's size and spatial structure are affected by each of these two types of drug.

# 5 Epidemiology

## 1. Reconciling the SEIR Model to Real-World Whooping Cough Dynamics

**Chris Bauch*, David Earn**

DEPARTMENT OF MATHEMATICS AND STATISTICS MCMASTER UNIVERSITY 1280 MAIN STREET WEST HAMILTON, ONTARIO CANADA L8S 4K1
BAUCH@ICARUS.MATH.MCMASTER.CA

Understanding the epidemic patterns of childhood diseases during the twentieth century has been a major goal of epidemic modelling. Recent work indicates that transitions in patterns of epidemics (e.g., from irregular to periodic epidemics) may be driven by long-term changes in birth rates and vaccination levels. Using this result, it has been possible to explain observed changes in patterns of measles epidemics as shifts between attractors of a seasonally forced SEIR model. In contrast, with parameters appropriate for whooping cough, the model has a unique attractor (an annual cycle), whereas multiennial cycles are observed. Using bifurcation theory, we show that real-world multiennial epidemics of whooping cough can be understood as 'ghosts of departed attractors' in the seasonally forced SEIR model.

## 2. Comparative Nonlinear Dynamics of Sympatric Childhood Infections

**Pejman Rohani*, Keeling, M.J. & Grenfell, B.T.**

DEPARTMENT OF ZOOLOGY, UNIVERSITY OF CAMBRIDGE
PEJMAN_ROHANI@HOTMAIL.COM

An important issue in the history of ecology has been the exploration of the relative importance of deterministic forces and processes noise in shaping the dynamics of populations. In this talk, we address this question by exploring the temporal dynamics of two sympatric childhood infections – measles and whooping cough – in England & Wales. We demonstrate that epidemics of whooping cough are strongly influenced by stochasticity; fully deterministic approaches cannot achieve even a qualitative fit to the observed data. In contrast, measles dynamics are extremely well explained by a deterministic model. These differences are shown to be caused by their contrasting responses to dynamical noise, due to different infectious periods.

## 3. Tuberculosis Control in the U.S.: a strategy to meet CDC's goal

**Baojun Song* and Carlos Castillo-Chavez*†**

*DEPARTMENT OF BIOMETRICS, CORNELL UNIVERSITY, ITHACA, NY, 14853
†DEPARTMENT OF THEORETICAL AND APPLIED MECHANICS AND DEPARTMENT OF STATISTICS, CORNELL UNIVERSITY, ITHACA, NY, 14853
SB47@CORNELL.EDU

Non-autonomous systems of ordinary differential equations are introduced to model the transmission of dynamics of tuberculosis and to fit U.S. tuberculosis incidence over the past five decades. Tuberculosis may be controlled in the U.S. under the criterion given by CDC (one case per million) by the year 2020 if at least 20% of the latently-infected individuals are successfully treated. The effect of HIV/AIDS after 1983 is included in the analysis via a model that incorporates a function that accelerates TB progression. It is shown that TB's case rate may be eventually controlled despite increases in the rate of TB progression due to HIV. Sufficient conditions for TB extinction and persistence are derived in terms of upper limits and lower limits of the mortality functions.

**Key words:** Tuberculosis, HIV/AIDS, non-autonomous system, tuberculosis control, demography, epidemiology.

## 4. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission

**James Watmough*†, P. van den Driessche†**

†University of New Brunswick
‡University of Victoria
watmough@math.unb.ca

Classical disease transmission models typically have only a single stable equilibrium. There is a threshold level of the reproduction number, $\mathcal{R}_o$, such that if $\mathcal{R}_o < 1$, then the disease dies out and if $\mathcal{R}_o > 1$, then the disease approaches an endemic level. In this simple case, disease control is a 'simple' matter of reducing the reproduction number. Many recent models show bistability over a range of reproduction numbers, where both the disease free equilibrium and an endemic equilibrium are stable. These results have important consequences for disease control. We present a general compartmental disease transmission model based on a system of ordinary differential equations. An analysis of the local centre manifold yields a simple criterion for the existence and stability of super- and sub-threshold endemic equilibria for $\mathcal{R}_o$ near one. This criterion, together with the definition of $\mathcal{R}_o$, is illustrated by several models, including multiple group, multiple strain, staged progression and vector-host models.

## 5. Spatial coherence in metapopulations

**David J.D. Earn***,

Department of Mathematics and Statistics, McMaster University, Hamilton, Ontario, Canada L8S 4K1
earn@math.mcmaster.ca

If a species has low population density everywhere simultaneously then it is at risk of global extinction. Consequently, spatially coherent population dynamics may increase extinction risk. For endangered species it may be important to avoid coherent dynamics, while for pests or pathogens coherence may facilitate the elimination of the species. This talk will review recent progress on conditions for local and global attraction to coherent solutions of metapopulation models[1] and discuss applications to vaccination strategies for infectious diseases.

1. Earn, D.J.D., Levin, S.A., Rohani, P., 2000. Coherence and Conservation. *Science* **290**, 1360–1364.

## 6. On Travelling Wave of Disease Infection with Diffusing Epidemic Vector

**Hiromi Seno ***, **Satoshi Kojima**

Department of Mathematical and Life Sciences
Graduate School of Science, Hiroshima University, Japan
seno@math.sci.hiroshima-u.ac.jp

In our mathematical model, we apply the idea of Kermack-McKendrick model for the dynamical relation between host and epidemic vector, and to introduce the spatial propagation of epidemic disease, we assume the random diffusion of host and vector in infinite one-dimensional space:

$$\begin{cases} \dfrac{\partial v_+(x,t)}{\partial t} &= D_v \dfrac{\partial^2 v_+(x,t)}{\partial x^2} + \alpha h_+(x,t) v_-(x,t) \\ \dfrac{\partial v_-(x,t)}{\partial t} &= D_v \dfrac{\partial^2 v_-(x,t)}{\partial x^2} - \alpha h_+(x,t) v_-(x,t) \\ \dfrac{\partial h_+(x,t)}{\partial t} &= D_h \dfrac{\partial^2 h_+(x,t)}{\partial x^2} + \beta h_-(x,t) v_+(x,t) - \gamma h_+(x,t) \\ \dfrac{\partial h_-(x,t)}{\partial t} &= D_h \dfrac{\partial^2 h_-(x,t)}{\partial x^2} - \beta h_-(x,t) v_+(x,t) + \gamma(1-\epsilon) h_+(x,t). \end{cases}$$

Susceptible host $h_-$ is infected by contact to infectious vectors $v_+$ with transmission rate $\alpha$, while the susceptible vector $v_-$ is done by contact to infectious hosts $h_+$ with transmission rate $\beta$. Parameter $\gamma$ is the recovery rate for infectious host. Recovered host can get the immunity with probability $\epsilon$, so that host without the immunity returns to susceptible with probability $1-\epsilon$. $D_v$ is the diffusion coefficient for vector population, and $D_h$ that for host one. We assume that the disease infection does not affect the mobility of host and vector, so that infectious and susceptible have the same diffusion coefficient, although vecter and host have different in general.

In our model, we focus the existence and the propagating speed of stationary travelling epidemic wave, and analyze the above-shown model by means of mathematically analytical and numerical methods. We try to consider the biological meanings of those obtained mathematical results and discuss the characteristics of epidemic travelling wave.

### 7. The evolution of virulence in spatially structured host populations

**Michael Boots *, Akira Sasaki**

DEPARTMENT OF BIOLOGICAL SCIENCES STIRLING UNIVESITY
MB13@STIR.AC.UK

Why are some diseases more virulent than others? Vector and water-borne diseases are generally more virulent than diseases spread by direct contagion. One factor that characterizes both vector and water-borne diseases is their ability to spread over long distances, thereby causing infection of susceptible individuals distant from the infected individual. Using a lattice model in which reproduction is local, but infection can vary from local to global we show that distant infection may lead to the evolution of a more virulent pathogen.

### 8. Chemostat Models with Time Delays for Bacteria and Virulent Phage

**Yasuhiro Takeuchi *, Hirotatsu Sakakibara***
**and Edoardo Beretta****

*DEPARTMENT OF SYSTEMS ENGINEERING, FACULTY OF ENGINEERING, SHIZUOKA UNIVERSITY, HAMAMATSU 432-8561, JAPAN
**ISTITUTO DI BIOMATEMATICA, UNIVERSITA DI URBINO, I-61029 URBINO, ITALY
TAYTAKE@IPC.SHIZUOKA.AC.JP

The dynamical properties of the time delayed chemostat model described by

$$\begin{aligned} \dot{r} &= \rho(C-r) - \phi_1(n_1+m_1) - \phi_2 n_2 \\ \dot{n}_1 &= n_1(\phi_1/e_1) - \rho n_1 - \gamma_1 n_1 p \\ \dot{n}_2 &= n_2(\phi_2/e_2) - \rho n_2 \\ \dot{m}_1 &= \gamma_1 n_1 p - \rho m_1 - \gamma_1 e^{-\rho l_1} n_1(t-l_1)p(t-l_1) \\ \dot{p} &= b_1\gamma_1 e^{-\rho l_1} n(t-l_1)p(t-l_1) - \rho p - \gamma_1 n_1 p \end{aligned} \tag{2}$$

are considered. Here $r(t)$, $n_1(t)$, $n_2(t)$, $m_1(t)$ and $p(t)$ are a concentration of the resource, the densities of two bacteria, an infected bacteria and bacteriophage, respectively. Further, $\rho$ is the rate of flow through the chemostat, $C$ is the input concentration of the resource, $\gamma_1$ is the attack constant of phage to the first bacteria, $e_i$ is the bacteria's consumption rate of the resource, $l_1$ is the latent period (the time delay between the attack by a phage on the first bacteria and the resulting reproduction of new phages) and $b_1 > 1$ is the reproduction rate of the phage from the infected first bacteria. The $\phi_i$ is the bacteria's taking up rate of the resource and satisfies $\phi_i(0) = 0$ and increasing in $r > 0$.

Note that the first bacteria is assumed to be sensitive to predation of the phage but the second is immune to predation. Some experimental data show that two bacteria (the first is resident and the second is a mutant) and phage can coexist. We consider the boundedness of the solutions of (1) and local (or global) asymptotic stability of nonnegative equilibria. We further show that the coexistence is possible for short latent period and for large reproduction rate of the phage.

## 6 Population Dynamics and Evolution

### 1. Metapopulation Extinction Caused by Mutation Accumulation

**Kevin Higgins*, Michael Lynch**

UNIVERSITY OF SOUTH CAROLINA AND UNIVERSITY OF OREGON
HIGGINS@DARKWING.UOREGON.EDU

Theory suggests that the risk of extinction by mutation accumulation can be comparable to that by environmental stochasticity for an isolated population smaller than a few thousand individuals. Here we

show that metapopulation structure, habitat loss or fragmentation and environmental stochasticity can be expected to greatly accelerate the accumulation of mildly deleterious mutations, lowering the genetic effective size to such a degree that even large metapopulations may be at risk of extinction. Because of mutation accumulation, viable metapopulations may need to be far larger and better connected than would be required under just stochastic demography.

## 2. Subtle temporal patterns in *Tribolium* population dynamics

**Aaron A. King*, R. F. Costantino, J. M. Cushing, S. M. Henson, R. A. Desharnais, and Brian Dennis**

DEPARTMENT OF ENVIRONMENTAL SCIENCE & POLICY, INSTITUTE FOR THEORETICAL DYNAMICS, AND CENTER FOR POPULATION BIOLOGY, UNIVERSITY OF CALIFORNIA, DAVIS
AKING@UCDAVIS.EDU

Ever since May first noted that complicated ecological time series might conceal intelligible deterministic structure, the search for patterns in ecological data has motivated much theoretical and empirical research. Recently, chaotic dynamics have been conclusively demonstrated in laboratory populations of the flour beetle *Tribolium castaneum*. Inspection of these experimental data reveals intriguing but quite subtle temporal patterns, which turn out to be predicted by the LPA model, a discrete-time, stage-structured, nonlinear, stochastic matrix model. Specifically, theory predicts that the stochastic dynamics should be strongly influenced by unstable cycles in the chaotic attractor of the model's deterministic skeleton. In order to quantify these patterns, we introduce a novel, model-based statistic, the *average rotation number*, and describe its use in the design of an experimental test of theoretically predicted temporal patterns. We sketch the mathematical, statistical, and experimental aspects of our approach and present preliminary experimental results involving nearly 2 years of data for 12 replicated cultures.

## 3. EFFECT OF HERBIVORE STOICHIOMETRY ON POPULATION STABILITY

**Roger M Nisbet [1], Erik B. Muller[1], Edward McCauley[2], James J. Elser[3], Tom Andersen[4], Sebastiaan A.L.M. Kooijman[5]**

1. UNIVERSITY OF CALIFORNIA, SANTA BARBARA, CA 93106.
2. BIOLOGICAL SCIENCES, UNIV. OF CALGARY, CALGARY, CANADA.
3. DEPT. BIOLOGY, ARIZONA STATE UNIVERSITY, TEMPE, AZ 85287.
4. NORWEGIAN ISTITUTE FOR WATER RESEARCH, P.O.BOX 173, KJELSAAS N-0411 OSLO, NORWAY
5. DEPT. THEORETICAL BIOLOGY, VRIJE UNIVERSITEIT, AMSTERDAM, THE NETHERLANDS
NISBET@LIFESCI.UCSB.EDU

There is a growing body of empirical evidence suggesting that regulation of proportions of the elements C:N:P in herbivores influences the growth of individuals, population dynamics, and herbivore community structure. Previous work by T. Andersen on simple models of zooplankton and their algal food has shown that nutrient limitation of herbivore growth may lead to herbivore extinction, the precise conditions depending on (a) the ratio of the minimum nutrient quota of the algae to the (fixed) quota in the herbivore, and (b) the relationship between herbivore growth rate and algal quota. We generalize these findings by developing new mechanistic representations of herbivore growth that use the concept of the synthesizing unit, recently proposed by S.A.L.M. Kooijman. This representation is tested against published data on the growth of individual Daphnia. We formulate population models based on the same assumptions regarding individual growth, and investigate conditions for the existence and stability of viable herbivore populations. We find that the viability of the herbivore population depends strongly on the details of assumptions regarding feeding, assimilation and maintenance.

## 4. A model of coevolution of egg appearance as a quantitative character in avian brood parasitism

**Fugo Takasu**

DEPT. INFORMATION AND COMPUTER SCIENCES, NARA WOMEN'S UNIVERSITY, NARA 630- 8506, JAPAN
TAKASU@ICS.NARA-WU.AC.JP

In avian brood parasitism, egg appearance plays a key to determine the reproductive success of both host and parasite, because some host has evolved a defense against brood parasitism such as an ability to recognize and reject parasitic eggs that look different from those of the host. This host defense, in turn, should select for counter defense of egg mimicry by parasite and the interaction between them has been thought to result in a coevolutionary arms race.

Egg appearance, however, is composed of many features such as background color, spottedness, blotches, etc., and all of which seem to be quantitative characters ranging continuously from one extreme to the another. It is known that there exist some inter and intra-clutch variations of egg appearance to some extent. Due to the continuum and the variation of egg appearance, the consequence of the arms race between host and parasite is not so simple as a conventional phrase says "The parasite chases the host which escapes from the parasite".

Then, how does the arms race proceed? In this presentation, I will give a mathematical model to explore the temporal change of the egg appearance of host and parasite as a quantitative character. The model is described by integro-difference equations and the analysis shows intriguing results as to the transient dynamics between them and the quasi-equilibrium state in which only discrete characters can survive both in host and parasite populations. Integro-difference equation is getting used as a tool to study population dynamics with quantitative character and I discuss the usefulness in terms of the case study of avian brood parasitism.

## 5. Evolution of linguistic coherence

**Natalia Komarova *, Martin Nowak, Partha Niyogi**

INSTITUTE FOR ADVANCED STUDY, PRINCETON.
NATALIA@IAS.EDU

I will give an overview of the recent work that has been done in an attempt to create a mathematical formulation of the evolution of language. I will speak about two major components of the language: the lexicon and the grammar. In a sense, languages evolve like individuals in a population: the fittest ones survive and their genomes get passed down generations, the less fit ones get eliminated. The two driving forces of evolution, selection and mutation (i.e. the mistakes when learning a language), can be incorporated into a system of ODE's called the evolutionary equations. Within this framework, it is possible to get some analitical insights into the dynamics of the language. One of the questions we ask is how accurate children have to learn the language of their parents in order for the population to be able to maintain a coherent language? Another one is what are the evolutionary forces that shape the Chomskian Universal Grammar?

## 6. Calculating the cost of altruism

**Klaus Jaffe ***

UNIVERSIDAD SIMN BOLVAR, CARACAS 1080, VENEZUELA
KJAFFE@USB.VE

Altruism is generally thought of as the behaviors, which benefit others, and thus benefit the group, at a cost to the actor. Extreme cases of altruism, in which an individual sacrifices its reproductive potential or its live in order to favor another individual, are common in nature and have been successfully explained in several cases by kin selection theory, providing a basis for Sociobiology. However, kin selection theory cannot explain all of the social phenomena that involve some kind of altruistic acts. Computer simulations have shown that economic considerations, rather than kinship, are better predictors of social behavior. In many real situations, the benefits to the actor and to the group are asymmetrical, but not necessarily negative to any of the parties. In such cases we speak of mutualism. Jet mutualism and altruism represent but two points in a continuous range of possibilities. Using an agent based computer simulation model, I explore a range of possible situations of conflict between the individual and the group. However, the simulations (over 40000) suggest that altruistic-mutualistic behavior is not beneficial even to the group, and in the best of the cases is just neutral, regarding the overall efficiency of the system in accumulating resources (GDP), compared to equivalent systems where no altruistic acts are allowed.

## 7. Scramble and Contest: Understanding the Dynamics of Individual Based Models

**David J. T. Sumpter[1*], Anders Johansson[2] & David S. Broomhead[3]**

[1]Centre for Mathematical Biology, Mathematical Institute, 24-29 St Giles' Oxford OX1 3LB, UK.,
[2] Mathematics Depatment, UmeåUniversity, SE-901 87 Umeå, Sweden,
[3] Mathematics Depatment, UMIST, P.O. Box 88, Manchester, M60 1QD, U.K.
SUMPTER@MATHS.OX.AC.UK

How do the behavioural interactions between individuals in an ecological system produce the global population dynamics of that system? We present a stochastic individual-based model of the reproductive cycle of the mite *Varroa jacobsoni*, a parasite of honey bees. The model has the interesting property that its population level behaviour is approximated extremely accurately by the exponential logistic equation or Ricker map. We demonstrate how this approximation is obtained mathematically and how the parameters of the exponential logistic equation can be written in terms of the parameters of the individual-based model.

The competition between individuals in our model of the Varroa mite resembles a 'scramble' for hosts, in that if too many individuals try to exploit the same host then they all fail to reproduce. Another type of competition commonly observed in ecological systems is a 'contest', where overcrowding of a particular host is resolved with a single successfully reproducing winner. We demonstrate how the population dynamics of 'scramble' and 'contest' competition differ, by deriving mean-field equations for our individual-based models. Our procedure demonstrates how study of animal ecology at an individual level can be used to derive global models which predict population change over time.

**Reference:** D. J. T. Sumpter & D. S Broomhead (2001) Relating Individual Behaviour to Population Dynamics, *Proceedings of the Royal Society of London: Series B* (in press).

### 8. Optimal Control of a Competitive System with Age-Structure

**Suzanne Lenhart**

University of Tennessee, Mathematics Department, Knoxville, TN 37996-1300 USA
LENHART@MATH.UTK.EDU

We consider optimal control of a first order partial differential equation system representing a competitive population model with age-structure. The controls are the proportions of the populations to be harvested, and the objective functional represents the profit from harvesting. The existence and unique characterization of the optimal control pair are established. Ekeland's variational principle is used to obtain the existence result. This work is joint work with Renee Fister of Murray State University.

## 7 Cell and Molecular Biology

### 1. Minimal Surfaces as Internal Manifolds of Biomolecular Structures

**Rubem Mondaini *, Eduardo Pereira Marques**

Head of Mathematical Biology Group of the Federal University of Rio de Janeiro

In this work, we emphasize the advantage of using Euclidean Steiner Minimal Trees and their associated minimal surfaces as the best candidates for manifolds of the internal structure of biomolecular configurations. The special motivation under this approach is to model the average distribution of atomic sites on these minimal surfaces, which are helicoidal forms. Their degenerated forms would be strands on a right circular cylinder. We present two applications concerning the use this approach. The first one calculates the internal radius of the A-DNA configuration. The second one is the calculation for a complex aggregate of RNA and proteins like the tobacco mosaic virus (TMV). Our agreement with experimental data is 94.6

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### 2. Diffusion Dynamics of Microtubules

**Ivan V. Maly**

INTEGRATED GRADUATE PROGRAM IN THE LIFE SCIENCES, NORTHWESTERN UNIVERSITY, CHICAGO, ILLINOIS, 60611-3008
I-MALY@NORTHWESTERN.EDU

Microtubules are protein polymers that giude the intracellular motility. Stochastic switching of a microtubule between states of elongation, shortening, and pause is described by dynamic instability model. Recently we have described dynamics in population of microtubules as apparent diffusion of their ends along their axes (Vorobjev et al., 1999, J. Cell Sci., 112:2277). In this work, I elucidate the genesis of the diffusion dynamics and evaluate accuracy of the diffusion model. I demonstrate that wandering of the end of a microtubule undergoing dynamic instability asymptotically approaches Wiener diffusion process, and derive asymptotic diffusion parameters from parameters of two- and three-state dynamic instability. In particular, the apparent diffusion coefficient of the end of a microtubule undergoing two-state dynamic instability is $D = k1 * k2 * (v1 + v2)^2/(k1 + k2)^3$, and its drift is $r = (k2 * v1 - k1 * v2)/(k1 + k2)$, where k1 and k2 are frequences of transitions from elongation to shortening and vice versa, and v1 and v2 are apparent absolute velocities of the end during microtubule elongation and shortening. Accuracy of diffusion model is evaluated by comparing its predictions with results of simulation of dynamic instability using dynamic instability parameters previously measured in cells. In newt pneumocytes (Cassimeris et al., 1988, J. Cell Biol., 107:2223), microtubule dynamic instability is two-state. In these cells, a microtubule tends to assemble, and both models predict that the stationary distribution of the microtubule length is exponentially ascending up to the cell radius, and lifetime of microtubule segments rapidly increases towards the centrosome. In BSC-1 cells (Dhamodharan and Wadsworth, 1995, J. Cell Sci., 108:1679)), microtubule dynamic instability is three-state. In these cells, a microtubule tends to disassemble, and both models predict that the stationary distribution of the microtubule length is exponentially descending and lifetime of microtubule segments is uniform everywhere in the cell. The predicted mean length of microtubules in the newt pneumocyces is 97 micrometers in dinamic instability simulations and 99 micrometers in the asymptotic diffusion model, as compared to the empiric estimate, 100 micrometers (Gliksman et al., 1993, Mol. Biol. Cell., 4:1035). The median lifetime of microtubules in the BSC-1 cells is 322 s in dinamic instability simulations and 265 s in the asymptotic diffusion model, as compared to the empiric estimate, 92-320 s (Saxton et al., 1984, J. Cell Biol., 99:2175). Thus, the biologically significant properties of the microtubule array as predicted by both models differ qualitatively between two cell types considered. However predictions of the simple, asymptotic diffusion model are in each case practically identical to predictions of the detailed, fundamental dynamic instability model being also consistent with the experimental data. Peculiar stochastic process of microtubule assembly thus converges at the cell scale to a kind of widespread in nature diffusion process. This suggests employment of the theory of diffusion processes in studying functions of microtubules in the cell.

## 3. Description of motor protein motility using stochastic models

**ANATOLY B. KOLOMEISKY**

RICE UNIVERSITY, DEPARTMENT OF CHEMISTRY, HOUSTON, TX 77005-1892
TOLYA@RUF.RICE.EDU

Recent advances in measurements of motor protein motility have underlined the need for the development of theoretical models to describe the experiments adequately. We present several classes of stochastic models[1] which account for the properties of processive molecular motors that move along linear periodic molecular tracks. In our approach the original analysis of Derrida (*J. Stat. Phys.* **31** (1983) 433-450) is extended to obtain *exact*, closed form expressions for the velocity, $V$, and dispersion (or diffusion constant), $D$, of discrete one-dimensional nearest-neighbor stochastic hopping models with detachments, branches, jumps and waiting-time distributions. Specifically, we can analyze in detail recent extensive experimental observations of individual kinesin molecules moving along microtubules *in vitro* under controlled loads, $F = 1$ to 8 pN, with [ATP]= 1 $\mu$M to 2 mM.

## 4. A MATHEMATICAL MODEL FOR ELONGATION OF A PEPTIDE CHAIN

**Donald A. Drew *, Andrew Heyd**

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DEPARTMENT OF MATHEMATICAL SCIENCES
RENSSELAER POLYTECHNIC INSTITUTE
TROY, NY USA 12180-3590
DREWD@RPI.EDU

One of the steps in protein synthesis is the elongation of the polypeptide chain. This is accomplished one amino acid at a time, facilitated by the ribosome and the tRNA molecules. An amino acid bound to a tRNA binds to the ribosome, catalyzed by elongation factor Tu. This complex enters the ribosome, and the codon recognition site on the tRNA is associated with the corresponding codon on the mRNA. If the amino acid-tRNA complex recognizes a correct codon on the mRNA, the complex is stabilized by interactions of the tRNA, mRNA and the ribosome. Formation of the codon-anticodon bond actives the hydrolysis of the GTP. This causes a conformational change of the EF-Tu complex. Next, the elongation factor unbonds and leaves the ribosome. The amino acid is bonded to the peptide chain. If the amino acid-tRNA complex recognizes the wrong codon, the complex is rejected, and the process starts again. In this paper, we present a mathematical model for the steps in the elongation process, and find the steady-state elongation rate as a function of the amino acid concentrations. In addition, we study the reset sub-process of the elongation process. The reset process is composed of another process involving an elongation factor, EF-G. The ribosome complex in state G above binds a molecule of EF-G. The GTP in the EF-G is hydrolyzed, and a conformational change occurs in the ribosome complex. In this motion, the mRNA is moved into position for the next codon to be matched, and the tRNA is dissociated and returns to the cytoplasm.

## 5. A SIMPLE GEOMETRIC MODEL FOR A SIMPLE UNICELLULAR ORGANISM

**Nima Geffen**

DEPARTMENT OF MATHEMATICS, UNIVERSITY OF BRITISH COLUMBIA, VANCOUVER BC, CANADA,
ON LEAVE FROM: THE SCHOOL OF MATHEMATICAL SCIENCES, TEL AVIV UNIVERSITY,
RAMAT-AVIV, ISRAEL.
GEFFEN@IAM.UBC.CA

Dark-field light-microcpy videos plus measurements based on them and electron microscopy results on Spiroplasma melliferum BC3, by S. Trachtenberg [1], suggested to him a helical geometry of this smallest, free-moving, self-sustaining organism, whose motion is governed by a longitudinal protein ribbon attached, at all of its points, to the membrane of the cell. The ribbon is composed of 6-7 parallel fibers. Based on this information, (given a couple of years before [1] was written), a complete geometrical model was proposed and used for re-organization and the re-interpretation of the measurements. The 'exact' location of the protein was deduced on mathematical grounds, and, at a later stage, so was the mechanism for a biologically acceptable change of sense. An appropriate un-wrapping was devised to calculate the strain and stress in the fiber of the ribbon, and elsewhere, as needed. These were to be compared with results of elaborate electron-microscopy and biochemical methods by S. Trachtenberg al. [2]. A parametric representation of the cell, with the location of the ribbon explicitly specified, is used to simulate graphically the geometry and motion of the cell. This complete motion can, putatively, be affected by length-changes of the fibers along the ribbon, including the observed change of sense (which was solved separately and integrated into the system in a seemingly biologically logical way). Although the mathematics is simple and the qualitative conclusions (i.e. the location of the ribbon along the minimal path along the 'straight' helical coil and the mechanism of change of sense), may seem obvious in hind sight (especially compared with the elaborate, arduous and sofisticated experiments and measurements), it has to be realized (and acknowledged) that the location of the ribbon (as stated in [1]), has been 'observed' after the a-priori prediction based on the geometric analysis, and that the figures could be obtained after the equations were put down. The model can now be summed up by one equation, describing to any desired detail and accuracy the seemingly observed motion. Due to the fact that some of the crucial quantities and locations are at the threshold of observability (and were, possibly, even more so at the time when this work was initiated by S. Trachtenberg), the mathematical qualitative conclusions and quantitative formulations have played a crucial role in the presentation and interpretation of the data and the final picture (mental and on paper) of the whole cell [1],[2]. The mathematical reasoning and the results are detailed below. It can, perhaps, be used to describe similar organisms of different dimensions, and to build toy-models of these creatures, and test their possibilities and performance in a game-like manner. The interaction between a straight-forward mathematical reasoning and formulation can thus be put to work for a better understanding of barely observable cells and learning the functional complexity achievable by such simple mechanical means. Further questions and direct extensions are pointed out.

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### 6. A Conservation Model for Density of Actin-Polymers in the Crawling Cell

**Diana W. Verzi *, Alex Mogilner**

INSTITUTE OF THEORETICAL DYNAMICS,
UNIVERSITY OF CALIFORNIA, DAVIS, CA
VERZI@ITD.UCDAVIS.EDU

Migration of animal cells is fundamentally important and is the most striking process underlying the phenomena of wound healing, morphogenesis and cancerogenesis. The front part of the migrating cell, a lamellipod, is a broad, flat cytoskeletal protrusion devoid of organelles. Behind the lamellipod is a roundish cell body, containing the nucleus and organelles. It is now widely accepted that the lamellipod contains the basic engine pulling the cell body forward.

Despite recent radical advances in cell biology and the biophysics of the motile cell, we still do not have a complete picture of how animal cells move across surfaces. One reason for this is that a huge variety of molecular mechanisms are involved in locomotion, which leads to a multiplicity and redundancy in force generation machineries and regulatory pathways. The current research is aimed at dissecting the complex processes of motility into simpler phenomena that can be more easily analyzed. Phenomenological models of cellular mechanics based on conservation laws and plausible constitutive relations have been formulated. We aim at incorporating a description of processes on a molecular-biological level into a comprehensive realistic model of migrating cells. We derive and solve numerically and analytically 1-D partial differential equations describing the cytoskeletal dynamics to develop an intuition of how biological behavior depends on essential mechanical and chemical parameters. Then, in order to make quantitative predictions of biological interest, we will develop realistic 2-D models of the moving cell. Our goals are to understand quantitatively the molecular origins of cytoskeletal mechanics and to model the motility related signal transduction processes. Such a model will have a predictive value in important biomedical and biotechnological situations.

## 8 Disease / Immunology

### 1. Using HIV-1 Sequences to Infer Historical Features of the AIDS Epidemic in the Democratic Republic of Congo

**Karina Yusim 1,2 *, Oliver G. Pybus 3, Martine Peeters 4, Tanmoy Bhattacharya 1, Eric Delaporte 4, Claire Mulanga 4, Bette Korber 1,2.**
**karina@t10.lanl.gov**

1 LOS ALAMOS NATONAL LABORATORY, NM 2 SANTA FE INSTITUTE, NM 3 UNIV. OF OXFORD, UK 4 IRD, MONTPELLIER, FRANCE

Studies of the evolutionary history of HIV enable to extrapolate into the past in order to make estimates of the age of the epidemic, and to model the historical growth of the epidemic. Evolutionary studies of the epidemic in sub-Saharan Africa are of key importance: sub-Saharan Africa accounts for more than 70 percent of the world's 34.3 million HIV-AIDS cases. The Democratic Republic of Congo (DRC), has some of the earliest AIDS cases, and virtually all subtypes of HIV-1 co-circulate there, suggesting that the region may have been a focus of the expansion of the epidemic. Thus, a detailed study of the evolution of epidemic in the DRC might shed light on the early stages of the global HIV epidemic.

We have undertaken a phylogenetic analysis of an extremely diverse set of HIV envelope sequences from the DRC sampled in 1997. These sequences cover all HIV subtypes, and thus represent a unique sample to study the epidemic. (In May 1997, Mobutu's regime ended, and troops from all over Sub-Saharian Africa have since occupied the DRC. Currently there are soldiers representing 12 African nations based in the DRC, and the mix of HIV-1 sequences currently circulating in the country may be more representative of recent political events than of the evolution of HIV in this region. Thus, it will not be possible to get a better dataset to address these questions in future.)

We applied the methods described in Korber et al., (Science. 2000, 288:1789) for timing of the most recent common ancsestor of epidemic strains of HIV-1 in DRC. Further, we studied the sequences with

the coalescent theory. Coalescent-based methods infer the history of population size and evolution from samples of gene sequences with reconstructed phylogenies [Pybus et al., Genetics 155: 1429].

The coalescent analysis of the DRC data resulted in the model of epidemic growth with increasing exponential growth rate of the infected population through time, suggesting that the early years of the M group epidemic in this region of Africa were characterized by an extended period of slow spread [Yusim et al., Proc. Royal Soc., in press]. This helps to explain how HIV-1 may have remained present but undetected for an extended period.

## 2. Estimating the number of HIV-infected individuals in Cuba

**Ying-Hen Hsieh *, Hector de Arazoza, Shen-Ming Lee, Cathy W.S. Chen**

DEPARTMENT OF APPLIED MTHEMATICS, NATIONAL CHUNG-HSING UNIVERSITY; DEPARTAMENTO ECUACIONES DIFERENCIALES, UNIVERSIDAD DE LA HABANA; DEPARTMENT OF STATISTICS, FENG CHIA UNIVERSITY
HSIEH@FISH.AMATH.NCHU.EDU.TW

Ever since the emergence of the global HIV pandemic, contact tracing has been debated as a control measure for HIV/AIDS. In Cuba, one of the measures of the National Programme for HIV/AIDS is the "Partner Notification Programme" which traces the sexual contacts of known HIV-seropositives. The program, which began in 1986, is carried out by the Epidemiology Departments at all levels of the Cuban health system through partner notification and interviews of the sexual contacts, who were tested for HIV every 3 months for a period of one year after the last sexual contact with the HIV-positive person, and are observed as long they remain in contact. Recent growth in tourism in Cuba has led to a re-emergence of prostitutes in the recent years. Perhaps not coincidentally, recent data have shown an increase in the number of HIV-positive contacts detected starting in 1996. We use the "generalized removal model" to estimate the number of HIV-infected Cubans by sexual contacts using the yearly HIV seroprevalence data obtained from the contact tracing program during 1991-1999. Empirical Bayes methodology is employed in the estimation. The results shows steady increase of the HIV-infected population throughout the decade. The observed large increase in the number of HIV detections in recent years is mainly due to increased detection of previous unknown HIV infecteds who have homosexual/bisexual contacts.

## 3. Immunological memory and the control of HIV infection

**Dominik Wodarz *, Martin Nowak, Jeffrey Lifson, Allan Thomsen**

INSTITUTE FOR ADVANCED STUDY, EINSTEIN DRIVE, PRINCETON, NEW JERSEY, 08540, USA
WODARZ@IAS.EDU

ABSTRACT: We present mathematical models to analyze the role of a memory cytotoxic T lymphocyte (CTL) response in viral infections. Contrary to the traditional view, the model suggests that antigen-independent persistence of an elevated number of precursor CTL (CTLp) is unlikely to protect the host from clinical symptoms upon re-infection. Instead, we find that antigen-independent persistence of memory CTLp is required to clear the virus during primary infection. Requirement of antigen for the long-term maintenance of CTLp results in failure to clear the infection and persistent replication. Experimental evidence indicates that CD4 T cell help is needed to generate memory CTLp that are capable of persisting without antigenic stimulation. CD4 T cells are an important target for HIV replication, and hence, virus specific helper cell responses can be impaired. Mathematical models taking these assumptions into account suggest that fast viral replication during the initial stages of the primary infection can result in failure to generate memory CTLp that can be maintained in the absence of antigenic stimulation. This has been supported by experimental data showing that HIV-specific CTL responses seen in the chronic phase of the infection vanish when virus load is reduced during drug therapy. According to the model, this could be the reason for persistent HIV replication and consequent disease progression. Modelling of drug therapy during the acute phase of the infection indicates that transient treatment can minimize the amount of virus induced helper cell impairment allowing for more effective initial immune sensitization. This results in the development of memory CTL responses that can be maintained in the absence of antigenic stimulation, and hence in long term control of HIV without continuous therapy. The model further suggests that in chronically infected patients, specific treatemnt schedules, either including deliberate drug holidays or antigenic boosts of the immune system, can lead to re-establishment of CTL memory. We present experiemtal data from SIV infected macaques supporting the theoretical predictions. The importance of timing and duration of therapy for succesful treatment is discussed.

## 4. Endocytosis and Tolerance in B Cells

**Yoram Louzoun (1) *, Martin Weigert (1), Gyan Bhanot (2)**

(1) Department of Molecular Biology, Princeton University, Princeton, NJ 08540
(2) Computational Biology Center, IBM Research, Yorktown Hts., NY 10598
YLOUZOUN@PRINCETON.EDU

B lymphocytes have two complementary role in the immune system activation. Their main role is the production of antibodies, and the second role is antigen presentation to T lymphocytes. These two roles are mediated by surface bound B cell receptors. Presentation of antigen is occurring after a receptor-ligand complex is endocytosed and the ligand is processed, and represented on MHC-II molecules. Antibody production is occurring when the B cell is activated by a large enough number of receptor-ligand complexes. We model the surface dynamics of receptors and ligands on the surface of a B lymphocyte and show that the balance between these two processes (endocytosis and activation) can explain the non-immunogenicity of low valence ligands, the low level of activation observed at high and low ligands concentration, the emergence of tolerance upon activation with high doses of ligands, and the tolerance of B cells with bivalent receptor. We incorporate all these features into a unified description of the mechanisms leading to B lymphocytes activation.

## 5. Quantitative Simulation of Germinal Center Dynamics

**Steven H. Kleinstein *, Jaswinder Pal Singh**

Department of Computer Science, Princeton University
STEVENK@CS.PRINCETON.EDU

Germinal centers play an important role in the immune response. They are the sites of affinity maturation where high-affinity B cells, formed through somatic mutation, are preferentially selected to proliferate. Although numerous in vivo and in vitro studies have elucidated the basic molecular mechanisms that underlie the germinal center reaction, it is still not well understood how these mechanisms fit together. Mathematical models can play an important role in solving this puzzle. Unfortunately, existing studies have either used models to explain qualitative, high-level behavior without comparing simulated dynamics with quantitative experimental data, or have presented validated models that do not simulate the underlying mechanism of selection, thus neglecting important constraints. To truly understand the mechanisms and their interactions, as well as the validity of the hypotheses incorporated in models, comprehensive models must be validated by comparison with specific experimental data.

In this study, we examine whether a specific mathematical model of germinal center dynamics, proposed by Oprea and Perelson, can reproduce experimental data from the primary responses to the haptens 2-phenyl-5-oxazolone and (4-hydroxy-3-nitrophenyl)acetyl. We develop formulas for estimating response-specific model parameters, as well as constraints for validating the model. In addition, we outline a general methodology for translating a continuous/deterministic model, expressed as a set of ordinary differential equations, into a discrete/stochastic framework. This methodology is used to create a new implementation of the Oprea and Perelson model that enables comparison with data on individual germinal centers. We conclude that while the model can reproduce the average dynamics of splenic germinal centers, it is at best incomplete and does not reproduce the distribution of individual germinal center behaviors. In addition to suggesting possible extensions to the model which can reconcile the dynamics with some aspects of the experimental data, we make a number of specific predictions that can be tested by in vivo experiments to obtain further insights and validation.

## 6. Optimal Decision Making of Individual Cells: A Case Study of Affinity Maturation

**Erich R. Schmidt *, Steven H. Kleinstein**

Department of Computer Science, Princeton University
ESCHMIDT@CS.PRINCETON.EDU

Individual lymphocytes make response decisions based on signals received from their environment. These cells coordinate with other cells of the immune system to produce an effective response. We present a framework to study this decision making process along with an example of its application.

We use a modified neural network to represent the internal decision making process of a cell. Signals from cell surface receptors are translated into probabilities of actions such as division or apoptosis. The

network is evaluated by determining how well the cell performs in a simulated environment. Optimization techniques are then used to find the 'best' cell program, within a set of biological constraints. As an example, this approach is applied to study the process of affinity maturation in germinal centers.

Specifically, we evaluate the ability of a clonal population of B cells to efficiently find the highest affinity points on a fitness landscape. In this case, the environmental signal is the B cell receptor affinity for antigen, and one decision the B cell can make is whether or not to mutate its receptor. We use an NK model for the landscape, with parameters adjusted to produce a realistic affinity landscape. This framework allows us to address a number of important questions including: (1) Are division and apoptosis independent processes or do they reflect separate outcomes of the same underlying decision? (2) What is the best mutation schedule? Specifically, should the mutation rate be proportional, or inversely proportional, to affinity?

## 7. Inducible Defense against Pathogens and Parasites: Optimal Choice among Multiple Options

**Emi Shudo *, Yoh Iwasa**

DEPARTMENT OF BIOLOGY, FUCULTY OS SCIENCES,KYUSHU UNIVERSITY
SHUDO@BIO-MATH10.BIOLOGY.KYUSHU-U.AC.JP

Defense against pathogen, parasites and herbivores is often enhanced after their invasion to the host's body. Sometimes different options are adopted depending on the identity and the quantity of the pathogen, exemplified by the switch between Th1 and Th2 systems in mammalian immunity. In this paper, we study the optimal defense of the host when two alternative responses are available, which differ in the effectiveness of suppressing the growth of pathogen (parasite, or herbivore), the damage to the host caused by the defense response, and the magnitude of time delay before the defense response becomes fully effective. The optimal defense is the one that minimizes the sum of the damages caused by the pathogen and the cost due to defense activities. The damage by pathogens increases in proportion to the time-integral of the pathogen abundance, and the cost is proportional to the defense activity. We can prove that a single globally optimal combination of defense options always exists and there is no other local optima. Depending on the parameters, the optimal is to adopt the early response only, the late response only, or both responses. The defense response with a shorter time delay is more heavily used when the pathogen grows fast, the initial pathogen abundance is large, and the difference in time delay is long. We also study the host's optimal choice between constitutive and inducible defenses. In the constitutive defense, the response to pathogen attack works without delay, but it causes the cost even when the pathogen attack does not occur. We discuss mammalian immunity and the plant chemical defense from the model's viewpoint.

Key words: inducible defense, adaptive immunity, Th1 and Th2 systems, plant chemical defense, time delay, constitutive defense.

## 8. Slug Bio-Control Dynamics

**David Schley *, Martin A. Bees**

DEPARTMENT OF MATHEMATICS AND STATISTICS, UNIVERSITY OF SURREY, GUILDFORD, GU2 7XH, UK.
D.SCHLEY@SURREY.AC.UK

Terrestrial slug damage is a huge problem in agriculture, and UK farmers alone spend up to £11 million ($17 million) per annum on chemical controls. Unfortunately, these can have a number of negative side effects, and it is be desirable to develop environmentally friendly alternatives.

The parasitic nematode *Phasmarhabditis hermaphrodita* has been shown to be effective against slugs and snails, with the advantage that it does not effect other organisms or the environment. At present, however, this method is too expensive to be considered commercially viable for use in conventional farming, even though nematode applications appear to protecting crops for much longer than standard chemical treatments.

The development of suitable control strategies is further hindered by the apparent chaotic and/or unpredictable nature of slug numbers, especially that of the most significant species, *Deroceras reticulatum*, which accounts for approximately 70% of the UK slug population.

We have considered a variety of mathematical models to help understand the population dynamics of this species, and its interactions with nematodes (and natural predators). Differential equation modelling requires the inclusion of a significant temporal delay in the life-cycle of both slugs and nematodes. Complex interactions between the species must also be considered, since these are important factors in the resultant spatial dynamics. Analytical and numerical results from these models will be presented, and compared to field data. Results so far give an insight into the dynamics of slug populations, and suggest the development of control strategies which maximise the efficacy of bio-controls and natural predators.

# 9 Spatially Explicit Models in Ecology

## 1. A new model for spatially structured populations

**Michael Doebeli *, Tim Killingback**

DEPARTMENTS OF ZOOLOGY AND MATHEMATICS UNIVERSITY OF BRITISH COLUMBIA EMAIL: DOEBELI@ZOOLOGY.UBC.CA

Stepping-stone models for the ecological dynamics of metapopulations are often used to address general questions about the effects of spatial structure on the nature and complexity of population fluctuations. Such models describe an ensemble of local populations in which reproduction is followed by dispersal to neighboring habitat patches. Reproduction in a given local population depends on the density of that local population, and a constant fraction of the local population disperses to neighboring patches. In such models, interesting dynamic phenomena, e.g. the persistence of locally unstable predator-prey interactions, are only observed if the local dynamics in an isolated patch exhibit non-equilibrium behavior. Therefore, the scope of these models is limited. Here we extend these models by making the biologically plausible assumption that reproductive success in a given local habitat not only depends on the density of the local population living in that habitat, but also on the densities of neighboring local populations. This would occur if competition for resources occurs between neighboring populations, e.g. due to foraging in neighboring habitats. With this assumption of non-local competition the dynamics of the model change completely. The main difference is that even if the dynamics of the local populations have a stable equilibrium in isolation, the uniform equilibrium, in which all local populations are at their carrying capacity, becomes unstable if the strength of non-local competition reaches a certain level, which can be calculated analytically. In this case the metapopulation reaches a new stable state, which is, however, not spatially uniform anymore and instead results in an irregular spatial pattern of local population abundance. For large metapopulations, a huge number of different, spatially non-uniform equilibrium states coexist as attractors of the metapopulation dynamics, so that the final state of the system depends critically on the initial conditions. The existence of a large number of attractors has important consequences when environmental noise is introduced into the model. Then the metapopulation performs a random walk in the space of all attractors. This leads to large and complicated population fluctuation whose power spectrum obeys a red-shifted power law. Our theory reiterates the potential importance of spatial structure for ecological processes and proposes new mechanisms for the emergence of non-uniform spatial patterns of abundance and for the persistence of complicated temporal population fluctuations.

## 2. How predation can slow, stop or reverse a prey invasion

**Mark A. Lewis*, Markus Owen****

*UNIVERSITY OF ALBERTA AND **UNIVERSITY OF LOUGHBOROUGH MLEWIS@MATH.UTAH.EDU

Observations on Mount St. Helens indicate that the spread of recolonizing lupin plants has been slowed due to the presence of insect herbivores, and it is possible that the spread of lupins could be reversed in the future by intense insect herbivory. In this talk I will investigate mechanisms by which herbivory can contain the spatial spread of recolonizing plants. The approach is to analyse a series of predator-prey reaction-diffusion models and spatially coupled ordinary differential equation models. The analysis yields qualitative conditions on the functional response of the plant to herbivory under which predation pressure can slow, stall or reverse a spatial invasion of prey. Theoretical predictions will be compared to the field data collected from Mount St. Helens.

## 3. The effects of dispersal on marine reserve design

**Dale R. Lockwood*, Louis W. Botsford and Alan Hastings**

UNIVERSITY OF CALIFORNIA, DAVIS DRLOCKWOOD@UCDAVIS.EDU

Marine reserves are increasingly viewed as an important tool in marine ecosystem management. Reserves can potentially be used to recover overharvested stocks, maintain biodiversity, and increase scientific understanding of marine ecosystems. The theoretical underpinnings of the design of large scale reserve networks are actively being developed.

We used integrodifference equations to provide a suitable model framework to represent the population dynamics of benthic marine invertebrates and sedentary demersal fish. These populations consist of age structured populations distributed more or less continuously along a coastline. The different points along the coastline are connected by dispersal of a poorly understood larval stage. Because of the uncertainty in the larval stage, a significant outstanding question is how much we have to know about the dispersal pattern to design reserves. Using a model with an infinite coastline, we showed that the effects of various dispersal patterns on persistence is more directly influenced by the mean dispersal distance rather than the kurtosis or number of long distance dispersers.

For a population distributed over a bounded domain with asymmetric kernels representing real dispersal patterns we developed a method for computing the equilibrium population as well as the total yield as functions of the size and shape of the reserve Network.

For additional biological realism, we added age structure to the basic framework. The addition of age structure indicates that the estimates of an equilibrium solution are valid for compensatory density dependence, but that overcompensatory density dependence introduces periodic and chaotic dynamics, especially in the case of post-dispersal density dependence. In such cases the dynamics depend not only on the fraction of the coastline but on the shape of the reserve pattern.

Because generalities with regard to total area or reserve layout are not likely to be universally applicable, but estimations on the lower bound of coastline required in reserve for persistence will be useful for starting reserve design.

## 4. How population discreteness and demographic stochasticity can slow biological invasions

**Robin E. Snyder** *

DEPARTMENT OF PHYSICS, UNIVERSITY OF CALIFORNIA, SANTA BARBARA, CA 93106
ROBIN@PHYSICS.UCSB.EDU

In describing the spread of an invading species, ecologists have traditionally written equations for the mean population density as a function of position and time, implicitly assuming that population discreteness is not important, that the fluctuations that arise from population discreteness (demographic stochasticity) have no net effect, and that the mean is representative of typical behavior. For a broad array of conditions, all three of these assumptions are false. Fluctuations do have a net effect, and because population discreteness *is* important, the mean is unrepresentative. In this presentation, I analyze a common class of one-dimensional, single-species invasion models and find three effects of population discreteness and demographic stochasticity on invasion speed: population discreteness, local extinctions, and rare but important long-distance dispersers. The result is that the equation for mean population density overestimates the invasion speed.

## 5. Dispersal and Intraspecific Competition in Discrete-time Patchy Environments

**Abdul-Aziz Yakubu** *, **Carlos Castillo-Chavez**

CORNELL UNIVERSITY AND HOWARD UNIVERSITY
AY32@CORNELL.EDU

A simple framework for the study of the effects of dispersal on the dynamics of a population experiencing density dependent discrete-time intra-specific competition in several patches is provided. The population dynamics in each patch are modeled by nonlinear functions of the densities and, therefore, capable of generating simple and complex (chaotic) dynamics. Conditions under which the full multi-patch system with dispersal behaves like a single patch system are discussed. The role of dispersal rates in generating multiple attractors where local populations are on simple cyclic non-chaotic attractors are studied. The results are applied to the bobwhite quail population model of Milton and Belair.

## 6. Lotka-Volterra Competition Model in a Lattice Space

**Hideo Ezoe** *, **Kanako Nakakita**

DEPARTMENT OF ENVIRONMENTAL SCIENCES, FACULTY OF SCIENCE, OSAKA WOMEN'S UNIVERSITY
HEZOE@CENTER.OSAKA-WU.AC.JP

We study an individual-based lattice model to investigate the effect of spatial structure on the competition of two species. Previously many works on lattice models have been studied to examine how population dynamics are affected by spatial structure of habitat, the most of which have been done mainly with computer simulations. Mathematical analysis can provide better perspective than computer simulations, although simpler models have been analyzed so far. Here we study a model of the competition between two species in a two-dimensional lattice space, which includes both of intra- and interspecific competition factors between neighboring individuals. To neglect the spatial structure of the model provides an analogue of Lotka-Volterra competition model (mean-field approximation). Applying *pair approximation*, which takes account of the correlation between only nearest neighborhood sites, we derive the condition for rare species to invade into the stable population of the other species. The result shows that with the spatial structure the invasion condition is often severer than without the spatial structure. Spatial structure has been commonly supposed to promote the coexistence of species. We show, however, that it may also play the opposite role.

## 7. Pattern Formation and Noise in Models of Plankton–Fish Dynamics in a Patchy Environment

**Horst Malchow**

INSTITUTE OF ENVIRONMENTAL SYSTEMS RESEARCH
DEPARTMENT OF MATHEMATICS AND COMPUTER SCIENCE
UNIVERSITY OF OSNABRÜCK, 49069 OSNABRÜCK, GERMANY
MALCHOW@USF.UNI-OSNABRUECK.DE

The impacts of variable planktivorous fish and noisy zooplankton mortality on phytoplankton-zooplankton interactions are described, using a minimal model of the nutrients-plankton-fish food chain (Steele & Henderson 1981; Scheffer 1991; Malchow 1993, 1996).
Locally, the influence of external forcing of planktonic predator-prey oscillations by fish school invasions and feeding is investigated. The space is divided into three patches of different phytoplankton growth, a first patch with high productivity, connected to the second with a productivity, linearly decreasing down to the level of the third patch. The effects of mobile fish schools on the plankton dynamics are described.
The plankton growth, interactions and transport are modelled with reaction-diffusion equations whereas the fish school motion is discrete and rule-based, depending on the local zooplankton density as well as on spatial position, previous direction and residence time (Malchow *et al.* 2000).
The emergence of stationary and travelling plankton population waves is presented. It is shown that not only cruising and feeding planktivorous fish schools but also noise can induce the planktonic patchiness.

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## 8. Models of spawning and feeding migrations of pelagic fish species in the North-Atlantic

**K Magnusson*, S Hubbard, P Babak, S Sigurdsson**
**sh246@raunvis.hi.is**

SCIENCE INSTITUTE, UNIVERSITY OF ICELAND, DUNHAGA 3,
107 REYKJAVIK, ICELAND

Some pelagic fish species, such as capelin (Mallotus villosus) and herring (Clubea harangus), undertake extensive feeding and spawning migrations. These movements are to a large extent governed by genetic factors, but the timing and route of the migrations are influenced by a variety of other factors: environmental conditions such as boundaries between warm and cold water masses, certain isotherms which the fish do not cross, oceanic currents, density of food, and internal variables such as the physiological state and the state of maturity of the each fish. In addition, the population density may also influence the extent of feeding migrations in particular.

Taking some of these factors into account, generic models of feeding and spawning migrations are developed. On a local scale, the movements of individual fish or small schools are governed by alignment forces whereby each fish (or small school) has a tendency to adapt its velocity to that of its neighbours. In addition, the speed and direction of the motion are influenced by a random perturbation. The probability density function for this random variable is parameterised such that a tendency of the fish to move in the direction towards a specified region can be varied. This directional tendency is strong in the period prior to the spawning season, but weak or non-existent on the feeding grounds. On feeding migrations, the gradient of food density defines an additional random force influencing the motion.

Boundaries are defined by specified isotherms as well as by specified depth contours. No-flux conditions hold at such boundaries, so dynamics are modelled such that schools do not cross but tend to move along these boundaries when they are encountered. Other "boundaries" i.e. borders between warm and cold water masses are only crossed when an internal state exceeds a critical value. This internal state, which can also influence other aspects of the motion, is modelled separately.

A discrete model is thus defined where the type of motion is different depending on the parameter values in the pdf for the random perturbations. The fish will move randomly in small coherent schools (feeding mode) but with zero net transport, for some parameter values. By varying these parameters, a phase transition occurs where the whole group will move in an ordered fashion towards a specified region (migration mode). The movements between spawning grounds and feeding grounds can thus be simulated as well as the behaviour on the feeding grounds. Analysis of the model is presented together with simulation results which can be compared to field data on the spatial distribution of capelin. Various hypotheses about the influence of environmental factors on the timing and the migration path can be tested.

# Posters

## 1. Formation of a Graded Cell Pattern along the Body-axis by Cell Behaviors thr ough the Signal Transduction

HONDA Hisao*[a], MOCHIZUKI Atsushi[b]

[a]HYOGO UNIVERSITY, KAKOGAWA, HYOGO 675-0101 JAPAN AND [b]DEPT. OF BIOLOGY, KYUSHU UNIVERSITY!"FUKUOKA 812-8581 JAPAN
HIHONDA@HUMANS-KC.HYOGO-DAI.AC.JP

The cell-cell interaction between nearest neighbors has been thought to be responsible for the pattern formation in development. Membrane-bound ligands, ephrins and their receptors, Eph proteins having tyrosine-kinase activity mediate contact-dependent cell interactions.These two species of molecules are known to direct not only repulsive effects among cells, but also attractive effects under the bilateral threshold control (H. Honda, J. Theor. Biol. 192, 235-246, 1998): While cells expressing the receptors are repelled by surfaces expressing lower or higher ephrin level than a critical level, the cells are not repelled by the special surface expressing the critical ephrin level. The cells adhere to the non-repulsive surface. On the other hand, the two species of molecules are known to show complementary expression in distinct cellular patterns, e.g., graded cell patterns along the proximodistal axis of the limb. Here we proposed a novel mechanism involving membrane-bound ligands and their receptors for cell pattern formations in multicellular animals. Each cells is assumed to express the ligands and receptors simultaneously, and these molecules work under the bilateral threshold control. Cells expressing similar level of ephrins (or receptors) are likely to gather with each other. We considered a cell mixture including various levels of receptors, but whose level of ligands are reciprocal to that of receptors in each cell. The cells in the mixture migrate and spontaneously form the graded arrangement in a computer simulation. The result indicates that the ephrins and receptors play a role as a mediator providing the positional information in morphogenesis. The differential cell adhesion hypothesis in morphogenesis can be also discussed with respect to cell adhesiveness and cell repulsiveness.

## 2. Simple Neuronal Model with Intrinsic Saturation of the Firing Frequency

**Charles E. SMITH *, Petr LANSKY, Roger RODRIGUEZ**

(CES) NORTH CAROLINA STATE UNIV.,(PL) ACADEMY OF SCIENCES OF CZECH REPUBLIC,(RR) CENTRE DE PHYSIQUE THEORIQUE, CNRS

Frequency coding is one of the basic forms of information transfer within the nervous system. It assumes that the frequency of uniformly sized action potentials varies with stimulation intensity (Adrian, 1928). As the stimulus intensity is increased, an increase in the neuronal activity follows. A survey of the role of the mean firing rate in a number of neuronal models was presented by Gerstner and van Hemmen (1992).

No saturation frequency exists as an intrinsic part of common simple neuronal models, which means that with increasing stimulation the firing frequency increases without any limit. This feature is clearly in contrast to observed neuronal behaviour. A common way to solve this problem is to add a dead time (absolute refractory period) to each interspike interval (ISI) calculated from the model (e.g. Tuckwell, 1988; Bugmann et al., 1997; Tal Schwart, 1997; Fusi Mattia, 1999). Some other methods are: by considering a negative feedback (Barbi et al., 1975), by adaptation (Ermentrout, 1998), or both (Pakdaman et al., 1999). Relative refractory periods, either due to a time-varying threshold or to a timevarying conductance, can also produce a saturation in firing rate (Jack et al., 1983).

Here we present a simple two-point, reversal potential model which inherently has a saturation frequency. The transfer function of this model is compared with the simple leaky integrate-and-fire model (LIF), the LIF model with reversal potentials, and a two pint LIF model. Numerical simulations illustrate the differences among the transfer functions of these three models and the two-point LIF model with reversal potentials for typical values of the parameters.

## 3. PROTOTYPICAL DATABASE FOR CURATION OF GENE TARGETS IN MAMMALIAN COLLECTING DUCT

RAYMOND MEJIA *, JOHN LEGATO, MARK A. KNEPPER, ROBERT A. STAR

MATHEMATICAL RESEARCH BRANCH, NIDDK
LABORATORY OF KIDNEY AND ELECTROLYTE METABOLISM, NHLBI
RENAL DIAGNOSTICS AND THERAPEUTICS, NIDDK
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD 20892-2690 U.S.A.
*http://mrb.niddk.nih.gov/cddb*

The mammalian kidney collecting duct plays an important role in the production of urine. Functional genomic and proteomic studies of the kidney offer new opportunities in the understanding of renal physiology and pathophysiology. Study of the collecting duct includes assessment of gene expression and protein regulation and abundance. For example, DNA and protein microarrays can be used to quantitate gene expression and protein regulation and abundance under varying physiologic conditions.

An Internet-accessible database has been designed for major collecting duct proteins involved in transport and regulation of cellular processes. The database serves to facilitate the design of microarray targets for the study of kidney collecting duct tissues, and serves as a prototype for databases designed for the study of other tissues. It includes links to curated base pair and amino-acid sequence data, relevant literature and related databases.

The database is designed to allow one to identify and obtain sequence data necessary to design a microarray. This is done through links to and search of several databases, including MEDLINE, LocusLink, GeneCards, Online Mendelian Inheritance in Man, Mammalian Gene Collection, and the I.M.A.G.E. Consortium.

Extension of the database is dynamic, and is done through a maintenance interface. This permits creation of new categories, updating of existing entries, and addition of new ones.

## 4. The Effect of Radiotherapy on the Colony Growth Model of the Tumor.

**Rei Motozono *, Akira Sasaki**

KYUSHU-UNIVERSITY

We have analyzed the radiotherapy strategy against tumor colonies, and examine how the tumor growth rate, the metastasis rate, and their colony size dependence influence the efficiency of radiotherapy. Tumor colony grows and generates a new colony by metastasis. A tumor colony is detected when it reaches 'detection size' B, and then it is treated with radiotherapy. If the detection size is larger than a 'critical size', the tumor proliferate indefinitly. The dynamics for the colony size distribution $\rho(x,t)$ are expressed as,

$$\frac{\partial \rho}{\partial t} + \frac{\partial}{\partial x} = \delta(x - A)g(x)\rho(x,t)q$$

$$g(1)\rho(1,t) = \int_1^B \beta(x)\rho(x,t)dx,$$

where $g(x)$ is growth rate of colony size $x$, The size of new colony is 1. When a colony is received treatment, it shrinks to size $A = pB(p < 1)$ with probability $q$, and destroyed perfectly with probability $1 - q$. When the growth rate of tumor is $g(x) = ax^{1-\gamma}$, the metastasis rate $\beta(x) = mx^{\alpha}$, the critical size is,

$$B^* = \left[\left\{1 + \frac{a}{m}(\alpha + \gamma)\right\}\frac{1-q}{1 - q \cdot p^{\alpha+\gamma}}\right]^{\frac{1}{\alpha+\gamma}}$$

The critical size $B*$ increase with $a/m$ and $p$, and decrease with $(\alpha + \gamma)$ and $q$. The results are: The tumor with *high* growth speed $(a)$, and low colonizing rate $(m)$ is easy to suppress by radiotherapy. Slowly growing and highly metastatic tumors are difficult to suppress. Reducing colony size radiotherapy (decreasing $p$) is not effective in suppressing tumor, but increasing the probability of the whole colony destruction (decreasing $q$) is very effective.

## 5. The effects of small dispersal rates on extinction times in a structured metapopulation model: does salmon straying affect population persistence?

**Mark F. Hill *, Alan Hastings and Louis W. Botsford**

INSTITUTE OF THEORETICAL DYNAMICS
UNIVERSITY OF CALIFORNIA
ONE SHIELDS AVENUE
DAVIS, CA 95616

Habitat destruction and declines in survival rates are critical factors leading to lower population persistence in a number of taxa, including Pacific salmon. We develop both a general analytical model and a simple simulation model describing structured metapopulations to study how weak connections between subpopulations affect the ability of a species to tolerate habitat loss and/or changes in survival. Our goal is both to develop general principles and to understand salmon population dynamics. The analytical model describes the dynamics of two density-dependent subpopulations, connected by dispersal, whose growth rates fluctuate in response to environmental and demographic stochasticity. We characterize how the mean time to extinction depends on the carrying capacity (reflecting the role of habitat destruction) and the growth rate (survival), for different levels of connectance, and show that small dispersal rates can significantly reduce the impact of habitat destruction and/or declines in survival on persistence. This effect, however, depends on the level of environmental variability and the relative difference in habitat quality between patches. To examine the importance of this general effect for Pacific salmon species, we develop a related discrete time model of six salmon subpopulations and parameterize it using data on Chinook abundance in the Snake River, Idaho. We find that increasing the percent of spawners reproducing in non-natal streams (i.e. straying) dramatically increased predicted extinction times, but that the effect of straying on mean extinction times is reduced if there is a strong Allee effect. In general, there has been little direct application of metapopulation theory to the management of salmon populations, in part because dispersal rates are so low. Our results suggest that such theory can have important conservation implications for salmonid populations and other homing fish species.

## 6. Rotating kinetoplasts and genetic exchange: beating random segregation in trypanosomatids?

**Nicholas J. Savill *,**

CENTRE FOR THEORETICAL MODELLING IN MEDICINE DEPARTMENT OF MATHEMATICS
HERIOT–WATT UNIVERSITY EDINBURGH EH14 4AS UK

The single mitochondrion of trypanosomatids contains roughly 5,000–12,000 circular DNA molecules called minicircles. They are linked together like chain–mail armour into a disk–shaped monolayer called the kinetoplast. During cell division the minicircles are replicated synchronously with nuclear DNA and are segregated into two daughter cells. How trypanosomatids segregate the huge number of minicircles is still a matter of debate but several studies make it clear that it is not quite perfect; replicated sister minicircles are unevenly segregated between daughter cells. This uneven segregation has detrimental effects by reducing cell viability. Two mechanisms have been proposed to ameliorate these effects, namely kinetoplast–rotation and genetic exchange. I will discuss the implications of these mechanisms for trypanosomatids in the light of previous quantitative modelling and their evolution based on previous phylogenetic analyses.

## 7. Modeling Animal Movements: Current Approaches and Challenges

**Louis J. Gross *, E. Jane Comiskey**

THE INSTITUTE FOR ENVIRONMENTAL MODELING DEPARTMENTS OF ECOLOGY AND EVOLUTIONARY BIOLOGY AND MATHEMATICS UNIVERSITY OF TENNESSEE

The combination of individual-based modeling methods, advances in telemetry information for locations of individuals, and the demands for realistic models in application to public policy issues involving endangered species presents new challenges to enable us to appropriately project animal movements. Additionally, the availability of parallel computing architectures enables us to conceptualize movement models in new ways that serial implementations would preclude. We will summarize the advantages and disadvantages of classic movement models based upon diffusion assumptions, and discuss how these models may be extended using agent-based approaches to deal with issues such as underlying spatial heterogeneity, barriers and corridors, and territoriality. This includes methods to link dynamic movement models to geographic information systems, and developing appropriate statistics to compare modeled movement to telemetry data. Applications to white-tailed deer and the Florida panther will be discussed, relative to assessing the impacts of alternative hydrologic plans for the restoration of the Everglades of South Florida.

## 8. Modelling the Malignant Progression from Low-Grade to High-Grade Astrocytoma via a Sequence of Cell Mutations

**Kevin Painter *, Eliezer Shochat, Nick Savill, Jonathan Sherratt**

CENTRE FOR THEORETICAL MODELLING IN MEDICINE, DEPARTMENT OF MATHEMATICS, HERIOT-WATT UNIVERSITY, EDINBURGH, EH14 4AS, UK.
UNIVERSITY OF EDINBURGH DEPARTMENT OF ONCOLOGY, WESTERN GENERAL HOSPITAL, EDINBURGH, EH4 2XU, UK

Tumours arising from the brain glia cells constitute the most common form of primary brain tumours in adults. They frequently affect the cerebral hemispheres, causing symptoms of headache, nausea and epileptic feats by compressing and infiltrating the adjacent brain. Despite considerable effort into elucidation of the molecular biology of tumourigenesis and the development of novel therapeutic approaches, the majority of these tumours remain incurable. Astrocytomas are classified by the degree of malignant appearance in the pathological examination into 4 Grades (I to IV (glioblastoma multiforme, GBM)). For example, GBM's are characterised by a high degree of both spatial and cellular heterogeneity, extensive vascularisation (angiogenesis) and high cell proliferation and invasion. Unsurprisingly, the grade of the tumour corresponds with an increasingly poor clinical prognosis; for a GBM, median survival time is just 8 months.

To explore the development of these tumours, we have formulated a detailed model to chart the progress of a tumour from a small homogeneous population to a tumour exhibiting the hallmarks of GBM above, via a stochastic sequence of mutations affecting different aspects of normal cell function. Our model demonstrates how tumour heterogeneity occurs, and highlights the problems associated with clinical treatment of high grade tumours. To examine this more closely, we have incorporated simple treatment in the form of surgery (excision) and radiotherapy to explore how macroscopically different tumours respond to treatment. In particular, we examine how differences in the mutational pathway (both in terms of mutation rates and sequence of mutations) can lead to variability in the growth time, appearance and response to treatment of the tumour.

## 9. Estimating cell lineage: Theory and application

**MOCHIZUKI Atsushi*, KOGA Makoto, OHSHIMA Yasumi**

DEPARTMENT OF BIOLOGY, KYUSHU UNIVERSITY

Cell lineage of multi-cellular organisms has been analyzed by introducing a genetic or chemical marker that is inherited from a cell to its daughter cells. To construct complete cell lineages, all the cells at different stages must be identified, and a single cell must be marked in each experiment. One of the authors, Mochizuki have studied a new method of estimating cell lineage based on distributions of intracellular markers observed at a single stage, which are introduced randomly at earlier stages. By the method, we can determine cell lineage without following development, by using automatically introduced markers, like transposons. Assumptions are: (1) cell lineage is invariant between embryos; (2) a small number of cells are marked in each experiment; and (3) the total number of replicate experiments is sufficiently large. Then we identify the most likely cell lineage pattern (or tree topology) as the one that requires the least marker insertions to be compatible with the observed distributions of cell markers. This method is essentially the same as the principle of persimony widely used for ancestral phylogeny reconstruction in evolutionary biology. Mochizuki developed an algorithm, clustering method, which can determine the correct lineage very quickly even if the number of cells is large. The efficiency of the clustering method in estimating the correct cell lineage is confirmed and shown to be very high by computer examination.

We applied the method to a part of nematode, C. elegans by using extrachromosomal arrays in cells. The array is slightly unstable and may be lost occasionally from each cell during cell division. By including GFP gene into the array, we obtain distributions of marked cells at the adult stage just by observing the lack of fluorescence. We could determine lineage of intestine cells easily. A lineage differing from the believed one was strongly suggested by the method.

## 10. Extinction Risk to bird populations from DDT Exposure

**Mayuko Nakamaru *, Yoh Iwasa Junko Nakanishi**

DEPARTMENT OF SYSTEMS ENGINEERING, SHIZUOKA UNIVERSITY, HAMAMATSU 432-8561, JAPAN

Currently there are few available methods that can quantitatively evaluate the impact of chemical exposure on population extinction. In this conference we'd like to propose the new method to evaluate the extinction risk and, as the examples we adopt into the herring gull population in Long Island and the sparrowhawk population in eastern England, which DDT had done serious damage to.

The method is based on a formula of the mean extinction time derived by the canonical model with a logistic equation as well as environmental stochasticity and demographic stochasticity. The intrinsic rate of natural population growth is obtained from data based on the recovering population after the prohibition of organopesticides or the rapidly increasing population from the low density. The effect of exposure to DDT in reducing the population growth rate was evaluated based on an age-structured population model, by assuming that age-specific fertilities (including chick survivorship) are density-dependent and sensitive to exposure to DDT, while age-specific survivorship is not. The results are expressed in terms of risk equivalent – the decrease in the carrying capacity that causes the same enhancement of extinction risk as chemical exposure at a given level. We show that this concept can be applied into the mitigation banking.

## 11. Rate of Clinically Detectable Metastasis from Breast Cancer

**Sylvia K. Plevritis** *

DEPARTMENT OF RADIOLOGY, STANFORD UNIVERSITY, STANFORD, CA

The rate of clinically detectable metastasis as malignant breast tumors grow is not known. We propose a stochastic model of metastasis to the lymphnodes and distant organs. We assume that tumors are spheroidal and that they grow exponentially. We consider two random events: (1) when the primary breast tumor clinically surfaces and (2) when nodal or distant metastasis is clinically detectable. We assume that the hazard rate for clinical surfacing of the primary tumor is proportional to its volume. We assume that the hazard rate for clinically detectable metastasis is a function of the first three moments of the volume of the primary tumor, that is, its volume, rate of change in its volume, and acceleration of change in its volume. The acceleration term has not been tested in this context to our best knowledge. Yet the acceleration term allows the possibility that faster growing tumors are more likely to metastasize when small than slower growing tumors. A joint density function is generated for primary tumor volume at clinical surfacing and primary tumor volume when nodal or distant metastasis is clinically detectable, based on a non-parametric distribution of tumor doubling times. The model is tested against population-based data in the NCI SEER tumor registry before screening mammography was recommended.

## 12. Formation of Retinal Mosaic Patterns in Zebrafish and Medaka

**Shusaku Tohya*†, Atsushi Mochizuki† & Yoh Iwasa†**

†DEPARTMENT OF BIOLOGY, KYUSHU UNIVERSITY, FUKUOKA 812-8581, JAPAN

In the fish retina, four types of cones photoreceptor cells (two single cones sensitive to Blue light, and to UV light, respectively, and double cones each consisting of a pair of red- and green-light sensitive parts) are two-dimensionally arranged in a very regular manner. This "cone mosaics" pattern differs between species. In the zebrafish mosaic, rows of single cones and those of double cones appear alternatively; whilst the medaka mosaic is isotropic, in which each blue-sensitive cone is surrounded by four double cones. Experimental studies suggest that the pattern formation must occur after the proliferation process presumably through differentiation and/or movement of cells.

Here we analyzed a spatial-Markov transition model for cell sorting process in which random rearrangement of cells each having fixed developmental fate exchange the position between nearest neighbors. The exchange rate of cells is affected by their cell-cell adhesion with the neighbors, and the adhesion between two cells depends on their types. We have performed exhaustive search for the parameter sets that can generate the two regular mosaic patterns. We demonstrate that the same model is able to generate both cone mosaics if the parameters are chosen appropriately. To understand the result of computer search intuitively, we calculated the parameter regions in which each of the two regular mosaic patter has a lower free energy than alternative deformed spatial patterns, in which free energy is calculated by the total adhesion and the number of configurations considering the temperature (e.g. strength of random movement). The prediction of this analysis could explain the computer simulations. Finally we discuss the species-difference of cone mosaic and the relation of cells property (distribution of adhesion molecules and the shape of cone cells) and the evolution.

## 13. Feeding Territory Formation of Animals in a Heterogeneous Environment.

**Hiroyuki Yokomizo *, Yoh Iwasa**

DEPARTMENT OF BIOLOGY,FUCULTY OF SCIENCES,KYUSHU UNIVERSITY

We studied the formation of feeding territories of animals in a heterogeneous environment. Assumptions are: The habitat is composed of many sites arranged in a 2-dimensional grid, in which the central part is the richer in resources than marginal areas. Each individual obtains resources from the sites in the foraging area, and the benefit increases with the total gain of the resources but it saturates for a large total gain. When multiple animals utilize the same site commonly, they share the resource acquisition rate equally. The total cost for an individual to pay is the sum of the costs for all the sites within its foraging area, in which the cost for a site increases with the distance from the center of territory and with the number of individuals utilize the same site. Each individual expands or reduces the foraging area at random, and the change occurs faster if the net benefit (benefit minus cost) is larger after the change than before the change. In the final pattern, [1] the territory size was smaller in the central part of the habitat than in the marginal areas. [2] When the total abundance of resources was rich (compared with the number of animals), the net benefit was larger for individuals in the central part of the habitat than those in the marginal areas. [3] When the resource availability was low, the net benefit became independent of the distance from the center of the habitat. [4] We also examined a group of heterogeneous individuals, in which, when two individuals with different strength use the same site, a strong individual either gains more resources or suffers a smaller cost than a weak individual. In the final pattern, strong individuals had territories closer to the center of the habitat than weak individuals.

## 14. A model for rotational movement of Dictyostelium cells in the multicellular stage

**Tamiki Umeda**

KOBE UNIVERSITY OF MERCANTILE MARINE
1-1-5, FUKAE-MINAMI-MACHI, HIGASHINADA, KOBE 658-0022, JAPAN

After the vegetative growing phase, cells of *Dictyostelium discoideum* aggregate chemotactically to form a mound of cells. It has been reported that coherent rotational motion of cells is often seen in the mound. Rotation of cells is also observed in a disc-shape cell aggregate, which are formed when cell motion is experimentally restricted to a plane [1]. The purpose of this study is to develop a mathematical model to describe the rotational cell movement.

In the previous study, we have proposed a mathematical model to explain the morphogenetic movement of cell aggregates [2]. The model was based on the assumption that the motive force of each volume element of cell mass is in dynamical equilibrium with intrinsic resistance, which acts against cell movement, and the internal pressure. In the model, the motive force was considered to depend only on the chemotactic signals. However, starved cells have a property to follow preceding cells with which they are in contact. This property is independent of cAMP chemotaxis and called "contact following". Here I incorporate this effect to the model by assuming that the direction of motive force is determined both by the chemotactic stimulus and the averaged velocities of neighboring cells.

Analytical study and numerical calculation of the model in two-dimensional space show that if the contact following is absent, cells aggregate to form a disc-shape structure and come to a standstill. However, if the effect of contact following becomes stronger than a certain critical value, cells rotate around the center of the disc. Further increase of the effect destabilizes the rotational symmetry of cell movements and gives a distorted shape of the cell mass. These results show the possibility that rotational movement of cells in the multicellular stage is caused by direct interactions among moving cells.

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## 15. Separation of Two Cell Clusters Can Be Performed by Differential Cell Adhesion

**Takano, Ryouji *, Yoh Iwasa, Atsushi Mochizuki ***

DEPARTMENT OF BIOLOGY, FACULTY OF SCIENCES, KYUSHU UNIVERSITY, FUKUOKA 812-8581

Tissue separation often takes place in developmental processes – a single continuous tissue differentiates into two tissues and then they are divided into two separate cell clusters as cells of surrounding tissue become inserted between them. Experimental studies have demonstrated an important role played by adhesive molecules in the separation process. For example, in an amphibian, neural tube is formed by

separation from neural plate and the two tissues show expression of different cadherin molecules just before the separation step.

Here, we ask whether tissue separation can be performed by differential cell adhesion only. We consider a two-dimensional lattice filled with three types of cells (black, white, and gray). In the initial state, a cluster of back cells and another of white cells are in contact, and both are surrounded by gray cells. We regarded that separation was successful if in the final state black cells and white cells kept their clusters but two clusters lost direct contact with each other as gray cells are inserted between them. Adhesion between neighboring cells depends on their cell types, and the six adhesion levels for different pairs of cell types need to be specified. Nearest neighbor cells exchange their location at random, but the movement occurs faster if it increases the total adhesion. We identified the conditions for six cell adhesion levels to realize successful separation of cellular clusters.

We also consider the following two necessary conditions for successful invasions: [1] adhesion between the same type should be larger than that between different types; and [2] the sum of adhesions of gray-black and of gray-white should be larger than the sum of adhesions of gray-gray and of black-white. All the cases realized successful separation in the computer simulations satisfied both of these conditions. However, the separation may take an extremely long time if the difference of the adhesion between the same type and of the different types is large.

## 16. A mathematical model of spatial propagation of infectious disease in a predator-prey system.

**Tsuyoshi KAJIWARA *, Tomoki OKITA**

DEPARTMENT OF ENVIRONMENTAL AND MATHEMATICAL SCIENCE FACULTY OF ENVIRONMENTAL AND SCIENCE TECHNOLOGY OKAYAMA UNIVERSITY

We consider a mathematical model for infectious disease caused by a parasite whose life cycles contained in two hosts, intermediate host and final hosts. Typical example is a case of Echinococcus multilocularis in Hokkaido, northern part of Japan. In this case, final hosts are Foxes and intermediate hosts are voles.

We construct a simple ordinary differential equation model describing a dynamics of infection between two hosts, and analysis this model mathematically.

We assume that main reason of propagation of infection is only the diffusion of final hosts as in the study of rabies by Murray el al, and construct a simple partial differential equation model adding a diffusion term to the equation describing the dynamics of final hosts.

By considering a stable manifold of the ordinary differential equation describing a traveling wave solution of the above partial differential equation, we get a threshold parameter of a speed of traveling wave solution, and also give an algebraic equation determining this value. By using a computer simulation using Crank-Nikolson method, this speed is almost equal to that of traveling wave solution of the original partial differential equation.

## 17. Mutability, Heritability and Evolvability in an Artificial Ecosystem

**Takashi Ikegami[2] and Koh Hashimoto [3]**

DEPARTMENT OF GENERAL SYSTEMS SCIENCES, THE GRADUATE SCHOOL OF ARTS AND SCIENCES, UNIVERSITY OF TOKYO, 3-8-1 KOMABA, MEGURO-KU, TOKYO 153-8902 JAPAN

A dynamical systems understanding of heritability at the ecosystem level is discussed. Over the years, experimental studies of the higher level group selection have been carried out (see e.g. C.J.Goodnight, PNAS 97 (2000) 9365). Many of them have reported that there exist significant responses against group selection with heritable variations. As distinct from individual selection mechanisms, the ecosystem has no genetic bases. Therefore heritability at the ecosystem level is not very reliable, as is observed in the experiments by Swenson et al. (PNAS 97 (2000) 9110)

In order to explain the higher level heritability, we propose a dynamical systems approach based on simulations of the high-dimensional replicator equation with mutation dynamics ( K.Hashimoto and T.Ikegami, J. Phys. Soc. Jpn. 70 (2001) 349). We assume that all variants are generated from within the groups of variants through mutations. Simulating the equation with a random interaction matrix

[2]ikeg@sacral.c.u-tokyo.ac.jp
[3]hasimoto@sacral.c.u-tokyo.ac.jp

and possible variants, we report that this system tends to have many attractors of fixed point type, chaotic and quasiperiodic ones. In addition, their basin boundaries appear to be riddled.

With this model, we carry out a heritability check experiment. We sample a small population of the system (i.e. truncating relatively small population variants) to create the next generation of the system when the system reaches an attractor. Through the successive creation of the system, we study the heritability of this system. As a conclusion, we report that gene-like variants appear to control the heritability of the system. In other words, these gene-like variants act as a key species. Based on this finding, the relation between evolvability and heritability will be discussed (see also discussions in T.Ikegami, J. Alife and Robotics 3 (1999) 242.).

## 18. Evolution from hierarchical bio-societies to well-made biomachines via semeiogenesis : A generalized view of life as a autopoietic cognitive neural-network machine

**Koji Ohnishi *, Hiroshi Shutou, Hajime Sawamura, Masaki Goda**

DEPARTMENT OF BIOLOGY, FACULTY OF SCIENCE, NIIGATA UNIVERSITY, NIIGATA, 950-2181, JAPAN

(1) Detailed analyses of tRNA gene clusters revealed that pre-tRNAs possess a "hammerhead structure" commonly found in self-cleaving replicable RNAs (such as virusoids), suggesting that proto-tRNA emerged as a virusoid-like riboorganism (RO). (2) According to the poly-tRNA theory (Ohnishi, 1993, 2001), earliest mRNAs would have evolved from some tRNAs (tRNA-Gly, tRNA-His) by means of interaction of a tRNA with anticodon-regions of the trrnD-type or rrnB-type poly-tRNAs. These poly-tRNAs are transcripts from tRNA-gene clusteres found in the Bacillus subtilis trrnD or rrnB operons, each containing tandemly arranged 16 or 21 tRNA genes. In such interactions (in "poly-tRNA model"), some tRNAs have been converted to be complementary to the 16- or 21-triplet-long RNA (48- or 63-base-long), resulting in the emergence of earliest mRNAs. Thus mRNAs have evolved from tRNA-ROs. If we consider that intracellular protein-making apparatus is a biomachine composed of tRNA-ROs and tRNA-derived, worker-like ROs (mRNAs, rRNAs, etc.), then such hierarchical (intracellular) RO'ic society seems to have converted to a well-made biomachine. (3) Bee-superorganism (bee-SO) (= bee eusociety) and multicellular animal body (consisting of germ-line unicell queens and somatic-line unicell workers) are also examples of queen-worker-type hierarchical society having evolved by kin selection (Hamilton, 1964). These biomachines are here called "queen-worker (qw-) type biomachines, whereas the genetic apparatus, consisting of queen-like tRNAs and worker-like tRNAs, is called a qw-like biomachine. (4) Why such hierarchical societies tend to evolve to be well-made biomachines ? A possible common underlying logic is that these machines might have worked as self-learning (and self-improving) hierarchical neural-network (NNw) machines. In "Model-I" for qw-type two-layered learning NNw-biomachine, fertile queens (or queen-cells) are units of output-layer, and sterile workers (or worker-cells) are units of input-layer. Inputs from environment are processed mainly by workers, and workers bahave altruistically to queens, by which DNA-information-flow equivalent to the flow from workers to queens could be made since most (3/4 in bee-SO, 1/1 in animal body) of DNA information is shared by queens and workers. The final output from every queen is DNA-information outputted from queen to the next-generation, which constitutes a feed-back-information flow for re-making the workers and queens of the next generation. First differentiation to workers is commonly made by some kind of parental manupilation (such as wasp's maternal manupilation to daughters or by Drosophila egg's bicoid-mRNA gradient made by maternal mRNAs). (5) In "Model-II" for the qw-like two-layered NNw-like, protein-making machine, both queens (tRNAs) and workers (mRNAs and rRNAs) are fertile (because they replicates in DNA-phase of RO's life cycle). However, DNA-replications occur simultaneously in queen-like tDNAs and in other worker-like DNAs (mDNAs and rDNAs), resulting in generating a feedback DNA-information flow of NNw-model essentially similar to the "Model-I". (6) Leaning process of a simplest two-layered NNw-model for Model-I, consisting of one queen and two workers, was simulated by "Back propagation method", resulting in markedly rapid learning of inputted pattern information by means of auto-selecting better set of connection weights. If teacher-signal is possessed by the NNw-system itself, then this NNw-machine works as a cognitive autopoietic, self-improving machine. (7) Another model clearly shows that "Species" could be a probablistic cognitive NNw-machine in which males and females are input-layer units, and fertilized eggs are output-layer units, which remake the males and females of the next generation. (8) In every of the above-mentiomed NNw-biomachines, semeio-genesis would be a critical step in converting the society to biomachine by generating appropriate connection weights of the NNw. Mature semeiotic systems are generally observed; genetic codes in tRNA-society-machine, bee-dance in bee-SO, hormones (semeiotic molecules) in animal body, pheromones and prenuptial displays in iso-specific society. Semeiotic maturation would make rapid information-flows necessary for efficient biomachines. (9) Semeiotic phenomenon is

a cultutre of human society or of some kind of bio-society. Thus sociomachinogenesis accelated by semeiogenesis is considered to be a kind of cultural evolution in various levels of society consisting of its own bio-individual-members such as ROs (in tRNA society), unicell animals (in animal body), bees (in bee-SO), and multi-cellular animals (in diploid iso-specific society). Evolution from early causal correspondence between de Sausdseures' signifier (signifian) and the signified (signifie) to highly matured arbitrary correspondence between them would be the most essential feature in semeiotic maturation, which is applicable to general semeiotic systems from genetic codes to human language systems. (10) Life or biomachine is thus considered to be some kind of cognitive (hierarchical and/or fully-connected) NNw-machine capable of self-learning and auto-poietically self-improving. Evolution is a kind of "general thinking" process of such cognitive biomachine, resulting in self-improving in every generation using DNA mutations. (11) Refs: Ohnishi, Endocytobiology V. 407-414,1993 ; Ann.NY Acad. Sci.,707, 524-528,1993 ; Proc. 6th Int. Conf. on Artificial Life Robotics, 344-349,2001.

## 19. TEXTBF TERMINAL STATES OF EVOLUTION IN SEXUAL POPULATIONS

TEXTBF JOZSEF GARAY * ZOLTAN VARGA

EOTVOS LORAND UNIVERSITY HUNGARY

The aim of the lecture: introducing the basic idea of the evolution game theory into population genetics. Let us consider a diploid, panmictic, sufficiently large sexual population in which each individual has a phenotype genetically uniquely determined by an arbitrary number of alleles located at an arbitrary number of loci, which are arbitrarily distributed on the chromosomes. Meiotic mutations and recombinations are also taken into consideration. The phenotypes are supposed to be in a frequency-dependant evolutionary game conflict.

For this situation the concept of an evolutionarily stable gamete distribution (ESGD) is introduced which is considered the terminal state of the evolution. As a generalisation of the replicator dynamics a gamete dynamics is also given. It is proved that an ESGD is a locally asymptotically stable rest point of the latter dynamics.

## 20. A Note on Stability and Similarity of Populations in a Model with Asymmetric Interaction

**Yoshiteru Ishida**

DEPARTMENT OF KNOWLEDGE-BASED INFORMATION ENGINEERING,
TOYOHASHI UNIVERSITY OF TECHNOLOGY

We first discuss the stability and convergence of the non-linear system:

$$\dot{v}_i = v_i(b_i - \sum_{j=1}^{n} p_{ij}x_j), \quad (i = 1, \cdots, n),$$

$$\dot{x}_i = (\sum_{j=1}^{n} k_{ij}v_j) - x_i(\sum_{j=1}^{n} c_{ij}v_j), \quad (i = 1, \cdots, n),$$

where $v_i$ and $x_i$ are time dependent variables; and $b_i, p_{ij}, k_{ij}$, and $c_{ij}$ are positive parameters. This model is a generalization of the model similar to those proposed by Nowak and May to study the interaction between the two competitive populations: HIV ($v_i$) and activated T-Cell ($x_i$).

Based on the results about dynamics and convergence of the relative population of $v_1/v_2$, stability (virus clearance) condition of the Nowak-May model is discussed. A similarity measure (which is a function of the parameters) between two strains is proposed. A result indicating dissimilar strains lead to unstable (virus is not cleared) systems is presented.

## 21. Stochastic Dynamics of Muscle and Ionic Channel of Neuron

**HIROYUKI Matsuura*, MASAHIRO Nakano**

NATIONAL GRADUATE INSTITUTE FOR POLICY STUDIES UNIVERSITY OF OCCUPATIONAL AND ENVIRONMENTAL HEALTH

We proposed new thermal models of muscle and Ionic Channel based on Stochastic Resonance (SR). SR is a kind of common phenomena in the nano region. And it is said that neuron reacts to the thermal noise, whose phenomena was called SR. In our model of Ionic channel of neuron, the ionic gate of conductance always changes by thermal noise currents and SR induced by thermal fluctuation of electrons. Starting from the equation of Hodkin-Huxley model, we analytically solved these equation by using perturbation method and numerical ones.

And another model which is a kind of thermal ratchets based on Nyquist theorem is related to the actin-myosin system of muscle. This new model is named Stochastic Inclined Rods Model(SIRM). SIRM has a simple structure, which is composed of an inclined spring, a myosin head, and bundle of rods. In the SIRM, the energy of motion is supplied from random thermal noise of water molecules generated through the heat of ATP hydrolysis. In an open and dissipative system, the myosin head works as a resonator of random noise, which accepts the energy through resonance. It is shown that the inclined rod and the spherical shape of G-actin are very important elements for the purpose of breaking the symmetry in the vibration of SR and of generating a one directional motion. When the myosin head interacts with the spherical potential of G-actin, the trigonometric wave of SR is distorted by the collision between the head and G-actin, and then it obliquely kicks the actin fiber by using the spring. It is thus shown that the inclined rod and the shape of the G-actin makes the SIRM move in one direction, even if the potentials between the myosin head and G-actin are perfectly symmetric.

## 22. Sympatric coexistence condition in a large community with complex interactions

**Kei Tokita and Tsuyoshi Chawanya***

LARGE-SCALE COMPUTATIONAL SCIENCE DIVISION, CYBERMEDIA CENTER, OSAKA UNIVERSITY
AND *GRADUATE SCHOOL OF SCIENCE, OSAKA UNIVERSITY

We report on asymptotic behavior of the diversity (i.e. the number of species) in a large-dimensional population dynamics with complex interspecies interactions, using both analytical and computational methods. Although ecologists in the 1950s and 1960s observed and believed that the stability of an ecosystem was maintained by the diversity of the species and their complex interactions[1], opposite results were obtained theoretically[2] in the 1970s. This is the so-called "paradox of ecology (diversity)", which has been attacked to solve by many researchers. Several theories offered a solution for the paradox in limited cases, e.g. for a system in which a habitat has spatial heterogeneity[3]. It seems, however, that there is not a solution yet in the case of sympatric coexistence of a large number of species, widely observed in nature, e.g. in tropical rain forests and coral reefs. In such a sympatric case, for a system of $N(\gg 1)$ species with fully random interactions, only order $O(1)$ of diversity can be survived in general because of mass extinction[4]. Contrastingly, here we present a condition for random interspecies interactions, with which a ecosystem can maintain a considerable number $(O(N))$ of species. This condition is nearly connected to a degree of symmetry of interactions and a "degree of zero-sum" in terms of game theory. We also discuss stability of the internal fixed point at which the $O(N)$ of survived species coexist, in particular in connection with the "persistence" of the system.

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## 23. Permanence for Delay Difference Nonautonomous Kolmogorov-Type Population Models

**Yasuhisa Saito ***,

DEPARTMENT OF MATHEMATICAL SCIENCES, OSAKA PREFECTURE UNIVERSITY, SAKAI 599-8531, JAPAN

In this paper we consider the permanence of the following nonautonomous Kolmogorov-type discrete population models with delay:

$$x(n+1) = x(n)\exp\{f(n,x_n,y_n)\}\, y(n+1) = y(n)\exp\{g(n,x_n,y_n)\}, \quad n \in Z^+ \tag{3}$$

where $Z^+$ denotes the nonnegative integer set, and $x_n$, $y_n$ are given as

$$x_n(s) = x(n+s), y_n(s) = y(n+s) \quad for\ s = -\nu, -\nu+1, \cdots, -1, 0 \tag{4}$$

with some integer $\nu \in Z^+$. The initial condition is as $x(s) \geq 0$, $y(s) \geq 0$ for $s = -\nu, -\nu+1, \cdots, -1, 0$, and $x(0) > 0, y(0) > 0$. We define that $X = \{\phi \mid \{-\nu, -\nu+1, \cdots, -1, 0\} \to R_+^2\}$ and $f, g : Z^+ \times X \to R$.

In case

$$f(n, x_n, y_n) = r_1[1 - x(n - k_1) - \mu_1 y(n - k_2)], g(n, x_n, y_n) = r_2[1 - \mu_2 x(n - l_1) - y(n - l_2)], \quad (5)$$

where $r_i > 0$, $\mu_i \geq 0$, and $k_i, l_i \in Z^+$ $(i = 1, 2)$, it is known that the system (1) is permanent if and only if $\mu_1 < 1$ and $\mu_2 < 1$ hold (cf. [1]). We make some assumptions on $f$ and $g$ which generalize the functions in (3) and would like to give a permanence result for system (1).

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## 24. Coevolution of Games and Strategies


**Yuya Kumagai (y-kumaga@jaist.ac.jp),**
**Takashi Hashimoto* (hash@jaist.ac.jp)**

SCHOOL OF KNOWLEDGE SCIENCE
JAPAN ADVANCED INSTITUTE OF SCIENCE AND TECHNOLOGY (JAIST)


The purpose of this research is to understand the dynamics of rules and individual behavior by expanding the framework of evolutionary game. In this study, rules are entities which regulate activities of individuals, such as grammars in language, norms and institutions in social activities.

There are two approaches to the rules in the context of game theory. One is that a rule is "a configuration of game", which is expressed, for example, as a payoff matrix in normal form game. The other is that an equilibrium state as a result of game is a situation in which a rule is established. In these two views, 'rule' does not change in time. In reality, however, individuals' actions are not only affected by a rule of game but also causes of change of the rule. That is, a rule of game can dynamically change under the influence of individuals' strategies.

To consider the dynamics of rules induced by interaction between games and individuals behavior, we introduce an evolutionary game theoretic model in which each individual plays many games at the same time with one strategy. Each game has its own weight which changes with the result of a play. The dynamics of population $p_i(t)$ of a strategy $i$ and that of weight $w^k(t)$ of a game $k$ are expressed by

$$p_i(t+1) = p_i(t) + (S_i - \bar{S})p_i(t) \quad ,$$

$$w^k(t+1) = w^k(t) + F^k w^k(t)/\tau \quad ,$$

where $S_i$ is the total payoff of an individual gained from all games; $\bar{S}$ is the average of the total payoff; $F^k$ is a function to determine the weight of a game $k$, that plays an important role to bond the strategies and the games; and $\tau$ is a parameter for difference between the time scale of changes in the strategies and the games. In addition to these dynamics, the mutation and the extinction of both strategies and games are incorporated.

We will report the results of simulations, e.g. changes of dominant strategy, equilibrium and the characteristics of total games, under some specific definitions of function $F^k$ such as variance and average of payoffs.

## 25. AN FFT-BASED METHOD FOR SIMULATING CARDIAC CONDUCTION IN A 3D BIDOMAIN


**Boyce E. Griffith*[1], Charles S. Peskin[1], Glenn I. Fishman[2]**

[1]COURANT INSTITUTE OF MATHEMATICAL SCIENCES
NEW YORK UNIVERSITY

[2]SECTION OF MYOCARDIAL BIOLOGY
MOUNT SINAI SCHOOL OF MEDICINE


To simulate cardiac conduction via the bidomain equations in three spatial dimensions, it is generally necessary (even when using an explicit scheme) to solve a large, sparse system of linear equations at each time step. Under certain assumptions, however, this linear system is amenable to the Discrete Fourier Transform (DFT). By enforcing periodic boundary conditions in the $x$ and $y$ spatial dimensions and by requiring that conductivity tensors be functions of $z$ alone, it is possible to transform the linear system via the DFT in the $x$ and $y$ spatial dimensions. The resulting system is tridiagonal and is easily solved in parallel. We discuss a DFT-based numerical method for the bidomain equations, present performance results for a parallel, FFT-based implementation of this method, and demonstrate its application to a three-dimensional model of the murine ventricular myocardium which accounts for fiber-angle distribution.


This work was supported in part by a Howard Hughes Medical Institute award to Mount Sinai School of Medicine.

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## 26. Interval Estimation of Mutation Rates Using Data from Fluctuation Experiments

**Qi Zheng**

DIVISION OF BIOMETRY AND RISK ASSESSMENT
NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH
JEFFERSON, ARKANSAS 72079

During the 1920s a dichotomy began to emerge among bacteriologists regarding the origin of certain bacterial mutants that could thrive in environments hostile to their wild-type parent strains (e.g., *E. coli* mutants resistant to bacteriophage T1). While some bacteriologists believed that mutations occurred regardless of their effects on the survival of the organism, others held that mutations could be directed in the sense that mutations were more likely to occur when the environment was favorable for the survival of the resulting mutants. Fluctuation experiments, devised by Luria and Delbrück to solve this controversy, is now a celebrated technique widely used not only for exploring various hypotheses originating from the controversy, but also for estimating mutation rates using data generated by fluctuation experiments.

A major obstacle in efficiently estimating mutation rates is lack of convenient methods for constructing confidence intervals for mutation rates. The issue received surprisingly little attention until 1994 when Stewart proposed a graphical method based on results from a simulation study. Although accurate for most practical purposes, the Stewart method was not convenient to use and lacked a rigorous theoretical foundation. Ironically, a clever yet not fully developed numeric method of computing confidence intervals has lain fallow since 1940 when Lea and Coulson first proposed it. The main goal of this presentation is to offer two useful modifications of the Lea-Coulson method. These modifications not only enhance computational efficiency, but also widen the scope of the applicability of the original method. The presentation also provides some details about a computer implementation of the two modified methods.

## 27. Multiple attractors and Metapopulations

**Janet Best *, Carlos Castillo-Chavez, Nancy Tisch**

DEPARTMENT OF MATHEMATICS, CORNELL UNIVERSITY; DEPARTMENT OF BIOMETRICS AND CENTER FOR APPLIED MATHEMATICS, CORNELL UNIVERSITY; DEPARTMENT OF BIOMETRICS, CORNELL UNIVERSITY

Coupling multiple patches often increases the occurrence of multiple attractors in mathematical models of population dynamics. Varying the intensity of coupling can then alter both the degree of synchronization of patches and the qualitative dynamics. W e investigate population synchronization in models with multiple attractors, beginning with a study (via analysis and simulation) of a discrete, deterministic model with two dimensions in each patch. While intermediate levels of dispersal often synchroni ze dynamics between patches with identical characteristics, even modest differences between patch parameters can result in more complicated conclusions. Even for identical patches the range of synchronizing dispersal varies widely with other parameters a nd may vary with attractor. We compare results with different numbers of patches and with some related models including a stochastic version, and we discuss implications for life histories and for persistence.

## 28. The Engineering Design of Neutrophil Chemotaxis

**Keith A. Erickson* and Adam P. Arkin**

JOINT GRADUATE GROUP IN BIOENGINEERING UNIVERSITY OF CALIFORNIA, SAN FRANCISCO AND BERKELEY LAWRENCE BERKELEY NATIONAL LABORATORY

Neutrophil chemotaxis plays an important role in the human immune system and serves as a model system for cell signaling. To effect chemotaxis, neutrophils detect a gradient of chemoattractant as small as 2their length, amplify this signal into a large intracellular gradient, and adapt the sensitivity of their sensory system to a wide range of absolute external chemoattractant concentrations. Furthermore, neutrophils integrate and prioritize multiple chemoattractant signals to accurately locate and eliminate a large percentage of all immune challenges. Chemotaxis is accomplished through G protein-coupled receptor signal transduction, ubiquitous in numerous cell types including B cells and cardiac myocytes. With over 600 molecules implicated in chemotaxis, there are numerous complications regarding cross talk, spatial localization, mechanics, and feedback, as well as large gaps in our knowledge of the chemical interactions, preventing a detailed understanding of this behavior. We have critically examined several models of neutrophil chemotaxis and have noticed discrepancies between their predictions and experimental observations. We explore the applicability of a combination of mathematical modeling and experimentation toward understanding the mechanisms behind neutrophil chemotaxis, with the goal of creating a theoretical framework from which to rationally develop pharmaceutical strategies to correct and control aberrant cellular behavior.

## 29. How fine-scale covariance, induced by localized feeding, stabilizes predator-prey systems with finite mixing speeds.

**Parviez R. Hosseini ***

DEPARTMENT OF ECOLOGY, EVOLUTION AND MARINE BIOLOGY, UNIVERSITY OF CALIFORNIA, SANTA BARBARA

Theoretical models of predator-prey dynamics have long assumed that the interactions of predator and prey occurred as if they were well-mixed particles. While this allows models to be formulated as functions of global averages (or sums), it implies that predators and prey are distributed independently at every instant in time. This assumption of independent distribution has strong effects on the dynamics of predator-prey systems, which are not necessarily credible. I will show a model that begins to account for a feeding induced negative covariance between predators and prey at an individual to individual level can stabilize predator-prey dynamics.

This work takes as its basis a spatial simulation incorporating prey carrying capacity and Type II functional response Using a mean-field equation that includes joint states between predator and prey, I show that slowly mixed systems are stabilized by a negative covariance prey and predator. This works for both the deterministic mean-field equations and the simulation. I will then demonstrate that this covariance is dynamic such that it can not be eliminated from the equations.

This mechanism is a simpler alternative to more complex wave phenomena. I argue that this negative covariance is likely to affect a wide variety of systems where individual prey and individual predators interact.

## 30. A Note on Symmetries for the Equations in Population Dynamics

**Yoshiteru Ishida**

DEPARTMENT OF KNOWLEDGE-BASED INFORMATION ENGINEERING,
TOYOHASHI UNIVERSITY OF TECHNOLOGY

Symmetries on differential equations have been studied extensively in mathematics using continuous groups as well as discrete groups.

In this note, we discuss symmetries on the equations of population dynamics such as the Lotka-Volterra model. Symmetries are based on indistinguishability after the transformations on the equations. By defining transformations on the level of species, we focus on symmetries that may have a significance in terms of population dynamics. One such symmetry is indistinguishability of the equations after adding a new species which happens to be the same as existing one in terms of characterizing parameters. Lotka-Volterra model is proved to have the symmetry. Application of the symmetry to constrain the expression of a diversity reflecting the number of species is also suggested.

## 31. Diffusion process monitored by fluorescence recovery after photobleaching: Some theoretical aspects

**Gerda de Vries* and Gustavo Carrero**

DEPARTMENT OF MATHEMATICAL SCIENCES
UNIVERSITY OF ALBERTA
EDMONTON, AB
T6G 2G1
CANADA

The technique of Fluorescence Recovery after Photobleaching (FRAP) has been used extensively to measure the mobility of proteins, made visible by means of a fluorescent tag, within the cell nucleus. In the FRAP experiments, a small region of the cell nucleus is bleached irreversibly. The recovery of fluorescence in the bleached region due to the mobility of the protein is recorded in order to estimate a diffusion coefficient for the protein. The classical quantitative analysis that has been followed for this estimation assumes a random walk model on an infinite spatial domain. However, the cell nucleus is a finite region bounded by a membrane. In the present work, we discuss how this oversight can easily lead to erroneous estimations of the diffusion coefficient. This may explain the variability of the diffusion coefficients reported in experimental papers. It might be reasonable to think that a bounded domain should be considered. However, we propose a simple method, based on the model on an infinite domain, that can be used to obtain an accurate estimation of the diffusion coefficient.

## 32. The Dynamics of Prostate Specific Antigen (PSA) as a Marker for Cancerous Growth

**Kristin R. Swanson [*,1,2,3], Lawrence D. True [2], J. D. Murray [3] Daniel Lin [4], Robert Vessella [4]**

[1] LABORATORY OF NEUROPATHOLOGY, HARBORVIEW MEDICAL CENTER
[2] DEPARTMENT OF PATHOLOGY
[3] DEPARTMENT OF APPLIED MATHEMATICS
[4] DEPARTMENT OF UROLOGY
UNIVERSITY OF WASHINGTON, SEATTLE, WA

Prostate specific antigen (PSA) is an enzyme produced by both normal and cancerous prostatic cells. Increased production of PSA by cancerous cells validates its use as a tumor marker. Although it is the most widely used serum marker to detect and follow patients with prostate adenocarcinoma, there are certain anomalies in the values of serum levels of PSA that are not yet understood. We developed a nonlinear dynamical systems model for serum levels of PSA as a function of the tumor volume. Our model results show good agreement with experimental observations and provide an explanation for the existence of significant prostatic tumor mass with a low serum PSA (1). This result can be very significant in attenuating the use of serum PSA levels to screen for prostatic cancerous growth.
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## 33. Resource competition among two phytoplankton species: the impact of the non-limiting nutrient

**Cor Zonneveld**

DEPT THEOR BIOL., FREE UNIVERSITY AMSTERDAM, DE BOELELAAN 1087, 1081 HV AMSTERDAM, THE NETHERLANDS

Essential nutrients affect growth in a Liebig fashion, i.e.

$$\mu(R_1, R_2) = \min\{\mu(R_1), \mu(R_2)\}$$

with $\mu$ the population growth rate and $R_j$ the potentially growth-limiting nutrients. According to the theory on resource competition, the maximum number of species that can coexist equals the number of potentially limiting essential resources. Phytoplankton cells are able to accumulate large quantities of non-limiting essential nutrients, far above the minimum requirement. This phenomenon is sometimes known as luxury consumption. Classic resource competition theory does not account for luxury consumption. In this presentation, I introduce a model that describes the kinetics of limiting as well as non-limiting nutrients. I demonstrate that while the basic predictions of resource competition theory still hold, luxury consumption affects the regions where stable coexistence is possible.

## 34. Spatio-temporal dynamics of childhood diseases in the US, 1950-present

**Alun L. Lloyd**

PROGRAM IN THEORETICAL BIOLOGY, INSTITUTE FOR ADVANCED STUDY, PRINCETON, NJ 08540

Using the historical incidence records of measles, mumps, rubella and chickenpox, I shall discuss aspects of the spatio-temporal dynamics of childhood diseases in the United States. For some of these diseases, the incidence records cover the period when mass-vaccination programs were introduced, and the impact of such programs both on spatial and temporal dynamics will be described.

The spatial coherence of epidemics across the country is of particular interest, partly because of the important role played by spatial effects in enhancing disease persistence. Both global and local mechanisms can give rise to synchrony between outbreaks, and these will be discussed both in terms of the data and with the aid of simple epidemiological models. These patterns of synchrony changed with the onset of vaccination, and I shall discuss the ability— or inability— of simple models to reproduce these patterns.

## 35. Estimating dispersal kernel from mark-recapture data

**Masami Fujiwara*, Michael Newbert, and Hal Caswell**

WOODS HOLE OCEANOGRAPHIC INSTITUTION

We present a new method of estimating distribution of dispersal distance (dispersal kernel) from mark-recapture data. A dispersal kernel is often estimated using mark-recapture experiment. A conventional method of calculating a dispersal kernel assumes that the distribution is normally distributed (i.e. diffusion process) and individuals remain within sampled areas. The first assumption limits the analysis of dispersal distance that is not normally distributed. The second assumption leads to underestimation of dispersal distance because individuals that dispersed outside of sampling areas are never recaptured. Our method eliminates these two assumptions. The new method uses integral equations to express probability of spatial mark-recapture data, and associated dispersal and recapture parameters are estimated using a maximum likelihood method. We also incorporate mortality and stage-transitions that occur in longer time scale than the dispersal process using a 'robust design' approach. Our method will allow re-examination of existing data sets and suggest redesign of future mark-recapture experiments that enable us to estimate mortality and stage-transition rates as well as dispersal kernel.

## 36. Efficient Shape Parameterisation for Biomedical Applications.

**M.I.G. Bloor*, C. Evans, M.J. Wilson**

DEPARTMENT OF APPLIED MATHEMATICS, LEEDS UNIVERSITY,UK.

The aim of the work is to develop a method for the parametric description of the geometry of biological objects with complex shapes, so that realistic analysis of their function and development can be carried out. Two different systems will be described in order to demonstrate the flexibility of the method, namely the human heart, where the complex changes in shape that take place during the cardiac cycle need to be modelled in order to understand the fluid mechanics, and the complex shapes adopted by biological membranes. In both cases a realistic representation of geometry and shape is required if the behaviour of the actual system is to be understood.

The method is based upon a boundary-value approach to geometry description in which smooth surfaces are produced as the solution to an elliptic partial differential equation; hence the method is commonly known as the PDE Method. Shape parameters are introduced through boundary conditions, which control the shape of the geometry models. Through a suitable choice of boundary conditions, realistic shapes can be produced. The particular value of the method lies in its ability to parameterise complicated shapes using a relatively small set of 'shape parameters', so that the model can quickly be changed to assess the effect of geometry upon the functionality of the system (or vice versa).

*The Shape Parameterisation of the Human Heart:* The aim of this work is to create a parametric model of the inner surfaces of the ventricles of the human heart in order to help understand the fluid flow within the ventricles during the cardiac cycle.

*The Shape Parameterisation of Biological Membranes and Vesicles:* This work will show how the PDE method may be used to parameterise the shapes adopted by lipid bilayers which are the most ubiquitous structural component of biological membranes In particular the paper will outline how the PDE method is able to accurately represent the shapes of minimum surface energy in particular the case of non-axisymmetric shapes.

## 37. Destruction of CD4 T Lymphocytes Alone Cannot Account for their Long-term Decrease in AIDS

**Yoram Louzoun (1) *, Irun. R. Cohen(2), Henri Atlan(3)**

1. Interdisciplinary Center for Neural Computation, Hebrew University, Jerusalem Israel and Department of molecular Biology, Princeton University Princeton NJ. 2. Department of Immunology, The Weizmann Institute of Science, Rehovot, Israel. 3. Human Biology Research Center, Hadassah Hebrew University Hospital, Jerusalem Israel. Correspondence and requests for materials should be addressed to Yoram Louzoun at the department of molecular Biology of the Princeton University.

Following previous models describing a quasi steady state (QSS) for the evolution of HIV infection and AIDS, we have developed a larger formalism simulating the long-term evolution of the total CD4 T cell concentration QSS, during the latent phase (In contradiction with ho et al., which model the staedy state obtained between the infected CD4 T cells the virions, and the immune response against these virions.) We show that the long-term evolution of the total CD4 population during the latent stage of HIV cannot be explained by the destruction alone of CD4 T cells, either directly or indirectly. The destruction of CD4 T cells can lead only to a quasi steady state with a lower concentration of CD4 T cells, but this steady state will be obtained within a few monthes. Thus CD4 destruction cannot generate the sustained long-term decrease in T cells leading to AIDS. We here suggest some workable explanations.

## 38. The importance of being discrete - life always wins on the surface

**Yoram Louzoun (1) *, Nadav M. Shnerb (2) ,Eldad Bettelheim (2) ,Sorin Solomon (2)**

Department of Molecular Biology Princeton University, Princeton NJ 08544
Department of Physics, Hebrew University. Jerusalem, Israel 91904

Many systems in chemistry and biology, (As well as in finance and social sciences) present emerging features which are not easy to guess from the elementary interactions of their microscopic individual components. In the past, the macroscopic behavior of such systems was modeled by assuming that the collective dynamics of microscopic components can be effectively described collectively by equations acting on spatially continuous density distributions. It turns out that quite contrary, taking into account the actual individual/discrete character of the microscopic components of these systems is crucial for explaining their macroscopic behavior. In fact, we find that in conditions in which the continuum approach would predict the extinction of all the population (respectively the vanishing of the invested capital or of the concentration of a chemical substance, etc), the microscopic granularity insures the emergence of macroscopic localized sub-populations with collective adaptive properties which allow their survival and development. In particular it is found that in 2 dimensions "life" (the localized proliferating phase) always prevails.

¿From Shnerb, Louzoun et al (pnas 2000)

## 39. HIV time hierarchy: Winning the war while, loosing all the battles.

**Yoram Louzoun (1) *, Uri Hershberg(2),Henri Atlan (3) Sorin Solomon(4)**

**(1) Department of Molecular Biology, Princeton University, Princeton, NJ 08544**
**(2) Interdisciplinary Center for Neural Computation, Hebrew University, Jerusalem Israel.**
**(3) Human Biology Research Center Hadassah Hebrew University Hospital, Jerusalem Israel.**
**(4) Racah Institute for Physics, Hebrew University, Jerusalem Israel.**
**ylouzoun@princeton.edu**

AIDS is the pandemic of our era. A disease that scares us not only because it is fatal but also because its insidious time course makes us all potential carriers long before it hands us our heads in a basket. The strange three stage dynamics of aids is also one of the major puzzles in describing the disease theoretically. Aids starts, like most diseases, in a peak of virus expression, which is practically wiped out by the immune system. However it then remains in the body at a low level of expression until later (some time years later) when there is an outbreak of the disease which terminally cripples the immune system causing death from various common pathogens. In this talk we will show, using a microscopic simulation, that the time course of AIDS is determined by the interactions of the virus and the immune cells in the shape space of antigens and that it is the virus's ability to move more rapidly in this space (it's high mutability) that causes the time course and eventual 'victory' of the disease. These results open the way for further experimental and therapeutic conclusions in the ongoing battle with the HIV epidemic.

(Form Hirshberg, Louzoun et al Physica A 2000)

## 40. Spatio-temporal pattern and long transients in discrete-time growth-dispersal models

**Aaron A. King* and Alan M. Hastings**

Department of Environmental Science & Policy, Institute for Theoretical Dynamics, and Center for Population Biology, University of California, Davis

Discrete-time growth-dispersal models can accurately represent the population dynamics of organisms in which reproduction and dispersal phases alternate. Previous studies have revealed the existence of extremely long transients and complicated spatio-temporal dynamics in such models. In the present study, we examine the dynamical etiology of these features, in both the discrete- and continuous-space settings. We find that, for sufficiently small dispersal, a very large number of stable and saddle-like invariant sets can coexist. Interestingly, the reasons for this are quite different in the continuous- and discrete-space cases. Our analysis sheds much light on the phase-space structures underlying long transients and patchy abundance distributions in these models.

## 41. Genesis of spatio-temporal pattern: a codimension-3 bifurcation in a spatial predator-prey model.

**Aaron A. King* and Alan M. Hastings**

Department of Environmental Science & Policy, Institute for Theoretical Dynamics, and Center for Population Biology, University of California, Davis

We elucidate the origin of certain spatio-temporal patterns in population dynamics through analysis of a minimal two-patch model of predator-prey interactions. The model includes a type-II functional response, intraspecific competition among predators, and diffusive dispersal of both species. The bifurcation in question occurs at the conjunction of the familiar predator-prey Hopf bifurcation and the Turing instability. We perform a local bifurcation analysis, computing the normal form and revealing thereby the existence of an interesting class of spatio-temporal patterns. The normal form analysis is complicated by the existence of a third degeneracy in higher order terms. We discuss the implications of these patterns with regard to spatio-temporal patterns in ecological systems generally and to coexistence among apparent competitors.

## 42. Clustering Patterns of Experimentally Defined CTL Epitopes: Implications for Antigen Processing and Vaccine Design.

**Karina Yusim 1,2 *, BETTE KORBER 1,2, VINCENT DETOURS 1,2, ALEXANDRE CHIGAEV 3, CAN KESHMIR 4**

1 Los Alamos Natonal Laboratory, NM 2 Santa Fe Institute, NM 3 University of New Mexico, NM 4 Technical University of Denmark, Denmark

The extreme variability of HIV proteins is a challenge for vaccine design. Data compiled in the Los Alamos HIV Sequence and Immunology Databases (hiv-web.lanl.gov) may help address it. The Immunology Database includes a comprehensive listing of hundreds of published HIV-1 cytotoxic T cell (CTL) epitopes from HIV-1 and is updated annually. The Sequence Database is the largest collection of HIV genetic data available today. One of the major trends emerging from the Los Alamos HIV Immunology Database is that experimentally observed CTL epitopes are clustered: epitope density is high in some regions of HIV proteins, while virtually no epitopes are found in others. We find that the entropy of HIV protein sequences is significantly anticorrelated with the density of experimentally observed epitopes. This suggests that CTLs respond primarily to conserved regions of HIV. This finding can be connected to antigen generaton. The first step of CTL epitope generation is the cleavage of viral proteins into short peptides by the proteasome, a protein complex found in the cytosol of cells. We investigated epitope clustering patterns using prediction of proteasome cleavage sites with neural networks [Keshmir et al., in press]. Our analysis takes into account HIV sequence variability. A correlation between proteasomal cleavage sites predicted to occur in many HIV variants and experimentally observed epitope boundaries was found. This result suggests that variable regions of HIV avoid CTL recognition because in many HIV variants these regions are not processed by the proteasome. The analysis suggests that some protein regions containing no known epitopes are refractive to processing. Thus, it may be possible to construct safer vaccines by excluding these regions, and yet keeping intact the breadth of immune stimulation. Using shorter HIV protein stretches might also allow for inclusion of a cocktail of variants in vaccine formulations. Thus there may be advantages in incorporating this epitope clustering and sequence variability information in vaccine design strategies.

## 43. Paradoxical Effects of Low Level Irradiation on Radiosensitivity of Mammals: Modeling and Experimental investigations

**Olga Smirnova and Morio Yonezawa**

Research Center of Spacecraft Radiation Safety Shchukinskaya st., 40, Moscow 123182, Russia
Division of Radiation Biology, Research Institute for Advanced Science and Technology, Osaka Prefecture University, 1-2 Gakuen-cho, Sakai, Osaka 599-8750, Japan

Studies of the effects of low level radiation on mammals are a challenging problem of the modern radiobiology and ecology. Difficulties in this field are, in particular, due to unusual (paradoxical) dose-effect relationships which are observed in some experiments. These results conflict with a radiobiological concept according to which the radiation hazard increases with accumulated doses. One of the paradoxical effects of low doses is acquired radioresistance in preirradiated animals. It is the modeling and experimental investigations of this effect that our work is devoted to.

It is shown experimentally [1-3] that a priming exposure to a low dose can induce radioresistance or radiosensitization in ICR mice. The manifestations of these effects are, respectively, reduced and raised mortality of the animals after challenging acute irradiation. The effect of low dose preirradiation depends on a time interval between priming and challenging exposures. In particular, acquired radioresistance is observed when this interval is equal to 2 weeks or 2-2.5 months.

Bone marrow death takes place in the conducted experiments. This form of mortality is caused by radiation-induced damage of a vital (critical) body system, hematopoiesis. In order to reveal the mechanisms of acquired radioresistance mathematical models of hematopoiesis are used. The models describe qualitatively and quantitatively the dynamics of the major hematopoietic lines (thrombocytopoiesis, lymphopoiesis, erythropoiesis, and granulocytopoiesis) in nonirradiated and singly irradiated mammals (mice) [4-6]. In the framework of the models we simulate the dynamics of these systems in mice exposed to priming and challenging irradiation. As an index of radiosensitivity of a hematopoietic line we choose the damage depth of its functional cell pool, namely, the minimal level of the functional cell concentration after challenging irradiation. Damping oscillations of radiosensitivity of the major hematopoietic lines are revealed. The period of radiosensitization is replaced by the period of radioresistance and so on, their duration being different for different lines. For instance, the peak of radioresistance in lymphopoietic and granulocytopoietic systems takes place, respectively,

on 16 and 55 days after the challenging exposure. The functional cells of these systems (lymphocytes and granulocytes in blood and granulocytes in tissues) play an important part in protection of a mammalian organism against infections which are a frequent reason of death in the case of bone marrow radiation syndrome. Thus, the model results agree with the experimental data and explain them. Besides, in the framework of the models two sets of factors are revealed, which determine, respectively, the state of radioresistance and the state of radiosensitization in thrombocytopoiesis, lymphopoiesis, erythropoiesis, and granulocytopoiesis systems of mice after priming irradiation. The developed models can be used for theoretical studies of the modification effects of low level exposures on radiosensitivity of mammals and for planning new experiments.

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## 44. A Mathematical Investigation of Swarming Behavior in Myxobacteria

**Angela Gallegos *, Alex Mogilner**

DEPARTMENT OF MATHEMATICS AND INSTITUTE FOR THEORETICAL DYNAMICS UNIVERSITY OF CALIFORNIA AT DAVIS

The coordinated movement of many cells, a process called swarming, allows bacteria to spread over a surface. We have theoretically investigated the mechanism of swarming of the bacteria Myxococcus xanthus. Our mathematical model consists of a reaction-diffusion equation describing density dependent random motion of the cells and their proliferation and death. This equation is coupled to another equation which describes the diffusion and depletion of the nutrient on which the bacteria feed. We perform scaling, dimensional analysis and numerical analysis to find the rate of spreading of the bacterial colony. We compare theoretical results with the experimental observations of Kaiser and Crosby [1] and Burchard [2].

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## 45. A coupled-model study of *Calanus finmarchicus* population distributions within the Labrador Sea

**Derek Tittensor, Brad deYoung**

DEPARTMENT OF PHYSICS AND PHYSICAL OCEANOGRAPHY, MEMORIAL UNIVERSITY OF NEWFOUNDLAND, ST. JOHN'S, NEWFOUNDLAND, CANADA

*Calanus finmarchicus* plays a critical role in the transfer of energy through trophic levels in the North Atlantic, both as a predator on phytoplankton and as prey for many species of fish. The modeling of population distributions and structure is therefore important as a diagnostic and predictive tool.

Two regions of high *C. finmarchicus* population density have been identified within the North Atlantic; one of these is located in the Labrador Sea. Although the physical oceanographic processes in this region are reasonably well understood, planktonic distribution data is very sparse. This study couples a *C. finmarchicus* population model, NPZ model, mixed-layer model and a three-dimensional circulation model of the Labrador Sea in an attempt to understand the physical and biological processes that influence *C. finmarchicus* distributions within the Labrador Sea.

## 46. A Model of Border Zone Arrhythmias

**Bradford E. Peercy *, James P. Keener**

DEPARTMENT OF MATHEMATICS, UNIVERSITY OF UTAH

There is evidence that the border between ischemic tissue and normal tissue in the heart is a potential site of anomalous electrical activity. Increased extracellular potassium, lower intracellular pH, and depletion of ATP are all cellular consequences of ischemia. These physiological responses affect the electrical properties of the ischemic cell by increasing the rest potential, reducing the upstroke velocity, and shortening the action potential duration (APD).[4] There is experimental evidence that interaction between ischemic cells and healthy cells may lead to spontaneous electrical activity [1], which in turn may lead to the development of cardiac arrhythmias.

There is three-dimensional structure to the border zone including a gradient of damaged cells in the border region between normal tissue and fully ischemic or necrotic tissue. However, the three-dimensional scenario with spatially complex border zone can be simply modeled by two coupled excitable cells. Each cell is modeled to mimic physiological properties of normal tissue and ischemic tissue, respectively. The model uses FitzHugh-Nagumo dynamics for a system of four coupled ordinary differential equations (ODEs), a transmembrane potential variable and a recovery variable for each cell. Analytical results show that for certain coupling coefficients the system of two coupled stable cells loses all stable rest states and becomes self-oscillatory. Using perturbation theory, a Poincaré map which details the trajectory of the recovery variables can be constructed and stability of the oscillations can be determined [5].

## 47. The biometrical analysis of the genetical control of competitive ability in mixed culture of Drosophila melanogaster

**Morteza Hemmat**

FACULTY OF SCIENCE, UNIVERSITY OF SHAHREKORD, P.O.BOX 115, SHAHREKORD, IRAN

The analysis involved the parental, F1, F2 and backcross generations derived from crosses between two highly inbred lines isolated from the Texas population of D. melanogaster. The competitive performance of each genotype in monoculture and in duoculture with a phenotypically distinct tester were assessed using a yield-density regression analysis. Appropriate genetic models were fitted using a variance weighted least square procedure and the resulting genetic components of the generation means used to define the genetical architecture of competition. The significant genetic components controlling inter-genotypic sensitivity (Cxy) were additive and dominance components of the progeny's own genotype ([dp] and [hp], and dominance components of the F1 maternal genotypes ([hm1] and [hm2], as well as additivetimes; dominance non-allelic interactions [j] and dominancetimes; dominance non-allelic interactions [l]. Heterosis was found to be determined by the progeny's own genotype [hp]¿[dp], and by the F1 maternal genotype [hm1]¿[dm]. Inter-genotypic competitive pressure (Cyx) was found to be controlled by additive and dominance effects of approximately equal magnitude. Heterosis due to the progeny's own genotype was found to play a part in controlling this parameter as shown by the relationship ([hp]¿[dp]).

## 48. Mathematical and Informational Model of One's Own Radiating Field

**Cornelia Guja, Sorin Baiculescu, Calin Dolcos, Lacramioara Muresan**

ROMANIAN ACADEMY, "FR. RAINER" ANTHROPOLOGICAL RESEARCH CENTER, P.O.BOX 35-13, BD.EROII SANITARI NR.8, 76241 BUCHAREST, ROMANIA, E-MAIL: RAINER@SUNU.RNC.RO

The paper presents significant results regarding the informational complexity and diversity of the biofield phenomena highlighted electrographically. There are correlations with the pattern matrix of the variability of electrogenic potential in the ontogenesis. We identify the specific biofield forms that characterize the juvenile type (hydric pattern) non-reactive hypotonic (mineral pattern), reactive hypertonic (dielectric pattern) and senescent types (semiconducting pattern), highlighting the structural isomorphism existing between them and the components of the attached pattern matrix. The paper presents the mathematical method of matrix cell generation, the law of their formation being also interpreted biologically. Informational quantification of the electrographically revealed biofield (Onicescu informational energy, informational entropy) are achieved by biomathematical methods. The application of the results obtained on sick people lots (psychoneuroendocrine, cardiovascular, etc. affections) and on aging people compared with the witness (healthy) lots introduces a new methodology called compared informational electrography (EglC). The paper presents the informational results obtained in this sense, that may be used to prospectively foreshadow various affections. Modelling of the radiating biofield recorded electrographically is done by almost periodical functions, also pointing out the biofield-cerebral potential dependence, as well as some biofeedback aspects.

## 49. Anthropological Compatibility-Incompatibility Identified by Methods of Self-evaluation-Mathematical Processing

**Cornelia Guja, Sorin Baiculescu, Calin Dolcos, Lacramioara Muresan**

ROMANIAN ACADEMY, "FR. RAINER" ANTHROPOLOGICAL RESEARCH CENTER, P.O.BOX 35-13, BD.EROII SANITARI NR.8, 76241 BUCHAREST, ROMANIA, E-MAIL: RAINER@SUNU.RNC.RO

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The paper determines the level of anthropological compatibility-incompatibility identified by self-evaluation methods. It establishes the individuals' integration degree within the lot to which they belong and the level of their bilateral individual compatibility. We used the results of the project draft of one's own anthropological biography made out at "Fr. Rainer" Center of Anthropology of the Romanian Academy, applied to a lot of 67 subjects. The data were processed in Excel 7 language, and the TEST program was created. According to the authors of the project draft, the employed methodology has in view the human being in the interface hypostasis, in permanent interaction with itself, with the environment and the fellow beings, in successive and simultaneous sequences. One's own anthropological biography includes the sum total of information organized according to the anthropological model of the human being studied as interface: I.Ecological Integrating; II. Biological Cultural; III. Physical-Chemical Sentimental; IV. Psychic Conscious; V. Cognitive Axiological; VI. Cyclic Evolutive; VII. Spiritual Transcendent. For each interface the project draft establishes a set of hypostases where each individual should find his place. Identifying the number of these situations for the total number of the 7 considered interfaces, we algebraically quantified the obtained results. They are matrix processed by means of the computer, compatibility-incompatibility resulting for each individual related both to the whole lot and to the individual, bilaterally. The file " SOCIAL INTEGRATION" and "BILATERAL INDIVIDUAL COMPATIBILITY' computes a subject's level of social integration within the lot to which he belongs, establishing the compatibility score for each individual. The general matrix of compatibility-incompatibility centralizes the obtained results. The paper results may be useful for analyzing the social integration processes, cohabitation, feedback of psychological processes and biosocial models.

## 50. Modeling the Computational Cell by Using the NWGrid and NWPhys Simulation Frameworks

**Harold Trease(1) *, John Miller(1), David Dixon(1), and Jim Schaff(2)**

(1) Pacific Northwest National Laboratory, (2) University of Connecticut Health Center

Discrete computational (mesh based) solution methods represent powerful, robust tools that can guide the understanding and interpretation of complicated experimental results, as well as assist in the design of new experiments. Computational mesh based tools and methods contribute in two critical areas, which are the reconstruction and mapping of experimental data into a discrete mesh and the simulation of experiments. Here we present two tools, NWGrid and NWPhys, that are being used at PNNL in the simulation of single cells and cell complexes. NWGrid is a multi-dimensional, unstructured, adaptive, hybrid mesh generation system and NWPhys is a computational physics toolbox that performs discrete integration of coupled PDEs. Both codes use a Frameworks design based on a scientific relational data base management system to be very flexible and extensible. Both codes are designed to be scalably parallel for distributed memory parallel computing system and have been run on a varie! ty of computing system ranging from one PC LINUX workstation to 6000+ processors of a multi-teraflop supercomputer. As part of this paper we will demonstrate how we use these tools as part of our cell modeling programs at PNNL. We will demonstrate the process of taking volumetric image data, produced by Confocal Microscopy, and reconstructing a computable discrete mesh by using NWGrid that can be solved by using our solver code, NWPhys. In addition to showing the algorithmic details for the two codes we will also show several examples to demonstrate our grid generation and solver capabilities applied to computational cell biology.

## 51. A Population Model of Prion Dynamics

**Meredith L. Greer ***

Department of Mathematics, Vanderbilt University, Nashville, Tennessee

My research models the development of prion populations replicating by nucleated polymerization. Prions are infectious, modified forms of normal cellular proteins, and are associated with many varieties of transmissible spongiform encephalopathies. I model polymer length as a continuous structure variable, measurable in thousands of polymer units. This results in the following nonlinear coupled system, for which we analyze existence, uniqueness, and steady state behavior.

$$v'(t) = \lambda - \gamma v(t) - \tau v(t) \int_{x_{min}}^{x_{max}} u(x,t)dx + \int_0^{x_{min}} x \left[ 2 \int_{x_{min}}^{x_{max}} b(\widehat{x})\kappa(x,\widehat{x})u(\widehat{x},t)d\widehat{x} \right] dx$$

$$u_t(x,t) + \tau v(t) u_x(x,t) = -\mu(x)u(x,t) + 2 \int_x^{x_{max}} b(\widehat{x})\kappa(x,\widehat{x})u(\widehat{x},t)d\widehat{x} - b(x)u(x,t)$$

We also compare numerical simulations to available data.

## 52. Mathematical Models of Cell Death in Human Preimplantation Embryos

**J. Stark*, S. Spanos**, R.M.L. Winston** and K. Hardy****

*Centre for Nonlinear Dynamics and its Applications, UCL, Gower Street, London, WC1E 6BT, UK.

**Institute of Reproductive and Developmental Biology, Imperial College School of Medicine, Hammersmith Hospital, Du Cane Road. London W12 0NN, UK.

Human preimplantation embryo development is characterized by high rates of developmental arrest during the first week *in vitro*, and the presence of apoptotic cells in blastocysts. It has been proposed that apopotosis (programmed cell death) and embryo arrest are related, and that apoptosis is regulated by maternally-derived and embryo-derived growth factors. However, these relationships are unclear and difficult to determine by conventional experimental approaches, mainly due to limited numbers of embryos available for study. Supplementation of experiments by mathematical modelling offers the potential of gaining maximum information from the data and of developing new hypotheses and experiments.

The starting point of our investigation was a retrospective analysis of 200 human blastocysts examined over the past decade. This reveals a striking shape which suggests that there is a strong correlation between embryo size and the rate of cell death, ie larger embryos appear to have lower rates of cell death. This is consistent with the hypothesis that human embryos produce survival factors, with larger embryos producing more. This could provide a mechanism by which only healthy growing embryos are selected to implant. Additionally, it is important to understand the relationship between observed levels of cell death and embryo arrest. In particular, are the observed levels of cell death sufficient to account for the high levels of human embryo loss in vitro, or are additional mechanisms acting to arrest the whole embryo? Both these issues are difficult to address directly since the available data is the end product of a number of cell cycles during which individual cells can divide or die. The relationship between the rate of cell death for individual cells and the observed distribution is therefore complex, precluding the direct use of standard statistical tests. Similarly, the dependence of the level of whole embryo arrest on the rate of cell death is not straightforward, and is complicated by the lack of information about the stage at which cell death begins.

To overcome these difficulties we recently developed a branching process model of cell division and cell death in embryos (Hardy *et al*, *Proc. Natl. Acad. Sci. USA*, **98**, 2001, 1655-1660). This allowed us to relate parameters such as individual cell death rates to global outcomes such as the shape of the distribution of live and dead cell numbers, or the arrest of the whole embryo. This showed that rates of cell death seen in human preimplantation embryos can only be reconciled with the high levels of arrest of such embryos if the developmental competence of embryos is already established at the 1-cell stage. It also predicted, and we subsequently confirmed experimentally, that cell death does not occur before the 8-cell stage. The onset of apoptosis thus coincides with a number of significant developmental events in the growing embryo, which may provide some clues to its causes and modes of regulation.

After briefly describing the model, this talk will show how it can be used to explain the shape of the dead cell distribution, and in particular to show that much of the apparent size dependence of the cell death rate is an artefact of the way that the data is plotted. When correctly analysed, the data does display a very weak size dependence, which however is not statistically significant. We shall conclude by discussing preliminary results of ongoing current experiments on mouse embryos designed to directly address the issue of the size dependence of cell death.

## 53. Cooperative Enhancement of Specificity in a Lattice of T-Cell Receptors

**J. Stark*, C.C.W. Chan* and A.J.T. George****

*Centre for Nonlinear Dynamics and its Applications, UCL, Gower Street, London, WC1E 6BT, UK.

**Department of Immunology, Imperial College School of Medicine, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK.

One of the most important properties of the immune system is its ability to discriminate between self and foreign peptides. In order to prevent damage to self and yet still provide adequate protection against pathogens, this has to be done with an astonishing degree of accuracy. Thus, for instance, it is known that 10-200 foreign antigens mixed with perhaps 100,000 self antigens on an antigen presenting cell (APC) are sufficient to trigger T-cell proliferation and effector response. This is remarkable, especially given that it appears that the T-cell receptor (TCR) discriminates almost exclusively on the basis of the duration of ligand engagement, which is a stochastic event. Previous models of how the T cell achieves its exquisite sensitivity and specificity rely on the concepts of kinetic proofreading to explain how TCR's discriminate ligands based on their dissociation time, and on the idea of multiple serial encounters by the peptide-major histocompatibility molecule (MHC) complex with different TCR's to explain its sensitivity. However, a problem with this scenario is that due to the stochastic nature of ligand dissociation, the T cell will be very sensitive to both the duration of ligand engagement and the ligand concentration, and it is difficult to see how the T cell can avoid being swamped by false positive signals from the myriad self antigens presented by the APC.

Recent experiments have documented both positive and negative cross-talk between nearby receptors (Germain and Stefanova, 1999, *Annu. Rev. Immunol.*, **17**, 467-522). Encounters of TCR with antagonist ligands (which bind for an intermediate duration) result in recruitment of inhibitor molecules to the receptor's local neighbourhood. Encounters with agonist ligands (which bind for a long duration) result in recruitment of protective molecules to the neighbourhood, which prevent docking of the inhibitor molecules. In this talk, we present the results of a Monte Carlo simulation of these effects (Chan, George and Stark, *Proc. Natl. Acad. Sci. USA*. in press). We find that the cross-talk can substantially enhance the specificity of the T-cell, at little cost to its sensitivity. In effect, the cross-talk allows the T cell to make more accurate decisions about the nature of the ligands on the APC by pooling information about ligands encountered by different TCR's. In addition, it has been experimentally observed that the degree of cross-talk (especially inhibition) varies during T cell maturation. Incorporating this in our simulation we are able to suggest possible solutions to several puzzles in developmental T cell biology, including how T cells can respond differently to a similar set of antigens presented at different stages, how a single ligand can generate a large T cell repertoire and why the sensitivity to weak ligands is reduced several hundredfold during T cell maturation, but the sensitivity to strong ligands remains unchanged. Finally, we speculate that feedback at a single receptor can provide a plausible alternative to the long chain of phosphorylation steps required in the standard kinetic proof-reading model.

## 54. Mathematical models for positive and negative regulation of gene expression

**Filipa Alves *, Rui Dilão**

Non-Linear Dynamics Group, Physics Department, Instituto Superior Técnico, Av. Rovisco Pais, 1049-001 Lisbon, Portugal

A considerable amount of experimental data on the expression of relevant genes involved in the development and physiology of several organisms is now available. Quantitative descriptions of these regulatory processes should establish basic models for the control of protein production. The action of the activators and repressors regulating the expression of each gene are, therefore, the building blocks of such mathematical models.

Here, we present a general mathematical framework in order to describe positive and negative regulation of gene expression and subsequent protein production. The basic construction considers genes as templates for protein production, where regulation processes result from activators or repressors connecting to DNA binding sites. This approach is very general and can be used as the basic tool for the construction of mathematical models for complex metabolic or developmental processes, where cascading sequences of gene activation and repression mechanisms are present. After deriving the general properties of this class of models, we apply it to the quantitative description of the regulation of the *lac* operon, involved in the lactose metabolism in *E. coli*.

## 55. A model for colour pattern formation in the butterfly wing of *Papilio dardanus*

**Dr. Anotida Madzvamuse *, Prof. Toshio Sekimura; Prof. Philip K. Maini and Dr. Andrew, J. Wathen**

DR. ANOTIDA MADZVAMUSE, OXFORD UNIVERSITY, COMPUTING LABORATORY, OXFORD, ENGLAND PROF. TOSHIO SEKIMURA, COLLEGE OF ENGINEERING, CHUBU UNIVERSITY, KASUGAI, JAPAN. PROF PHILIP K. MAINI, CENTRE OF MATHEMATICAL BIOLOGY, MATHEMATICAL INSTITUTE, UNIVERSITY OF OXFORD, UK. DR. ANDREW J. WATHEN, OXFORD UNIVERSITY, COMPUTING LABORATORY, OXFORD, ENGLAND.

A butterfly's wing is a thing of beauty – in more ways than one. Not only is it beautiful to look at, but analysing how the intricate patterns seen in the wings of the butterflies presents a beautiful mathematical problem.

We therefore present a model colour pattern formation on the wing of the butterfly wing *Papilio dardanus*. This butterfly is well known for the spectacular phenotypic polymorphism in the female of the species. The study of these patterns is based on a model biological spatial pattern generator, the Turing reaction–diffusion system. This system is solved using the finite element method, a robust, efficient numerical technique with capabilities of dealing with complicated irregular shapes (as will be illustrated). We show that numerical simulations of a reaction–diffusion model on a geometrically accurate wing shape produce spatial patterns which are consistent with many of those observed on the butterfly. Our results suggest that the wing colouration is due to a simple underlying stripe–like pattern of some pigment–inducing morphogen. We focus on the effect of key factors which determine the pattern selection, namely the parameter values for mode selection, threshold values which determine colour, wing shape and boundary conditions. The generality of our approach should allow us to investigate other butterfly species. The relationship between these key factors and gene activities is also discussed in the context of recent biological advances.

## 56. Intraguild Predation and Chaos

**Kumi TANABE* and Toshiyuki NAMBA**

DIVISION OF NATURAL SCIENCE, GRADUATE SCHOOL OF SCIENCE, OSAKA WOMEN'S UNIVERSITY

Food web architecture and species interactions are of crucial importance to influence stability of a community.

Ecological interactions are often nonlinear, and it is known that the nonlinearity sometimes gives rise to very complicated fluctuations of populations.

Simple Lotka–Volterra models of food webs have been used to make several predictions on food web structure, which include a general lack of omnivory. However, recent elaboration by Gary Polis (1991) has shown that omnivory may be common in nature. In their pioneering work in 1978, Pimm and Lawton revealed that chains with omnivory tend to have unstable equilibria or stable ones with long return times. Therefore, omnivory should have a destabilizing effect. However, they did not study asymptotic behavior of solutions when equilibria are unstable.

Intraguild predation is a kind of omnivory in which the predators feed on not only the prey but also the prey's resources. Recently, Holt (1997) found that there can appear a limit cycle, when an equilibrium loses stability in the Lotka–Voltera model with intraguild predation. On the other hand, McCann and Hastings (1997) considered a model of intraguild predation with the type II functional responses and showed that intraguild predation can work as a stabilizing agent. Therefore, there exists a discrepancy between the results of these two models. However, both models have never been explored in the whole range of parameters.

In this presentation, we investigate a three-species Lotka– Volterra chain with intraguild predation, and show that intraguild predation sometimes induces chaos. Chaos can readily appear when ingraguild predators prefer resources to prey but the resources are poorer in quality for the predators. It will be also shown that the route to chaos is familiar period doubling bifurcations and period doubling reversals.

## 57. A mechanistic model of entomopathogenic nematodes and their hosts

*Christopher J. Dugaw*[1], **Alan M. Hastings**[2], **Donald R. Strong**[3]

[1]MATHEMATICS, U.C. DAVIS, ONE SHIELDS AVE., DAVIS, CA, 95616, dugaw@math.ucdavis.edu [2]ENVIRONMENTAL SCIENCE AND POLICY, U.C. DAVIS, ONE SHIELDS AVE., DAVIS, CA, 95616, amhastings@ucdavis.edu [3]EVOLUTION AND ECOLOGY, U.C. DAVIS, ONE SHIELDS AVE., DAVIS, CA, 95616, drstrong@ucdavis.edu

We modeled the interactions of the entomopathogenic nematode *Heterorhabditis marelatus* and its insect host *Hepialus californicus*. The nematode lives in the soil and attacks the larval stage of the host. The free-living infective juveniles of the nematode enters a host through a spiracle or other opening and then regurgitates a symbiotic bacterium, *Photorhabdus luminascens*, into the inside of the host. The bacteria kills the host and provides a protected environment for the nematode to reproduce. After a period of about six weeks several new infective juveniles emerge from the host cadaver. Young, small hosts give rise to few if any new infective juveniles, while large hosts can produce up to 420,000 new individuals. The hosts are univoltine, where as the nematodes reproduce continuously throughout the wet season when the host caterpillars are present in the soil. These two different modes of reproduction lead to a model which uses a continuous time description within a year to obtain a discrete map describing year to year dynamics. A system of delay-differential equations are integrated over a fixed period of time (i.e. the length of the wet season) to generate the discrete return map. The adult moth stage of the host disperses widely, so it is assumed that a constant number of hosts hatch each year. We model the hosts' growth in size, and assume the number of new infective juveniles emerging from a host cadaver is proportional to its size. The dynamics of the model are explored for various levels of initial host density, individual host growth rates, and nematode infectivities.

## 58. Reaction-diffusion equations for population genetics

**Bronwyn Bradshaw-Hajek*, Philip Broadbridge**

INSTITUTE FOR MATHEMATICAL MODELLING AND COMPUTATIONAL SYSTEMS UNIVERSITY OF WOLLONGONG, AUSTRALIA 2522

By several routes, continuum modelling of gene frequencies during spatial dispersion of a population arrives at a reaction-diffusion equation with cubic source term. This is at odds with the quadratic source term proposed by Fisher in 1937. When *any* number of pre-existing alleles compete for a single locus, the frequency of a new mutation is described by a system that miraculously collapses to a single equation if the total population is known. This result is proved by induction. Some practical analytic solutions are derived by the method of non-classical symmetry reduction. The solutions obtained are found using specific boundary conditions and are different from previously derived travelling wave solutions.

## 59. A Mathematical Model of White Blood Cell Engraftment Following Autologous Peripheral Blood Stem Cell Transplantation

**Brian M. Murphy*, Stephen J. Merrill[1], Ann LeFever[2] Denise Kirschner***

* DEPARTMENT OF MICROBIOLOGY AND IMMUNOLOGY
UNIVERSITY OF MICHIGAN, ANN ARBOR, MI
[1] MARQUETTE UNIVERSITY, MILWAUKEE, WI
[2] ST. LUKE'S MEDICAL CENTER, MILWAUKEE, WI

An available treatment for a number of high-risk or metastatic cancers is the use of high-dose chemotherapy followed by a transplant of a patient's own (autologous) peripheral blood stem cells (PBSCs). The success of a PBSC transplant, characterized by long-term disease-free survival or delayed time to relapse, depends on the patient's ability to *engraft*, or to generate a functioning, self-sustaining hematopoietic system with near-normal blood cell levels following transplant. In the case of breast cancer, clinical results of stem cell transplants are generally favorable, yet problems such as high relapse rates and delayed engraftment times still exist. Therefore, a better understanding of the mechanisms of hematopoietic reconstitution, and thus engraftment, may be of benefit. We developed a mathematical model of white blood cell (WBC) engraftment kinetics following high-dose chemotherapy and a PBSC transplant. The model is based on the architecture and microenvironment of bone marrow, which can be viewed as a redeveloping system following a PBSC transplant. The model includes this feature by assuming an initial autocatalytic process in the proliferation of granulocyte and lymphocyte precursors, possibly related to exogenous colony stimulating factors used as part of the transplant procedure. Model solutions identify surprising hyperbolic kinetics of WBC engraftment, allowing for a natural definition of time to engraftment (TTE). Based on the TTE, we create a control chart using Monte Carlo simulation to monitor the progress of a patient's engraftment and identify problems at early time points. This clinical tool is a significant improvement upon current post-transplant monitoring procedures.

## 60. The Effects of Different HIV-1 Strains on Human Thymic Function

**Ping Ye *, Denise Kirschner**

DEPARTMENT OF MICROBIOLOGY AND IMMUNOLOGY
UNIVERSITY OF MICHIGAN MEDICAL SCHOOL

Studies of HIV-1 infected humans indicate that the thymus can be infected by HIV-1. In many of these patients, the decrease in thymic output of T cells has been observed together with a significant $CD4^+$ T cell decline and disease progression during HIV-1 infection. This phenomenon is more evident in pediatric patients who depend heavily on their thymus to generate new T cells. We hypothesize that HIV-1 causes T cell regenerative failure within the thymus which has a profound impact on disease progression. Further, different HIV-1 strains (R5 and X4) may impact thymic dysfunction to different degrees. In order to study thymus infection with HIV-1, we first develop a mathematical model that describes normal human thymopoiesis. Our results show that the number of total thymocytes, and the relevant subsets, namely ITTP, DP, SP4 and SP8 cells, increases to a maximum value at the age of one, then decreases at the rate of 5% per year, matching human data. Building on this model, we include the dynamic interactions between different HIV-1 strains and thymocytes. In order to capture the significant differences likely played by the thymus in children and adults, our model includes the effects of an age dependent involution process. Our results demonstrate that thymus infection with different HIV-1 strains induces thymic dysfunction to varying degrees, contributing to differences in disease progression as is

observed in both HIV-1 infected children and adults. The underlying mechanisms may include the pattern of coreceptor expression on thymocytes, the virulence of viral strains, and the ability of thymocytes to support viral replication. The model also suggests that thymic infection in children is more severe than in adults, particularly during X4 infection. This response is likely due to both a higher viral load and a more active thymus. Highly active antiretroviral therapy (HAART) is then explored using the model. Our results indicate that with adequate suppression of viral replication in both the blood and thymus during treatment, thymic reconstitution of immune cells can occur. Our model further predicts observed clinical data from both HIV-1 infected pediatric and adult patients, including blood $CD4^+$ T cell counts and T cell Receptor Excision Circles (TRECs) which represent recent thymic emigrants.

## 61. A Delay Differential Equation Model for Tumor Growth

**Minaya Villasana*, Ami Radunskaya**

CLAREMONT GRADUATE UNIVERSITY AND POMONA COLLEGE

The problem of modelling cancer growth and its interaction with other cell types is a very complex one and researchers have usually focused on particular issues. The idea is always to gain sufficient insight on the underlying process to able to explain, predict or control the disease. It has been shown that in order to eradicate tumor cells, the immune system plays in important role, without which a cure is impossible. For this reason, this work focuses on tumor growth and its interaction with immune cells. We consider the application of a phase specific drug. The inclusion of this type of protocol, calls for a model that would distinguish between phases of the cell cycle. A natural way to do this is by using Delay Differential Equations.

An analysis of the drug free system is performed to gain sufficient information about the different types of dynamics that can arise. This is achieved by examining the stability of the fixed points that arise in the system. This information will be useful in demonstrating the occurrence of a Hopf Bifurcation as a parameter of the model is varied , and therefore proving the existence of periodic solutions. There is a brief discussion on the nature of the basins of attraction for coexisting stable fixed points with and without drug. Finally, the parameters involved in the model will be estimated from data and optimal control techniques will be used to design optimal drug protocols.

With this work, we hope to gain sufficient knowledge about the underlying dynamics of the system and assess the effect of the drug on tumor cells to design effective drug protocols aimed to eradicate the disease. However, this model is not intended to be used by clinicians to treat their patients, but rather as a tool for exploring the efficiency of different drugs and their effects.

## 62. Epidemic Waves in a Discrete Time Model of Bark Beetle Infestation

**Kelly Blàck*, James Powell, Jesse Logan, and Barbara Bentz**

DEPARTMENT OF MATHEMATICS AND STATISTICS, UTAH STATE UNIVERSITY (KELLY.BLACK@UNH.EDU),
DEPARTMENT OF MATHEMATICS AND STATISTICS, UTAH STATE UNIVERSITY
USDA FORESTRY SCIENCES LABORATORY, LOGAN UT

A discrete time model to approximate the spatial and temporal dynamics of Mountain Pine Beetle outbreaks is presented. The model is constructed using a simple approximation to the growth of the trees coupled with the nonlinear redistribution of the beetle population and transmission model which incorporates the Allee effect of beetle mass attack.

In addition to providing an introduction to the model, an analysis of the linear stability of the system is given. The primary focus, however, will be in examining the conditions necessary for traveling waves. We use a 'test function' approach to determine sufficient conditions for successful establishment of a bark beetle outbreak and to determine a range of speeds at which epidemic waves propagate. Numerical examples indicate that travelling waves propagate at the slowest possible speed, comparing favorably with our analytic results.

## 63. Individual diversity, ecosystem dynamics.

**E. Pachepsky *+, J. W. Crawford*, J. L. Bown*, G. R. Squire+**

*UNIVERSITY OF ABERTAY DUNDEE, DUNDEE, SCOTLAND +SCOTTISH CROP RESEARCH INSTITUTE, INVERGOWRIE, SCOTLAND

Despite the importance of biodiversity for the health of the planet, current understanding of the origins of diversity and its effects on ecosystem properties is still incomplete. In fact, there are still no explanations, in terms of physiological and environmental parameters, for the most commonly observed patterns of diversity such as the species abundance distribution and the species area curve. Clear insight is obscured because of the complexity of ecosystems in their multi-scale organisation and in the large number of parameters affecting the underlying processes. The prevalent approach in modelling diverse communities is to consider populations at the scale of species. However, such a species-based approach ignores individual interactions and variation, and often leads to models that cannot be described in terms of measurable parameters. The approach presented describes a community in terms of a collection of diverse individuals defined by physiologically-based traits. This approach is implemented in an individual-based simulation model. The results show the trade-offs, arising among physiological traits of individuals in a community, required for sustenance of diversity. Given these trade-offs substantial diversity is observed in the model, even at small spatial scales. Moreover, the patterns of diversity in the model agree with those observed in natural ecological communities. The results indicate that a consideration of the link between individual characteristics and community dynamics is necessary for better understanding and wiser management of ecosystems.

## 64. Density-Dependent Matrix Population Model with Weight Total Density

**Svetlana Efremova**

DEPARTMENT OF MATHEMATICS,
SAINT PETERSBURG STATE TECHNICAL UNIVERSITY,
29, POLYTECHNICHESKAYA STREET, ST.PETERSBURG 195251, RUSSIA

We consider a density-dependent Leslie model with three age classes where a total density is a liner combination of stage densities with different weight coefficients. The main goal of this article to clarify how these coefficients affect the dynamics of this model in special cases.

Let $x_i(t)$ denote a population density in age class $i$ at the time $t$ and $M(t) = \sum_{i=1}^{3} c_i x_i(t)$ the weight total population density in time $t$. Then the population in the year $t+1$ can be related to population in the year $t$ by the equations:

$$\begin{aligned} x_1(t+1) &= \mu e^{-\beta M(t)} \left( b_2 x_2(t) + b_3 x_3(t) \right), \\ x_i(t+1) &= e^{-\alpha M(t)} a_{i-1} x_{i-1}(t), \qquad i = 2,3. \end{aligned} \tag{6}$$

Here $a_i$ –survival and $b_i$ birth coefficients are independent on $M(t)$;

$a_i$ must satisfy $0 < a_2 < a_1 < 1$; for $b_i$ we assume $b_1 = 0, b_2 > b_3$;

$\mu$ – a control parameter; $\mu b_i$ – give the maximum birth rates in age class $i$;

$e^{-\beta M(t)}$ and $e^{-\alpha M(t)}$ – express the effect of the weight total density on the birth and survival rates; parameters $\alpha$ and $\beta$ are nonnegative.

With following notation $y_i(t) = c_i x_i(t)$ and $\sum_{i=1}^{3} y_i(t) = M(t)$ the system (6) reduces to system:

$$\begin{aligned} y_1(t+1) &= \mu e^{-\beta M(t)} \left( \tilde{b}_2 y_2(t) + \tilde{b}_3 y_3(t) \right), \\ y_i(t+1) &= e^{-\alpha M(t)} \tilde{a}_{i-1} y_{i-1}(t), \qquad i = 2,3 \end{aligned} \tag{7}$$

with equal density effects from each stage and new parameters:

$\tilde{b}_i = c_1 b_i / c_i, \quad \tilde{a}_{i-1} = c_i a_{i-1} / c_{i-1}$ for $i = 2,3$.

It is shown that the positive equilibrium points of the system (1) and (2) exist under the same conditions. In special case when $\alpha = \beta$, conditions for local stability of the equilibrium points of these two systems are equal to each other too. But for different values of $\alpha$ and $\beta$ it is not true.

In conclusion some patters of transition from regular behavior to chaos will be demonstrated.

## 65. Parasite Transmission Modes and The Evolution of Virulence

**Troy Day *,**

UNIVERSITY OF TORONTO TORONTO, ONTARIO, CANADA

A mathematical model is presented that explores the relationship between transmission patterns and the evolution of virulence for horizontally transmitted parasites when only a single parasite strain can infect each host. The model is constructed by decomposing parasite transmission into two processes, the rate of contact between hosts, and the probability of transmission per contact. These transmission rate components, as well as the total parasite mortality rate, are allowed to vary over the course of an infection. A general ESS condition is presented that partitions the effects of virulence on parasite fitness into three components: fecundity benefits, mortality costs, and morbidity costs. This extension of previous theory allows one to explore the evolutionary consequences of a variety of transmission patterns. I demonstrate two ways in which transmission modes can affect virulence evolution; by imposing different morbidity costs on the parasite, and by altering the scheduling of parasite reproduction during an infection. These results are illustrated with an example that examines the hypothesis that vector-borne parasites should be more virulent than non-vector borne parasites (Ewald 1994). The validity of this hypothesis depends upon the way in which these two effects interact, and it need not hold in general.

## 66. Permanence of multihost-parasitoid systems

**Ryusuke Kon*, Yasuhiro Takeuchi**

DEPARTMENT OF SYSTEMS ENGINEERING, FACULTY OF ENGINEERING,
SHIZUOKA UNIVERSITY, JOHOKU 3-5-1, HAMAMATSU 432-8561, JAPAN

The interactions of hosts and parasitoids are modeled by difference equations because of their non-overlapping generations. It is difficult to predict an asymptotic behavior of such systems , so that we examine the condition for permanence, which requires that all solutions eventually enter and remain in a region with a non-zero distance from the boundary.

By using the technique in Hofbauer *et al.* (1987) and the theory of an average Liapunov function (Hutson, 1984), we examine the condition for permanence of the following 2-host 1-parasitoid system:

$$\begin{cases} H_1(t+1) &= \lambda_1 H_1(t) \exp[-\mu_1 (H_1(t) + H_2(t)) - a_1 P(t)] \\ P(t+1) &= \sum_{i=1}^{2} b_i H_i(t) (1 - \exp[-a_i P(t)]) \\ H_2(t+1) &= \lambda_2 H_2(t) \exp[-\mu_2 (H_1(t) + H_2(t)) - a_2 P(t)]. \end{cases} \tag{8}$$

A local stability analysis of a positive equilibrium of system (1) was carried out by Comins and Hassell (1976). The sufficient condition for permanence of system (1) in the absence of $u_1$ or $u_2$ was obtained by Kon and Takeuchi (preprint).

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## 67. Recurrent habitat disturbance and species diversity in a multiple-competitive species system


**Kyoko Osawa *, Fugo Takasu[1], Kohkichi Kawasaki[2] and Nanako Shigesada[1]**

GRADUATE SCHOOL OF HUMAN CULTURE, NARA WOMEN'S UNIVERSITY, KITA-UOYA NISHI-MACHI, NARA 630-8506, JAPAN

[1]DEPT. OF INFORMATION AND COMPUTER SCIENCES, NARA WOMEN'S UNIVERSITY, KITA-UOYA NISHI-MACHI, NARA 630-8506, JAPAN

[2] DEPARTMENT OF KNOWLEDGE ENGINEERING AND COMPUTER SCIENCES, DOSHISHA UNIVERSITY, KYO-TANABE 610-0321, JAPAN



To address how species interactions, dispersal and environmental disturbances interplay to affect the spatial distribution and diversity of species, we present a compartment model in which multiple species undergo competitive interaction of Lotka-Volterra type in a patchy environment arranged in a square lattice. Dispersal of species occurs between adjacent patches. Disturbances are periodically imposed on a central part of environment in a belt-like block or island-like block of various sizes where each species is perished for a certain time interval and then allowed to recover for the rest of a disturbance cycle. We deal with a case that the local population dynamics within each patch is analytically determinable and has multiple locally stable equilibrium states, when there is no environmental disturbance. We further assume a trade-off between the reproductive rate of species and its dispersal ability. With these settings, we numerically examine how the spatio-temporal distributions of species are affected by changes in the pattern, size and duration of disturbances. The results demonstrate that (1) in the undisturbed area, environmental disturbances could generate asymmetric heterogeneous distributions of species; (2) in the disturbed area, species with higher dispersal abilities quickly invade and preferentially recover their population during the post disturbance period, being temporarily relieved of competition from other species. These mechanisms collectively lead to increased species diversity in the whole habitat, functioning best when both the size and duration of disturbances are intermediate. Especially, the belt-like disturbance is more effective than the island-like disturbance in supporting asymmetric distributions for a wider range of duration of disturbance.


## 68. Modeling biological invasions into fragmented environments


**Noriko Kinezaki *, Kohkichi Kawasaki[1], Fugo Takasu[2] and Nanako Shigesada[2]**

GRADUATE SCHOOL OF HUMAN CULTURE, NARA WOMEN'S UNIVERSITY, KITA-UOYA NISHI-MACHI, NARA 630-8506, JAPAN [1] DEPARTMENT OF KNOWLEDGE ENGINEERING AND COMPUTER SCIENCES, DOSHISHA UNIVERSITY, KYO-TANABE 610-0321, JAPAN [2]DEPT. OF INFORMATION AND COMPUTER SCIENCES, NARA WOMEN'S UNIVERSITY, KITA-UOYA NISHI-MACHI, NARA 630-8506, JAPAN


Environments for living organisms are often fragmented by natural or artificial habitat destruction. Here we focus on how such environmental fragmentation affects the range expansion of invading species. We consider a single-species invasion in an environment in which favorable and unfavorable habitats are arranged regularly in a striped pattern, where the habitat widths are assigned $l_1$ and $l_2$, respectively. Thus, spatio-temporal changes in the population density is given by the following diffusion-reaction equation,

$$n_t = \nabla \cdot D(x) \nabla n + (\epsilon(x) - n)n, \tag{1}$$

where $\epsilon(x) = 1$ ; $D(x) = 1$ in the favorable habitat and $\epsilon(x) = \epsilon$ ; $D(x) = D$ in the unfavorable habitat. We first numerically solve (1), for the case when a few propagules are initially released at the center. The results demonstrate that the population grows faster in the favorable habitat than in the unfavorable habitat, forming a wavy range front of an oval-like shape. The rate of spread toward any radial direction tends to be periodic in accordance with the spatial period so that the average speed becomes constant. Based on these properties, we derive an analytical formula for the average speed to any radial direction.

Analyses of the formula show that when $l_2$ is smaller than a threshold, the range has an oval-like shape elongated in the direction of the stripes when $D$ is small or large, and at an intermediate $D$, it shows roughly a circular shape as in the homogenous environment. On the other hand, when $l_2$ is larger than the threshold, the elongated shape becomes more rounded and shrunken with larger $D$ and ultimately goes to extinction.

## 69. COEVOLVING METACOMMUNITY EXTINCTION PROBABILITIES: A QUANTITATIVE GENETIC MODEL


**James W. Haefner *,**

DEPARTMENT OF BIOLOGY AND ECOLOGY CENTER, UTAH STATE UNIVERSITY, LOGAN UT 84322-5305
(JHAEFNER@BIOLOGY.USU.EDU)

Most predictions of extinction probabilities ignore evolution and community interactions, yet recent studies document rapid evolution in some plant and animal species. Quantitative genetic recursion (QGR) models combine population dynamics with the evolution of quantitative traits (body size). I describe a QGR model of 2 prey and 1 predator populations in which parameters are size-dependent so that populations are dynamic and body sizes (parameters) coevolve in all populations. In numerical simulations without spatial structure, the presence of predation induces complex dynamics of population numbers and evolving body sizes depending on genetic heritabilities. Evolutionary dynamics vary from stable fixed points at low heritability, to regular oscillations and chaos-like dynamics at intermediate heritabilities, and back to fixed points at extremely high heritabilities. I have added to this QGR model size-dependent dispersal among metacommunities and examined a range of parameter values in which, when evolution does not occur, one or more populations either go extinct or reach extremely low numbers. When evolution is added, the range of parameters at which extinction occurs is reduced, effectively lowering the probability of extinction. These model results suggest that nature reserve designs should incorporate community interactions and the potential for evolution of ecologically relevant traits.

## 70. Global Stability Analysis of a Stage-Structured Time-Delay Model

**Bo Feng *, Yasuhiro Takeuchi**

DEPARTMENT OF SYSTEMS ENGINEERING, FACULTY OF ENGINEERING
SHIZUOKA UNIVERSITY, JAPAN

We propose a time-delay model of one species, which has a life history and has been exposed to Environmental Hormones. The individual members of the population will grow through two stages, immature and mature. We sort the species into two groups: the affected or abnormal group ($N_{ai}(t), N_{am}(t)$ denote its immature and mature populations, respectively) and normal group ($N_{ni}(t), N_{nm}(t)$ denote its immature and mature ones, respectively). We obtain the model as the following system of retarded functional differential equations

$$\begin{cases} \dot{N}_{ai}(t) &= \alpha_1 N_{am}(t) + \alpha_2 N_{nm}(t) - \gamma N_{ai}(t) \\ & \quad -\alpha_1 e^{-\gamma\tau} N_{am}(t-\tau) - \alpha_2 e^{-\gamma\tau} N_{nm}(t-\tau) \\ \dot{N}_{am}(t) &= \alpha_1 e^{-\gamma\tau} N_{am}(t-\tau) + (\alpha_2 + \mu\alpha_3) e^{-\gamma\tau} N_{nm}(t-\tau) \\ & \quad -\beta N_{am}(t)(N_{am}(t) + N_{nm}(t)) \\ \dot{N}_{ni}(t) &= \alpha_3 N_{nm}(t) - \gamma N_{ni}(t) - \alpha_3 e^{-\gamma\tau} N_{nm}(t-\tau) \\ \dot{N}_{nm}(t) &= \alpha_3(1-\mu) e^{-\gamma\tau} N_{nm}(t-\tau) - \beta N_{nm}(t)(N_{am}(t) + N_{nm}(t)) \\ N_{am}(s) &> 0, N_{nm}(s) > 0, \text{ on } -\tau \le t \le 0 \\ N_{ai}(0) &> 0, N_{ni}(0) > 0 \end{cases}$$

where $\alpha_i (i = 1,2,3), \beta, \gamma, \tau$ are positive constants. The effect of the delay on the populations and the affection of environmental hormone are considered. We prove the positivity and boundedness of the solution and the uniform persistence of the system with mature group. We show that under suitable hypotheses there exist stable nonnegative equilibria. A boundary equilibrium, which is composed of only abnormal populations, is shown to be always globally stable when the coexistence equilibrium does not exist, by using the Lyapunov-LaSalle invariance principle. We find that the positive equilibrium point will be globally asymptotically stable under some conditions, that is, the population will survive although the environmental hormone gives some affection to their productivity.

## 71. A Dynamic Energy Budget Model to Determine the Optimal Length of Animals

**Glenn Ledder**

DEPARTMENT OF MATHEMATICS AND STATISTICS, UNIVERSITY OF NEBRASKA–LINCOLN

We construct a dynamic energy budget model for an arbitrary animal species, subject to the requirements that the adults do not care for their young and that the shape of an organism is not significantly altered as it grows and matures. The resulting model consists of three ordinary differential equations to determine the size (length) of the organism, the probability of survival, and the total amount of reproductive effort, all as functions of time. The essential question to be investigated for the model is that of what is the energy allocation strategy that will optimize the expected lifetime reproductive effort. In order to make further progress without restricting the investigation to a given species, we make the simplifying assumption that the species under consideration allocate all surplus energy to growth until achieving a particular length $X$ and subsequently allocate all surplus energy to maturation and reproduction, where surplus energy is taken to be the energy remaining after maintenance needs are satisfied. While this assumption is not strictly accurate for any species, it is a reasonable qualitative approximation for many. With this additional assumption, we have a problem of optimizing the expected lifetime reproductive effort as a function of the mature length. Ultimately, we obtain results regarding the optimal mature length as a function of several input parameters, including the density of predators, a parameter measuring the effect of prey size on the predation rate, and the death rate due to factors unrelated to predation. A secondary product of the analysis is the probability of survival to mature size, given in terms of the same parameters. Finally, we show that the model is capable of predicting a variety of qualitative phenomena, such as the existence of species that combine a large mature size with a very low probability of survival to maturity.

## 72. Effects of the oscillation in scale-eaters' lateral asymmetry polymorphism on the maintainance of polymorphism and species coexistence.

**Satoshi Takahashi*, Michio Hori**

NARA WOMEN'S UNIVERSITY

Scale-eating chiclid fish in Lake Tanganyika exhibit polymorphism in their mouth opening direction. Frequencies of morphs oscillates around the equilibrium, 0.5, in c.a. 5-year period, due to strong frequency dependent selection. Effects of this oscillation in two competing scale-eaters system have been investigated numerically as well as analytically. In most of cases, it promotes the coexistence of morphs in each species, while its effect to the coexistence of species depends on the growth periods of two species.

## 73. Simulating Ozone Damage To A Single Leaf

**Eric Calhoun*, Richard Reif and Dr. Eric Marland**

DEPARTMENT OF MATHEMATICS APPALACHIAN STATE UNIVERSITY

The mechanisms of damage to plant life by the air pollutant ozone are important to understand the potential effects of increased ozone exposure and for analyzing possible management strategies for sensitive areas. Our model is constructed and analyzed to quantify cellular damage. The model simulations will help understand cellular and plant responses to increased ozone levels and to characterize damage from different ozone exposures with the same mean level.

## 74. Implementation of Wavelets and Artificial Neural Networks to Patterning Movement Behaviors of Chironomid Larvae in Response to Sub-Lethal Insecticide Treatments

**Tae-Soo Chon*, Cheol ki Kim1, Inn-Sil Kwak, Mi-Young Song, Eui-Young Cha1, Eung Chon Cho2**

DIVISION OF BIOLOGICAL SCIENCES, PUSAN NATIONAL UNIV., PUSAN, 609-735 KOREA
1DEPARTMENT OF COMPUTER SCIENCE, PUSAN NATIONAL UNIV., PUSAN, 609-735 KOREA
2DIVISION OF MATHEMATICAL SCIENCES, KENTUCKY STATE UNIV., FRANKFORT, KENTUCKY, USA

Wavelets were implemented to pattern the movement tracks of an aquatic insect, Chironomus sp, after treated with an organophosphate insecticide, diazinon. The fourth instar larvae of Chironomus sp. were individually placed in an observation cage (6cm X 7cm X 2.5cm) at temperature of 18° with the light condition of 10LL: 14DD. Sublethal concentrations of diazinon (0.01ppm - 0.001 ppm) were exposed to the test insects in observation cages, and the two-dimensional movement tracks were individually observed for four days (1 day; before treatment, 3 days; after treatment) by using an auto-sensing system with an image processor. The treated individuals showed characteristic behaviors: irregular locomotive movements and the "ventilation activity occurred more frequently after the treatments of the insecticide. Basic functions including Daubechies series were implemented to the spatio-temporal data of the movement tracks, and Discrete Wavelet Transforms (DWP) mappings were produced to characterize different types of movements. The wavelet model was able to segment different patterns of movement and to point out time changes in patterns as input data were sequentially provided to the model. The parameters regarding amplitude terms on different dilations were further classified with an artificial neural network, Adaptive Resonance Theory. Through the process of training with the artificial neural network, different movements in response to the chemical treatment were learned in an unsupervised manner, and consequently the network was able to predict the pattern of new input data. Through Invert Discrete Wavelet Transform (IDWT) the image reconstruction for the movement tracks for the classified pattern was further possible. This combined computational patterning with the wavelet and the artificial neural network could be an alternative for in situ biomonitoring tool for detecting the presence of toxic chemicals in environments.

## 75. Random Urn Model: A simple learning system for i-state configuration IBM

**Yukihiko Toquenaga**

INSTITUTE OF BIOLOGICAL SCIENCES, UNIVERSITY OF TSUKUBA

Random Urn Model (RUM) is a simple and fast algorithm for learning for i-state configuration individual-based models (IBMs). Its learning algorithm is a variant of relative payoff sum (RPS) learning rules (Harley 1981, Regelmann 1984). RPS learning rules are efficient for static tasks but prone to be stuck for variable environment. To overcome this weakness, I supplemented it with a memory flush mechanism inspired by self-organized criticality (Jensen 1998).

I applied this algorithm for solving a classical central foraging problem proposed by Horn (1968). In the simulation, virtual birds forage in an arena from tentative roosts located by local enhancement. Resource distribution in the arena changes alternatively from even to clumped. This problem was too difficult for random foragers to survive. Locally omniscient foragers could maintain themselves in the arena. Individuals equipped with RUM performed almost equivalently with the omniscient foragers.

RUM can replace conventional learning systems (neural networks, genetic algorithms, and etc.) that require intensive calculation. RUM is very light and can be combined even with heavy Geographic Information Systems as well as popular IBM simulators (StarLogo, Swarm, and etc.).

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## 76. Periodic and quasi-periodic behavior in resource dependent age structured population models

**Rui Dilão*, Tiago Domingos**

GRUPO DE DINÂMICA NÃO-LINEAR. INSTITUTO SUPERIOR TÉCNICO. AV. ROVISCO PAIS, 1049-001 LISBOA, PORTUGAL

To describe the dynamics of a resource dependent age structured population, a general non-linear Leslie type model is derived. The dependence on the resources is introduced through the death rates of the reproductive age classes. The conditions assumed in the derivation of the model are regularity and plausible limiting behaviors of the functions in the model. It is shown that the model dynamics restricted to its $\omega$-limit sets is a diffeomorphism of a compact set, and the period-1 fixed points of the model are structurally stable. The loss of stability of the non zero steady state occurs by a discrete Hopf bifurcation. Under general conditions, and after the loss of stability of the structurally stable steady states, the time evolution of population numbers is periodic or quasi-periodic. Numerical analysis with prototype functions has been done, and the conditions leading to chaotic behavior in time are discussed.

## 77. Harvesting in a resource dependent age structured population model

**Rui Dilão*, Tiago Domingos, Elman M. Shahverdiev**

GRUPO DE DINÂMICA NÃO-LINEAR. INSTITUTO SUPERIOR TÉCNICO. AV. ROVISCO PAIS, 1049-001 LISBOA, PORTUGAL

We analyse the effect of harvesting in a resource dependent age structured population model, deriving the conditions for the existence of a stable steady state as a function of fertility coefficients, harvesting mortality and carrying capacity of the resources. We show that the harvesting yield can be periodic, quasi-periodic or chaotic, depending on the dynamics of the non harvested population. In some situations, for populations with large fertility numbers and erratic behaviour in time, small harvesting mortality can lead to abrupt extinction, but larger harvesting mortalities can lead to controlled population numbers by avoiding over consumption of resources.

## 78. Effects of simplifying stage-structured models on demography of long-lived seabirds

**Christine Hunter *, David Fletcher**

DEPARTMENT OF ZOOLOGY UNIVERSITY OF OTAGO DUNEDIN NEW ZEALAND
DEPARTMENT OF MATHEMATICS AND STATISTICS UNIVERSITY OF OTAGO DUNEDIN NEW ZEALAND

We explore how simplifying stage-structured matrix models affects population growth rate and perturbation analyses using the Short-tailed Shearwater (Puffinus tenuirostris) as a case study. Using deterministic matrix models we assess whether reducing; i) the number of pre-breeder age classes, ii) the number of breeding age stages, or iii) both, affected projected population growth rate (l), sensitivity analyses and elasticity analyses. Models with reduced pre-breeder structure projected slightly higher population growth rates but other simplifications had little influence on l. Simplification of model structure did not alter rankings of the sensitivities or elasticities of l to demographic parameters except for a higher ranking for the sensitivity of l to maturation rate in models with reduced pre-breeder structure. In general the change in the response of l to demographic parameters was greater when the number of breeding age stages was reduced than when the number of pre-breeder age classes was reduced. Expected lifetime event probabilities did differ among model structures. The possible effect of model structure on these measures should be acknowledged if they are to be used as internal validity checks or to assess population status. Our analyses show that population growth rate and perturbation analyses of deterministic stage-structured models can be expected to be robust to simplification of the number of model stages. Although our results are specific to the Short-tailed Shearwater they are likely to be relevant to other long-lived species with similar life history characteristics of high adult survival and low fecundity.

## 79. Permanence of Mathematical models with Intraguild Predation

**Masahiro Yamaguchi*, Yasuhiro Takeuchi**

GRADUATE SCHOOL OF SCIENCE AND TECHNOLOGY,
SHIZUOKA UNIVERSITY

There are numerous examples in natural communities of strong IGP (Intraguild Predation), that is killing and eating of prey species as a predator that also can utilize the resources of the prey (Polis et al. 1989). Many important problems in applied ecology involve a significant component of IGP. Holt and Polis (Holt and Polis 1997) had analyzed the population- and community-level implication of IGP. They clarify the condition for coexistence in systems with IGP and highlight the rich potential for alternative stable states. Further they show that IGP can generate unstable dynamics, which can lead to transient phases of low population densities and a heightened risk of extinction.
In this presentation we consider a Lotka-Volterra model with IGP as follows:

$$\begin{aligned} \dot{x} &= x(r_1 - x - \alpha y - \beta z), \\ \dot{y} &= y(-r_2 + \epsilon\alpha x - \delta_1 y - \gamma z), \\ \dot{z} &= z(-r_3 + \mu\beta x + \theta\gamma y - \delta_2 z). \end{aligned} \tag{9}$$

Here, $x$, $y$ and $z$ are respectively the density of the resource, the IGprey(Intraguild prey) and the IGpredator (Intraguild predator). The difference between (1) and the model Holt and Polis considered (Holt and Polis model) is that the former includes the parameter presenting self-density-dependency for IGprey and IGpredator but the latter does not. We show that adding this parameter changes the dynamics of the systems a little. Also, our research is especially focused on the permanence, which ensures the survival of all species. We obtain the sufficient condition and the necessary condition for the permanence. Further, we examine whether the unstable dynamics is chaos.

## 80. Mathematical Modeling of Human Chest Cavity Pendulum System

**Akinori Shiraishi:**
**Shiraishi Hospital, and Shiraishi Institute for Biophysical Research 1-11-11, Kosei-cho, Okayama-city, 700-0985 Japan***

Respiration and heartbeats in the chest are well known phenomena as life evidences. They have been carrying out O2 intake and distribution into the human body. Although, human being is strange about the existence of another function as human chest cavity pendulum system, but obviously this pendulum system skillfully has been undertaking the chronometer function by gravity potential so long as human alive.

Therefore human ontogeny is believed to repeat phylogeny in development process from embryo to baby, and also it is the same as to control gravity potential for human physical exercise. At first, infant do not walk on the earth at all, but grownup child could be able to walk everywhere. Thus, human chest cavity pendulum system has the function to utilize and accept the gravity, and at once to make gravity shield barrier in human body itself, so that becoming familiar with gravity potential in human evolution. This pendulum is composed from the heart; aorta, lungs and chest wall, and each function and structure build human chest pendulum system.

Chest wall builds cycloid curvature along human body longitudinal axis length, and anterior concave part of this curvature is faced and contacted to heart frontal surface. Lungs and respiration secures to maintain the necessary space for free motion in this pendulum system and to keep its cyclic angular velocity. Aorta is conceived to have the function to make free from the friction due to other tissues against this pendulum motion on chest cycloid curvature, acting just same like as the string of pendulum. Heartbeats function is acting as a pressure producing powerful pendulum as well as pendulum weight itself. This pendulum in the chest cavity is working in constrained motion dynamics and adjusting the gravity potential to us. Actually, human body inside is free from the gravity in human space on the earth, so that our life procedures exist in good controlled circumstances like the space shuttle free from gravity potential.

Human gravity potential sensitivity obviously exists in chest pendulum system. Usually it is reduced or adjusted by gravity shield barrier e.g. muscles exercise, and controlled by breath and heartbeats regulating nerves or human body surface pressure.

## 81. Evolutionary dynamics of growth strategy in game-theoretical situations in cannibalistic amphibians

**Joe Yuichiro Wakano *, Yukihiro Kohmatsu, Norio Yamamura**

CENTER FOR ECOLOGICAL RESERACH. KYOTO UNIVERSITY

Cannibalistic amphibian larval morphs, being characterized by greater head widths than typical morphs and therefore advantaged by having a larger mouth, provided a basis for the construction of a simple model of cannibalism that describes the growth dynamics of body shape. As the relative head sizes of interacting individuals determine the occurrence of cannibalism, the situation is game-theoretical. Because natural enemies more often predates individuals in more unbalanced body shape, there should exist the optimal growth schedule. Necessary condition for an evolutionarily stable strategy (ESS) is derived analytically and sufficient condition is checked by evolutionary simulation. When the probability of cannibalism is low, an ESS exists. In such cases, the body shape is more balanced (less adaptive to cannibalism) when predation pressure is higher and population density is lower. When the probability of cannibalism is high, there is no ESS. For such cases, a computer simulation of the evolutionary dynamics revealed that the dominant growth strategy changes cyclically. Development of a more detailed model of individual-based population dynamics showed that the qualitative results of the simple model held for the individual-based model. Accompanied by cyclic evolution, the number of surviving individuals at metamorphosis oscillated. The game theoretical models suggested that the evolutionary dynamics of cannibalism change drastically depending upon environmental conditions.

## 82. Bayesian modeling of HIV-1 dynamics during multiple interruptions of suppressive antiviral therapy

**Simon D. W. Frost (1) *, Javier Martinez-Picado (2), Lidia Ruiz (2), Bonaventura Clotet (2), and Andrew J. Leigh Brown (1, 3).**

(1) DEPARTMENT OF PATHOLOGY, UNIVERSITY OF CALIFORNIA, SAN DIEGO, USA. (2) HOSPITAL UNIVERSITARI GERMANS TRIAS I PUJOL, BADALONA, SPAIN. (3) INSTITUTE OF CELL, ANIMAL AND POPULATION BIOLOGY, UNIVERSITY OF EDINBURGH, SCOTLAND.

Our understanding of the dynamics of HIV-1 infection within the host has benefited greatly from the application of viral dynamics models to estimate key parameters, such as the rate of viral population turnover within the host, from measurements of viral load obtained from infected individuals at several timepoints. Usually such models have been fitted to data using a 'two-stage' process, where parameter estimates are obtained for each individual (often by a least-squares approach), with subsequent statistical analysis of these parameter estimates. This approach runs an increased risk of type I error for two main reasons. Firstly, viral dynamics parameters obtained for each individual may be biased due to few viral load measurements and/or measurements below the limit of detection. Secondly, errors in individual parameter estimates are not accounted for when average parameter values are compared between groups. We implement a Bayesian approach to fit viral dynamics models which helps to overcome these problems. Censoring of viral load measurements at the limit of detection and the placing of constraints on parameter values result in less biased estimates of viral dynamics parameters at the individual level, and errors in individual parameter estimates are taken into account when calculating averages. A Bayesian approach also has the additional advantage of producing readily-interpretable probability distributions for each parameter. We apply this approach to the dynamics of viral rebound during multiple interruptions of therapy in 11 chronically HIV-1 infected individuals with a prior history of viral load suppression during therapy. We demonstrate a shift in viral dynamics over successive interruptions (a) to lower rates of viral rebound, representing increased control of viral replication, (b) higher viral loads present at the beginning of each interruption, representing increases in long-lived viral reservoirs, and (c) an increased tendency to display spontaneous drops in viral burden, which may reflect a complex interaction between viral replication and the host immune system.

## 83. Why Sex Change is Common in Fishes, but Not in Plants? Role of Information in Size-dependent Sex Allocation:

**Kumazawa, Takao *, Iwasa, Yoh**

DEPARTMENT OF BIOLOGY, KYUSHU UNIVERSITY

Sex reversal is relatively common among coral fishes, whilst it is rare among terrestrial plants in which simultaneous hermaphroditism is much more prevailing. We here propose that the availability and the accuracy of the information on the state of neighboring competitors might be responsible for this difference.

We consider a sex-allocation game played by a pair of individuals which are chosen randomly from a population that is composed of individuals of either large or small size. At the time of decision making of sex allocation, each player knows the exact size of its own but also knows the size of the competitor with some error. To be concrete, each player determines its sex allocation based on an available cue that is correlated with the competitor's size–the strength of correlation indicates the degree of reliability of the cue. the ESS is calculated considering the size of the two players, inbreeding depression, and potential shortage of male gametes (e.g. sperm/pollen limitation). If both inbreeding depression and the shortage of male gametes are strong, the ES sex allocation is very sensitive to the availability and the accuracy of the information. Under these conditions, small players often become male and large players become female when an acculate cue is available, whilst players in both size tend to be hermaphroditic producing both male and female gametes at the same time. In the other conditions, however, the information does not significantly affect the ES sex allocation. These results support the interpretation that sex change is rare and hermaphroditism is prevailing among terrestrial plants because of the availability of the reliable cue concerning the competitor's size among fish much more among plants.

## 84. 3D Simulations of bacterial flagellar motion by the Immersed Boundary Method

**Sook Kyung Lim*, Charles S. Peskin**

COURANT INSTITUTE OF MATHEMATICAL SCIENCES, NEW YORK UNIVERSITY

We introduce a mathematical and computational model of bacterial flagella equipped with reversible rotary motors. The direction of motor's rotation determines whether the flagella wrap around each other to form a superflagellum that can propel the cell body through the fluid, or whether the flagella fly apart and the cell body just tumbles in place.

We use the Immersed Boundary (IB) method to study the interaction between the flexible flagella and the surrounding viscous fluid as governed by the incompressible Navier-Stokes equations.

Although the goal is to model a whole bacterium (*E. Coli*) and its six to eight flagella, current work is on the warm-up problem of two or three flagella attached (via their motors) at their base to a planar wall. Two cases are compared: one in which the flagella rotate so that helical waves propagate away from the wall, and another in which the direction of rotation is reversed so that the helical waves propagate towards the wall. The motions of the interacting flagella and the surrounding fluid are compared to those of isolated flagella.

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## 85. The role of asymmetric mutations in the development of new lineages for influenza B virus

**Prasith Baccam *[1], Philip Gerrish[1], Ismael Velazaquez[2], Catherine Macken[1]**

[1]LOS ALAMOS NATIONAL LABORATORY, [2]UNIVERSIDAD AUTONOMA METROPOLITANA

The influenza B virus differs from the influenza A virus because the former lacks distinct hemagglutinin serotypes. Influenza B hemagglutinin does, however, have distinctly different lineages that have co-existed since about 1976 and are characterized by the Yamagata/16/88-like variants and the Victoria/2/87-like variants. Furthermore, serum derived from Yamagata-like variants provides better protection against Victoria-like variants than does serum derived from Victoria-like variants against Yamagata-like variants. The goal of this study was to examine the molecular evolution of influenza B hemagglutinin variants to understand how the two lineages may have arisen and how the asymmetric cross-protection may have occurred.

Previous work with mathematical simulations led us to believe that different virus variants can only co-exist in a stable manner if their differences result in symmetric cross-protection. Thus, we hypothesized that the development of distinct lineages for influenza B hemagglutinin arose initially from amino acid changes of a conservative nature eventually followed by changes of a non-conservative nature. At some point, geographical separation may have also played a role in the separation of these lineages.

We used phylogenetic analysis to examine 57 influenza B hemagglutinin sequences from 1940-1989. We found that the earliest mutations in the Yamagata-like ancestor and the Victoria-like ancestor around 1976 were mostly conservative changes, and subsequently, non-conserved changes were accumulated. Interestingly, around 1987-1988, more conservative changes were observed in both lineages. If our hypothesis holds true, then these latter conservative changes might signal the development of new lineages. Additional phylogenetic analysis with an expanded data set of sequences from 1940-2000 confirmed that the Yamagata-like and Victoria-like lineages did indeed develop distinct sub-lineages. In agreement with our hypothesis, we found that most conservative changes were observed in the sub-lineages during the period of 1988-1989, coincident with the development of the new sub-lineages. Interestingly, the other conservative changes were observed among the Yamagata-like sub- lineages around 1994 and coincided with the further splitting of the sub-lineages. We hypothesize that the accumulation of conservative changes may precede critical non-conservative changes and thus may be used to predict the development of new lineages for the influenza B virus.

## 86. A Strong Bias in Estimating Ecological Processes from Spatial Data, and a Method of Bias Correction Based on Bootstrap Sampling: A Case Study of Neotropical Panamanian Forest.

**Akiko Satake(1) *, Yoh Iwasa(1), and Stephen P. Hubbell(2)**

(1) Biology, Kyushu University, Fukuoka 812-8581, Japan. (2) Botany, Georgia University, Athens, GA 30602, USA.

Treefalls in forests create canopy holes or "gaps", which are subsequently filled by the growth of young trees or the branch extension of neighboring trees. Studies of gap spatial dynamics in tropical and subalpine forests have demonstrated that new gaps are more likely to occur adjacent to pre-existing gaps, indicating a strong link of gap formation and the state of neighbors. We study a spatial Markov process for gap dynamics, in which the forest is composed of many sites arranged on a regular square lattice. Each sites is either a gap or a non-gap, and changes its state between the two stochastically. The rate of transition is a sum of independent rate and neighbor-dependent rate increasing with the number of gap sites in the surroundings [1]. If the rate of transition is estimated by maximum likelihood method from spatial data in two consecutive years, independent transition rate is consistently overestimated but neighbor-dependent rate is underestimated. We show the reason for this bias, which is produced whenever multiple transition events occur in the neighbors. This bias exists in estimating interacting parameters from spatial data in any continuous-time spatial Markovian models. We then adopted a bias correction method based on a Bootstrap sampling [2], which was very effective. The model was applied to the data from a 50 ha plot of a neotropical forest in Barro Colorado Island, Panama. We also study a pair-approximation analysis of the model and show that the predictability of the analysis was greatly improved if the Bootstrap bias correction of parameter estimation was adopted. [1] Kubo T, Iwasa Y Furumoto N. (1996) JTB 180: 229-246. [2] Hakoyama H Iwasa Y (2000) JTB 204: 337-359.

## 87. Dynamics of Two-Strain Influenza with Isolation and Cross-Immunity

**Miriam Nuno *, Carlos Castillo-Chavez, Maia Martcheva, Zhilan Feng**

Cornell University

The evolution of influenza type A virus is tightly linked to a non-fixed evolutionary landscape driven by tight coevolutionary interactions between hosts and influenza strains. Cross-immunity, host isolation, and age-structure are three important factors responsible for the coexistence and dynamics of multiple strains of influenza. Here, it is shown that cross-immunity and host isolation are enough to support the possibility of multi-strain epidemics. In fact, sustained oscillations with reasonable periods are possible. We establish the possibility via Hopf-bifurcation theory, and illustrate our results with simulations. The length of the period agrees with reported data.

## 88. Pigmentation Patterns in the butterfly wing of *Papilio dardanus*

**Toshio Sekimura *, Anotida Madzvamuse[1], Andrew J. Wathen[1] and Philip K. Maini[2]**

Department of Biological Chemistry, College of Bioscience and Biotechnology, Chubu University, Kasugai, Aichi 487-8501, Japan

[1]Oxford University Computing Laboratory, Wolfson Building, Parks Road, Oxford OX1 3QD, UK

[2]Centre for Mathematical Biology, Mathematical Institute, University of Oxford, 24-29 St Giles', Oxford OX1 3LB, UK

The butterfly ***Papilio dardanus*** is well known for the spectacular phenotypic polymorphism in females that has evolved as different geographic races have come to mimic an array of different model spiecies in theier specific regions. The females show more than a dozen different wing color patterns, of which several mimic different species of unpalatable danaids, other butterflies, and moths.

We have developed a reaction-diffusion model for the formation of wing color patterns, which has been simulated on a geometrically accurate wing domain. Our results show spatial patterns that are consistent with many of observed on the butterfly, for example, global patterns which cover the whole wing surface. We also find a hierarchy in relatedness of female patterns by combination of some key factors of mathematical and computational analyses, which is strikingly consistent with another one obtained by a morphmetric analysis. The discussions on the relatedness hierarchy are very interesting from the evolutionary point of view.

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## 89. A New Method for Estimating the Parameters of Disease Dynamics

**Mojdeh Mohtashemi***

MIT LABORATORY FOR COMPUTER SCIENCE
AND
HARVARD SCHOOL OF PUBLIC HEALTH

Mathematical models have proven vital to understanding the dynamics of microparasites and their behavior under interaction with host's defense components or anti-parasitic therapy. To better understand the pathogenesis of a microparasite, the role and significance of host's defense mechanisms, and the efficacy of therapeutic regimen, there is an ever increasing need for quantification of the related pathological, immunological, and therapeutic parameters of the system under study.

Most dynamical systems, to be reasonably representative of the underlying disease dynamics, are nonlinear and contain more than one variable. Such inherent complexities significantly reduce the chance of obtaining analytic solutions for the interacting variables. Furthermore, for most infections, there is seldom data available on more than one component. Such obstacles in achieving the task of parameter quantification, have motivated investigators to research alternative methods of inference from limited information. One such approach for estimating the parameters of a multi-dimensional nonlinear system of ordinary differential equations is based upon reducing the number of equations, thereby reducing the degree of nonlinearity, by making stability assumptions for durations of interest.

We propose an alternative approach for estimating the parameters of a nonlinear system of ordinary differential equations based on the elimination method to transform a system of $n$ ordinary differential equations into a single equation of order $n-1$ in one variable, usually the variable for which quantitative information exists. The new parameters in the reduced system will then be combinations of the original parameters. In addition, there are $n-1$ differential operators of the variable of interest to estimate. To estimate the system parameters, the differential operators must first be estimated. This methodology is quite useful when inference based on analytic solutions are desired, yet stability assumptions do not apply or are not realistically reasonable.

## 90. Spatial Pattern Formation in a Model Ecosystem: Exchange between Symbiosis and Competition

**K. TAINAKA*, N. TERAZAWA, N. YOSHIDA, N. NAKAGIRI, and Y. TAKEUCHI**

DEPARTMENT OF SYSTEMS ENGINEERING, SHIZUOKA UNIVERSITY, HAMAMATSU 432-8561, JAPAN

There are many different interaction between species, such as mutualism (symbiosis), parasitism and competition. Recently, ecologists have been interested in various relationship between the number of species in a food web. The relationship between two predators which share a prey is represented by competition. On the other hand, the predators often have the indirect relationship of mutualism; increase in the number of one predator often increases the ability of prey defense for the predator. This is an advantageous situation for the second predator. The population size of the second predator tends to increase. An example of such a two-predator system is a couple of cichlid fishes in the African lake (Tanganyika); one attacks prey from the behind, while the other attacks the same prey from the front. In the present paper, we apply a lattice Lotka-Volterra model to such a two-predator system and illustrate that the exchange of relationship between competition and symbiosis takes place, depending on values of a parameter. While interaction parameters between species are fixed, spatial distribution of species naturally evolves into a specific pattern of either competition or mutualism.

## 91. Ecological Eigenvalue Problem Approach for Behavioral Analysis of Tumor

**Mitsuo Takase ***

3013-1-503 FUTOOCHOU KOUHOKU-KU YOKOKAMA, 222-0031, JAPAN
03154@NIFTYSERVE.OR.JP

Whether tumor cells can become prosperous or not is ecological problem. Here, a mathematical model like an eigenvalue problem is proposed to achieve the following purposes. This model is the first step for the purposes. Some of them are partly known from the model presently and shown.
Purposes
(1)To know how often tumors grow in human beings in comparison with other animals from the point of evolution, immune system, etc.
(2)To know in what state and by what probability tumors grow.
(3)To know how bad tumors can be cured enhancing health by immunity etc., which human beings have by nature, with auxiliary healthy methods. Moreover, what healthy methods and life are most efficient?.
(4)To know whether mathematical or simulation models can become a supporting method to know tumor states with inspections to make remedy strategies.

2. Mathematical model:
{x}=(1/r)[A][S]{x} (1): eigenvalue expression
{ym}=[A][S]{ym-1}; m=1,2,3,... (2): recurrent expression
The norm of the {x} is 1. r, [A], [S] and {x} change like a step function at each metastasis.
r.....the largest eigenvalue. This means the increase rate of tumor cells at all the positions, where there are tumor cells, of a body.
{x} .....the eigenvector. Each element xi of the vector means a tumor cell density rate at position i of the body.
{ym} .....the vector whose element yim means tumor cell density at position i of a body and at time m.
[S].....increase matrix of cells. Each diagonal element sii i=1,...,n means the increase of cells at each position. All the elements except the diagonal elements are zero. sii depends on the increase rate of tumor characteristics and each local tumor environment.
[A].....the matrix which expresses metastasis. Each diagonal element aii=1 i=1,...,n. aij, which is not a diagonal element,

is usually zero and becomes a small value only for an instance by probability. This probability depends on the scale, the location, the characteristics and the local environment of each existent tumor at another location j from where tumor cells are transported.

3. Process from the usual state without any tumor to tumor production Frequently tumor cells are produced, but they are usually weak and killed in a short time. r=1-e<1 is kept for broad kinds of tumor cells by NK cells etc. in immunity. When tumor cells with bad characteristics appear or immunity level becomes low for a period, by probability the tumor cells rest long and adhere to a tissue producing veins and make a tumor colony.

4. Meaning of recovery from tumors A tumor colony etc. have advantages for the tumor cells and increase r, because a tumor with an environment to protect from NK cells etc. is prosperous and rests. Therefore, the recovery means to keep r<1 for a long time using chemotherapy etc. and to destroy the colony and the environment and to reach r=1-e<1 without therapy.

5. Discussion:
(1) Long keeping of r=1-e¡1 is necessary for the complete recovery after the disappearance of a tumor. z1 is the number of tumor cells. z2 is the number of tumor cells at disappearance of tumor. z3 is a few tumor cells just before the recovery. Then, the term from z1 to z2 is m1=log(z2/z1)/logr, and the term from z2 to z3 is m2=log(z3/z2)/logr.
(2) An immune level and a production probability of tumor cells with a strongly increasable, adhesive, vein productive and survival characteristics can become main factors for r>1, so there is possibility for the production probability of a tumor to be known with these data.

## 92. THE ESS REPRODUCTIVE SCHEDULE OF TWO GROUPS OF MALE FROGS, DIFFERING IN MATING ADVANTAGE, MORTALITY COST, AND INFORMATION.

**Genki Wada*, Yoh Iwasa**

DEPARTMENT OF BIOLOGY, FUCULTY OF SCIENCES, KYUSHU UNIVERSITY, FUKUOKA 812-8581, JAPAN

In some frogs, sexually active males emit vocal signals to attract females. But not all adult males are active every night. In this paper, the ES schedule of reproductive activity of males is calculated. Assumptions are: reproductively active males wait for the arrival of receptive females in a mating arena. Each female mates with a single male and then leaves. Active males have a higher mating success but suffer a higher mortality than inactive males. There are two groups of males with different body size; large males have an $\alpha$ times higher chance of mating than small males. Larger males tend to suffer more than smaller males when active. The initial number of males in the two groups are given. The ESS fraction of reproductively active males in each group was solved as a function of date using dynamic programming.

[Smooth dependence on the reproductive advantage] The ESS level of reproductive activity schedule is rather insensitive to the change in $\alpha$(relative mating success between the two groups).

[Abrupt change with relative daily mortality] It critically depends on the relative magnitude of daily mortality of active males between two groups. Males with a higher daily mortality when active tend to be less reproductively active than the males with a lower mortality. The ES activities of the two groups depend smoothly on $\mu_l$ and $\mu_s$ where when $\mu_l > \mu_s$ or when $\mu_l < \mu_s$, but they change abruptly when $\mu_l = \mu_s$.

[Role of information] We studied the case with an asymmetry in available information between two groups – one group of males know the mean reproductive activity of the other group when they choose their reproductive activity. In the ESS, irrespective of the relative size, the males who know the activity of the other group tend to show all-or-none activity. whilst the males who don't know the other group's activity often take an intermediate level of activity.

## 93. Scale independent representation and analysis of biological sequences using iterative maps

**Jonas S Almeida*, Susana Vinga, Madylin Fletcher**

DEPT BIOMETRY EPIDEMIOLOGY, MEDICAL UNIV SOUTH CAROLINA, CHARLESTON, SC, USA, INST TECNOLOGIA QUIMICA E BIOLOGICA / UNIV NOVA LISBOA, R QTA GRANDE, 6, 2780 OEIRAS, PORTUGAL, BELLE W BARUCH INSTITUTE OF MARINE BIOLOGY AND COASTAL RESEARCH, UNIV SOUTH CAROLINA, COLUMBIA, SC, USA

The authors have recently established that the scale independent representation of genomic sequences by iterative maps is also a modeling technique (Jonas S. Almeida et al. (2001)). Analysis of genomic sequences by Chaos Game Representation, Bioinformatics 17: 429-437]. We have subsequently extended the basic technique to represent Markov Chain tables of non-integer order. Given the fact that redundancy is characteristically built in Biological sequences, the maximal functional correlation is expected to take place for a fractal sequence resolution. The extraction of non-integer order Markov Chains is illustrated for both Prokaryote and Eukariote sequences, for individual genes and for full genomes. In addition, the generalization of the iterative mapping for other alphabets was achieved by defining unit n-block domains. Consequently, iterative mapping may represent the bridge between discrete and continuous domains that will allow the use of well established statistical mechanics techniques to analyze biological sequences.

## 94. The Wright-Fisher Model with stochastically varying population size

**Akinori Sano**

INSTITUTE OF NATURAL SCIENCES, NAGOYA CITY UNIVERSITY

Let $N_t(\omega') := Nn_t(\omega')$ be a right-continuous stochastic process describing the population size, where $N$ is a positive constant. For fixed $\omega' = \omega_0$, we define our model.

We consider a 2-allele model including mutation and selection. The allele $A_1$($A_2$ resp.) changes to $A_2$($A_1$ resp.) with rate $u/N$($v/N$ resp.) per generation. Suppose that the selection coefficient is $s/N$, and the heterozygous effect is $h$ (See Gillespie's book, Population, Genetics A Concise Guide, pp.52-54). The frequency of $A_1$ at generation $k$ is denoted by $X_N(k)$, which changes to $X_N^{**}(k)$ after mutation and selection. The law of $X_N(k+1)$ is given by $P\left[X_N(k+1) = \frac{j}{N_{k+1}}\right] = \binom{N_{k+1}}{j}\{X_N^{**}(k)\}^j\{1 - X_N^{**}(k)\}^{N_{k+1}-j}$. Put $N_k = N_{\frac{k}{N}}(\omega_0)$. Define $x_N(t) = X_N([Nt]) + (Nt - [Nt])(X_N[Nt] + 1) - X_N([Nt])$, and the trajectries of the Markov chain $\{X_N(k)\}$ are embedded into the space of continuous trajectries. The limitting process of $x_N(t)$ as $N$ tends to infinity is realized as the solution $\{x(t)\}$ of the following stochastic differential equation.

$$dx(t)(\omega) = \sqrt{\frac{1}{n_t}x(t)(1-x(t))}dB_t^{\omega_0} + b(x(t))dt \quad (1)$$

with initial condition $x(s) = x \in [0,1]$ where $b(x) = u - (u+v)x + sx(hx + (1-h)(1-x))$.

SDE(1) with $b(x) = -ux$ can be applied to the infinite allele model. We can obtain the equation which the average heterozygosity $H(t)$ satisfies. Namely

$$\frac{d}{dt}H(t) = -\frac{1}{n_t}H(t) + 2u(1 - H(t))$$

which appears in Iizuka(2001). Define $\psi(t) = \int_0^t (1/n_u)du$. The time changed process $y(s) = x(\psi^{-1}(s))$, where $x(t)$ is the solution of SDE (1) with $b(x) = 0$, can be shown to be the neutral diffusion without mutation and selection. As an application, we can obtain the distribution of the coalescence time of 2 genes, which is related to Griffiths-Tavaré(1994).

## 95. Evolution of Dispersal in Spatially Structured Heterogeneous Habitats

**David Hiebeler** *

DEPT. OF BIOMETRICS, DEPT. OF ECOLOGY AND EVOLUTIONARY BIOLOGY, AND CENTER FOR APPLIED MATH, CORNELL UNIVERSITY

Dispersal is a key aspect of an individual's life history, since it determines the context within which the rest of that life history is played out. Also, habitat loss and fragmentation play an increasingly important role in the fate of populations. I investigated the evolutionary stability of local versus long-distance dispersal strategies (e.g. wind-dispersed seeds versus clonal growth, or seeds with varying dispersal distances), on heterogeneous landscapes with varying amounts of suitable habitat and varying levels of spatial correlations in habitat type. The effects of the spatial distribution of habitat on the two dispersal strategies was mapped out. When the habitat is highly clustered, short-distance dispersal is advantageous, since those seeds will be more likely to land on suitable habitat. For many patterns of habitat distributions, long-distance dispersal is advantageous since it reduces competition between siblings by reducing spatial clustering of the population. There are also some habitat distributions for which neither strategy can invade the other, and those for which the two strategies can invade each other, i.e. they coexist. Spatially explicit stochastic computer simulations were used, which take approximately one week to run, as well as pair approximations, which take less than two seconds to numerically solve and which predict the simulation results quite accurately.

## 96. Population dynamic interference between two childhood diseases.

**Chris. J. Green** *, **Pejman Rohani, Bryan. T. Grenfell**

DEPARTMENT OF ZOOLOGY, UNIVERSITY OF CAMBRIDGE, CAMBRIDGE, CB2 3BU, U.K.

Many single infection models of infectious diseases assume no ecological interaction between different pathogens. However, as different parasites effectively compete for susceptible hosts, there may be an indirect interference effect of one species on the dynamics of another through the removal of such hosts, be it temporary or permanent. This effect may be amplified in human populations, as following an acute infection individuals often convalesce at home, and are therefore temporarily shielded from subsequent reinfection with a different parasite. Depending on the pathogenicity of the disease and/or host condition the infected individual may also die, resulting in permanent removal from the susceptible class of the other disease. We present a two disease model to examine this hypothesis, and show significant dynamical consequenses are predicted. We look for this interference signature in historical data for measles and whooping cough deaths in European cities.

## 97. Dynamics of Naive and Memory CD4$^+$ T-Lymphocytes in HIV-1 Disease Progression

**Seema H. Bajaria*#, G.F. Webb[1], Miles Cloyd[2], Denise Kirschner***

* DEPARTMENT OF MICROBIOLOGY AND IMMUNOLOGY, THE UNIVERSITY OF MICHIGAN MEDICAL SCHOOL, ANN ARBOR, MICHIGAN

# DEPARTMENT OF BIOMEDICAL ENGINEERING, THE UNIVERSITY OF MICHIGAN, ANN ARBOR, MICHIGAN

[1] DEPARTMENT OF MATHEMATICS, VANDERBILT UNIVERSITY, NASHVILLE, TENNESSEE

[2] DEPARTMENT OF MICROBIOLOGY AND IMMUNOLOGY, UTMB, GALVESTON, TEXAS

The typical progression of HIV-1 infection is fairly consistent across populations – a gradual depletion in $CD4^+$ T cells over 8-10 years together with a viral load that reaches a set point early on and then rises in end stage disease. As HIV-1 infection results in immune system dysfunction, understanding the dynamics of key cells in the immune response, namely $CD4^+$ naive and memory T cells, can help elucidate the typical progression through acute, asymptomatic, and end stage disease. As the majority of infection occurs in the lymphoid reservoir, the circulation of cells between the two compartments of blood and lymph tissues (LT) is an essential component of immune-viral dynamics. An important mechanism of $CD4^+$ T cell depletion is homing-induced apoptosis, which is upregulated during infection. We develop a virtual human infection model based on naive and memory subsets of $CD4^+$ cells, infected cells, and virus circulating between blood and LT. Our model is novel in that it is the first to predict the three-stage behavior of both long-term non-progressors as well as typical progressors, based on respective host and viral characteristics. We further predict the mechanisms of HAART treatment on cell and viral dynamics in both blood and lymph tissues.

## 98. Joint Population Dynamics of Loblolly Pine and Southern Pine Beetle: A Simulation Model

**John Bishir*, James H. Roberds**

*Department of Mathematics North Carolina State University Raleigh, NC USA 27695-8205, USDA Forest Service Southern Research Station Harrison Experimental Forest 23332 Highway 67 Saucier, MS USA 39574

A computer simulation model was developed to examine patterns for deployment of selected genetically improved tree clonal material, in the presence of a known pest or pathogen. This talk reports on model simulation of the interaction between Loblolly Pine, an economically important forest crop in the southeastern U.S., and the Southern Pine Beetle, the major pest for this species. Initial impetus for the model, and the focus of these simulations, is the growing private and government interest in use of clonally propagated seedlings in commercial stands. The central question is: What deployment patterns - e.g., clonal blocks or random mix of seedlings from all clones - produce the greatest yield? In the model studies, beetle population dynamics, together with associated stand growth and mortality, are simulated from time of planting until harvest. Deployment patterns are compared in terms of average total merchantable volume of timber per hectare at time of harvest.

## 99. Evolutionary Basis of Bioinformatics Education: Phylogenetic Profiling to Investigate Evolutionary Traffic in Genes Complementary to Protein Trafficking in One Cell with Three Genomes

**John R. Jungck *, Sam Donovan and John Greenler**

BioQUEST Curriculum Consortium, Department of Biology, Beloit College, 700 College Street, Beloit, WI 53511
@beloit.edu
://www.bioquest.org/bioinformatics)

With the extraordinary number of opportunities available to scientists with expertise in bioinformatics, numerous institutions are beginning to develop courses and curricula at both the undergraduate and graduate level. In response to this challenge, the BioQUEST Curriculum Consortium (BioQUEST = Quality Undergraduate Educational Tools and Simulations in Biology), a fifteen year old national curricular reform initiative, in collaboration with EOT-PACI (Education, Outreach and Training - Partnership for Advanced Computing Infrastructure), is developing problem solving approaches to bioinformatics that stress the foundational importance of evolutionary biology. While many definitions for bioinformatics exist, Ming-Ying Leung and J. Aaron Cassill (NSF DUE EMD Award - 9981104) have defined bioinformatics as the "study [that] integrates mathematical and computational techniques with biological knowledge to extract, organize, and interpret information from a wealth of genetic sequence data obtained from various genome projects." This foregrounding of mathematics and computer science in bioinformatics education has meant either that students major in these two disciplines with a minimal exposure to biology or that students in biology take almost all of their cognate coursework in these two areas. Unfortunately, both types of extant programs have to date ignored any deep education in evolutionary biology. BioQUEST has a long history of trying to help undergraduates learn long term strategies of research by working on open-ended problems with powerful professional tools with a consistent learner-centered pedagogical philosophy: problem posing, problem solving, and persuading peers. In this case, we (http://www.bioquest.org/bioinformatics) have combined the use of a powerful bioinformatics package, Biology Workbench, (http://biology.ncsa.uiuc.edu) (http://workbench.sdsc.edu) developed at the supercomputer centers at the University of Illinois and the University of California San Diego, with typologies of evolutionary problem solving that we have developed to differentiate between spatial, temporal, and genealogical hypotheses or between evolutionary, genetic, and developmental biological levels of analysis. With bioinformatics, evolutionary biologists have the potential to inform students on how it is a powerful heuristic for interpreting DNA, RNA, and protein sequence homology based upon orthologous, paralologus, and xenologous relationships.

The BioQUEST Curriculum Consortium is funded through 2004 by grants from the Howard Hughes Medical Institute, EOT-PACI (Education, Outreach and Training - Partnership for Advanced Computing Infrastructure), and several awards from the National Science Foundation (Three NSF DUE EMD Awards including: Biology Student Workbench: Inquiry Tools for the Use of Molecular Data in Undergraduate Biology NSF Award Abstract 9950689).

## 100. Modelling collective cell behaviors using statistical field mathematics

**E.G. D'Ambrogio** *,

UNIVERSITAT DEGLI STUDI DI TRIESTE, TRIESTE, ITALY

An interesting phenomenon observed in computer simulations of stochastic models for capillary network formation, is the tendency towards cell density modulation as a consequence of parametric resonance phenomena and threshold effects, (E.G. D'Ambrogio, 2001). The present study deals with further, non-linear, developments of this kind of reaction-diffusion models, taking into account the influence of radiation. The electromagnetic debate has gathered novel interest in Italy, since electromagnetic pollution due to strong radio-frequency sources has been detected in residential areas. When the field strenght is sufficiently high, the threshold and, or, the resonance for stimulated processes in the cell population will be reached, so that the non-linearity will enter the dynamics of the system and noticeable, or even new, phenomena can be expected. The purpose of the present work is to discuss the biological relevance of a theoretical approach to the multibody interaction problem in cellular populations based on the classic, electro-hydrodynamic, formulation of a set of one-dimensional partial differential equations involving different cell species. One recognizes that the approach provides a way, which depends on the assumption regarding the origin of the field, to derive the analytical background for modelling a rather wide class of problems of cellular dynamics. In particular, the capabilities of the model will be shown: i) to provide intriguing aspects regarding loops of wessels in tumor related angiogenesis; ii) to reproduce some qualitative features of the tumor-immune system competition as already known within the context of nonequilibrium statistical mechanics. We conclude the presentation with some remarks regarding the problem of the parametric identification.

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Morabito, Sacerdote, Pontrelli, Zanetti夫妻, 竹内, 佐々木, 望月, 中垣, 伊藤, 三村
斎藤, 瀬野, 佐藤, 稲葉, 松下, Pugliese, 向

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# 報告記

瀬野裕美（広島大学大学院 理学研究科 数理分子生命理学専攻）

この研究集会は日本応用数理学会とイタリア応用数学会の後援のもとで行なわれる日ー伊共同研究集会の第2回でした。第1回はナポリで行なわれ、トピックスは数値解析だったということです。この回は日本で行なうことになり、主に数理生物学に焦点を当てたものとして，三村昌泰氏が日本側の実際的アレンジを行ったものです。報告記を掲載していただくには少々日数も経ってしまい，報告書として投稿させていただくには，新鮮さが欠けるかも知れませんが，とても刺激的な研究集会でしたし，幸い，組織委員会のお手伝いを経験させていただきましたし，感想文もかねた報告文を敢えて投稿させていただくことにしました。

研究集会は，神戸駅からタクシーで15〜20分の高台にある神戸インスティテュート[1]で，参加者は原則として全泊の泊まりがけ4日間で行われました。講演は全て招待講演の形で行われ，日本側から15，イタリア側から6の計21の30分講演が11月13日午後2時から16日午前11時30分までのプログラムに組まれました。実際には，各講演の持ち時間が30分とはいえ，各講演の間にbreakも込めた15分間の間隙時間がとってあり，講演にとっても，聴衆にとってもゆったりしたプログラムとなっています。このようなゆったりとしたプログラムは，講演数を十分に小さくし，日程を延ばすか，1日の総講演時間をのばすことによって実現できるでしょうから，一般には実現が難しいかも知れません。実現できるならば，講演者にとって，次の講演の開始

[1]同施設については，http://www1.biz.biglobe.ne.jp/~kobeinst/を参照してください。

時間を犯さないようにという緊張や，プログラム全体の遅れを気にしなければならない意識が必要ないのは相当に気持ちが楽なのではないでしょうか。また，場合によっては，質疑応答にあてることのできるように用意された時間15分ですら足りないということもあるかもしれませんが，実際には，15分という間隙の時間長は，講演直後に司会の方を通じて質疑応答を行うだけではなく，次の講演の開始までに直接講演者に話をしにいくのにも十分であり[2]，この意味でも，15分が適当だったと思われます。もしも，これが20分だと，プログラムが少々間延びしてだれてしまったかもしれません[3]。なお，午前の9:00〜11:30，午後の14:00〜17:15が集会のメインディッシュであり，夕食後の時間は，集会のおいしいデザートにとってありました。

ヨーロッパで開かれる国際研究集会のプログラムでは，しばしば，(とりわけ) お昼から午後の時間帯がゆったり作ってあることが多く，また，日照時間の長い（高緯度の）場所で開かれた場合には，夕方から夜7時や8時にかけてのセッションというのもままあります。今回の研究集会は，決してそのような場所で開かれたわけではありませんが，参加者全員が会場に併設されている宿泊施設に宿泊して，という特徴もあり，夕食の始まる6時近くまでのんびりと構えて講演，議論を行ったため，ほとんど毎日，夕食時間ぎりぎりまで講演もしくは議論が行われていました。夕食後には，会場の施設の別室（談話室のような感じの場所）に移動し，懇親会というパターンでした。懇親会では，いろんなグループがいろんな議論（やお喋り!?）をしていたのですが，もちろん，研究に関わること，学問のあり方から，日本文化の話まで話題は実に多種多様でした[4]。なお，国際研究集会では，しばしば，開催日程の中日あたりに午後の半日自由な（一切の講演がない）時間がもうけてあるプログラムが作られますが，今回のプログラムでは，11月13日午後2時から16日午前11時30分まで講演はびっちりでした。イタリア人参加者の観光は，会期前もしくは会期後という形にしていただくということになりましたが，参加者からのそれに対する不満は聞かれませんでしたし，そうした半日の自由時間をとったがためにプログラムが窮屈になるという滑稽な選択肢をとらなかったのは結局は正解だったと思います[5]。観光のための自由時間は会期中はありませんでしたが，イタリア人参加者らは，会での交流を十分に楽しんでいたと思います[6]。

さて，この研究集会の講演者と講演題目をプログラム順に並記すると次のようになります：

**Gianluigi ZANETTI (Cagliari, ITALY)** "Computational Emodynamics in Realistic Vascular Geometries"

**Toshio SEKIMURA (Nagoya, JAPAN)** "Pattern Formation in Lepidopteran Wings"

**Hisashi INABA (Tokyo, JAPAN)** "Endemic Threshold and Stability in an Evolutionary Epidemic Model"

**Hiromi SENO (Hiroshima, JAPAN)** "Dynamics between Limited Immune Response versus Polymorphic Viruses: A Possible Cause of Hazard"

**Giuseppe PONTRELLI (Roma, ITALY)** "Advances in Modelling Vascular Flows"

**Hisao HONDA (Hyogo, JAPAN)** "Cell Pattern Formation by Cell Behaviors Through the Signal Transduction"

**Atsushi MOCHIZUKI (Fukuoka, JAPAN)** "Mathematical Models for Developmental Pattern Formation: On Cone Mosaic of Retina and Strips of Coating in Fish"

**Toshiyuki NAKAGAKI (Saitama, JAPAN)** "Path Finding Among Scattered Food-Sites by True Slime Mold"

**Takashi MIURA (Kyoto, JAPAN)** "Morphogenesis of Embryonic Lung Epithelium in Vitro: Possible Relationship with Theoretical Models"

**Mitsugu MATSUSHITA (Tokyo, JAPAN)** "Pattern Formation due to Reproduction and Motion of Bacterial Cells"

**Alberto MORABITO (Milano, ITALY)** "Multi-state Markov Model for Analysing Disease History Data"

**Andrea PUGLIESE (Trento, ITALY)** "Models for Macroparasites. and Metapopulations: Different Problems. Similar Methods"

**Kazunori SATO (Shizuoka, JAPAN)** "Effect of Habitat Loss on Population Dynamics"

**Akira SASAKI (Fukuoka, JAPAN)** "Host-Parasite Coevolutionary Cycles in a Metapopulation: a Pacemaker and the Red Queen"

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[2]これは，話を十分にできる，という意味ではありません。話をするきっかけを作ることができる，という意味です。実際の議論や話をする時間は会期中に相当あったのですから。

[3]もちろん，これは，この研究集会についての感想であり，ほかの研究集会では，20分程度やより長い方が適当であることもあるでしょう。

[4]実際，イタリア側の参加者の多くが初めての日本訪問でした。

[5]大体，観光目当てで研究集会に参加するなどというのは，組織委員会に失礼であるばかりか，他の参加者にも失礼な無教養な態度ではないでしょうか。確かに，国際研究集会の多くが，観光地やリゾート地で行われていますし，それは，参加者数を増やそうという組織委員会の意図もあるやもしれません。しかし，研究集会に参加する最も価値ある意義（そして，最も面白い目的）は，参加者らとの交流であることを忘れてはならないのではないでしょうか。もちろん，これは，研究集会へ参加した際に，開催地の観光をすることが無教養であると述べているのではありません。研究集会の参加者らとの交流を深める上で観光自体が意味あるものであることも否定できない事実です。研究集会への参加者の「態度」が重要なのです。（以前，スペインで開かれた国際研究集会に参加した際に，この意味で恥ずかしく思われるような日本人参加者の一団があったことを思い出します）

[6]もちろん，ほとんどのイタリア人参加者は，会期前もしくは会期後に少なくとも1日は観光できる時間をスケジュールに持っていましたし。

**Yasuhiro TAKEUCHI (Shizuoka, JAPAN)** "Chemostat Models with Time Delays for Bacteria and Virulent Phage"

**Yuzo HOSONO (Kyoto, JAPAN)** "The Propagation Speeds of Travelling Waves for Autocatalytic Reaction-Diffusion Equations"

**Youhei FUJITANI (Tokyo, JAPAN)** "A Reaction-Diffusion Model for Genetic Interference"

**Giovanni NALDI (Milano, ITALY)** "Mathematical Neuroscience: Neurons, Networks and

**Laura SACERDOTE (Torino, ITALY)** "On The Study of a Periodically Stimulated Neuron with Reversal Potential by Means of Different Mathematical Tools"

**Yoshiaki ITO (Tokyo, JAPAN)** "Particle Systems on Graphs and Interacting Populations"

**Masayasu MIMURA (Hiroshima, JAPAN)** "Self-organized Patterns in Biological Systems"

数理生物学ではなく（！），数理生物学に焦点をあてた応用数理の研究集会という特色から，生物学者，医学・生理学者からの参加は日本側からの２名のみで，広い意味での応用数理の研究者が集う研究集会となりました。イタリア側の参加者の人選については，イタリア側の実際的アレンジを行った V. Capasso 氏に一任されたものです。残念ながら，開催時期が，イタリアでの研究費申請の時期にあたっていたこともあり，最終的な参加者のリストが確定したのは，10 月下旬のことだったと記憶しています。Capasso 氏によって作成された最初のたたき台となったイタリア側の参加者のリストは，最終的には相当に変わらざるを得なかったのです。今回のこの研究集会への参加を楽しみにされていた幾人かのイタリア人研究者ら（イタリア側の参加者組織を実質的に行う労を執った Capasso 氏を含む）については，とても残念です。（実は，日本側の参加者リストが確定したのもその時期だったような...）

さて，以前から私が持っていたイタリアの数理生物学関連の応用数理への印象で，今回のこの研究集会でより強くなったものがあります。それは，数理モデルの研究が，相当，実用性をにらみながら行われている雰囲気です。それは，決して，イタリアの数理生物学が実際的に実用化されているものが多いということを意味しているわけではありません。実際のところ，やはり，理論研究としての性格は否定しがたいものでありながらも，現実の現象研究に向けてのものであるという色合いがそれらの研究発表に顕著に見られるということです。しかし，一方，今回のイタリア側参加者のほとんど（全員？）が数学者もしくは数学をバックグラウンドにもつ研究者でした。

概して，ヨーロッパ（もしくはヨーロッパ起源）の数理生物学関係の国際研究集会に出席すると，数学者もしくは数学をバックグラウンドにした研究者がほとんどであることに驚かされます。もちろん，数理生物学の動向にはお国柄があり，「ヨーロッパ」とひとまとめにして印象を述べるのはあまりに浅薄かもしれませんが，少なくとも，ヨーロッパで開かれた Mathematical Biology や Theoretical Biology という内容を有した国際研究集会で，参加者の内，生物学者もしくは生物学をバックグラウンドにした研究者の割合が 1 割を超えていたものを私は知りません。ヨーロッパで開かれた数理生物学に関する国際研究集会に出席されたことのある他の研究者の方の感想も似たり寄ったりではないでしょうか。

さて，上記のプログラムを見ていただくとおわかりのように，イタリアの参加研究者の講演は，医学・生理学系が多かったのです。これも私が以前から持っていた印象の一つなのですが，どうもイタリアのお国柄か，イタリアの数理生物学関連の研究では，実際の研究者との共同研究も含めて，とりわけ，現実の現象研究に「近い」ところでの数理モデル研究の研究対象は，医学・生理学系で多く，対して，生態学系の数理モデル研究では，数学的なものが多いように思われます。もちろん，学際研究としての数理生物学の裾野は相当に広いのですから，それらはすべからく数理生物学の研究ではあるのですが... 私の感じるイタリアのお国柄というところでしょうか。

一方，日本側の参加者の場合，医学・生理学系の数理モデル研究の応用数理研究者にもっと参加していただければよかったのですが，実際のところ，医学・生理学系の日本の研究者と応用数理の間の交流はまだこれから活発になるだろうという可能性ばかりが先行して，実際の研究に携わっておられる応用数理の研究者は少ないのではないでしょうか（私個人の印象です。間違っているとしたら，それはすばらしいことです！）。少なくとも私は，医学・生理学には，応用数理の寄与できる，あるいは，応用数理にとって非常に面白い問題が少なからずあると思っています。日本のいわゆる『数理生物学』が相当に生態学に偏ってきたのは，決して病的なことではなく，宿命的であったのでしょうし，その偏りはともかくも，その発展において，国際水準の研究，研究者が育ってきたという，むしろ理想的な歴史を持っているのだと思います。しかし，今日，日本で『数理生物学』あるいは『数理生物学の研究』といったとき，生態学関連の研究であるような印象[7]を持ちかねない

[7]決して間違った印象ではないでしょう。

とすれば，そして，それをそのまま無意識に受け入れているとしたら，それは，残念なことでしょう。なぜなら，それは，決して，生態学以外の研究分野に関わる数理生物学を振興できるものではないからです。もちろん，それを妨げるものでもないわけですが，だから別に構わないという消極的な立場ではなく，積極的にこれからの数理生物学がより面白い発展をしてほしいという立場からすれば，生態学以外の分野に関わる数理生物学も（これまでの「数理生物学」の歴史に則った上で）振興されていくことが望ましいと思われます。これまでの偏りは，生態学以外の研究分野から数理生物学もしくは応用数理へのアプローチ，数理生物学もしくは応用数理から生態学以外の研究分野へのアプローチがいずれも希少なものだったからでしょう。だから，これから，生態学以外の，医学や生理学を含む分野に対して，数理生物学，応用数理はより積極的に広報されていくべき（数理生物学，応用数理からのアプローチ）ですし，その広報が医学や生理学における数理生物学，応用数理の認識，そしてそれらとの交流，共同研究が意義あるものであるという意識を生み出す（医学，生理学からのアプローチ）もとにもなりうると考えられます。そのような前向きの循環的相互作用が今後生まれていくことを心から期待したいと思います。

ところで，この研究集会は，セミクローズドでした。ここでセミクローズドという意味は，

- 講演者は全て組織委員会による招待講演である。
- 全講演者に対して，会期中にかかる費用相当を組織委員会が援助できる体制をとった。
- 会場の確保に際して，基本的に講演者総数によるサイズ選択をした。
- 基本的に泊まり込み参加者間の交流を目的としたプログラムが作成された。
- 講演者以外への広報活動はとりたてて行わなかった。

一方で，

- 参加費[8] を定め，参加者から徴収した。
- 当日参加の聴衆を拒むわけではなく，当日参加者も想定した準備がされていた[9]。

というこの研究集会の特徴を指しています。このようなセミクローズドな研究集会の場合，組織委員会による集会組織の見通しが立ちやすい，集会における不確定要素が少なく，プログラムを立てる上で自由度が高い，という利点が考えられますが，自由参加による研究集会の活性度までは期待できないことになります。たしかに，セミクローズが故の和気藹々さによって，時間の超過がそれほど気にならない[10] わけですし，プログラム変更の自由度も相当高かったと思います。このことは，腰を据えてじっくりと科学的な議論をする（できる）雰囲気につながりますから，大きな学会などのように，ベルトコンベアー式に次から次へと短くわかりにくい講演が流れてくる研究集会とは雲泥の差があると言わざるを得ないでしょう[11]。しかし，そのような雰囲気だからこそ，いろんな若い研究者や研究者の卵の方々には，味わっていただきたいと思いました。これは，上記の，この研究集会のセミクローズドという特徴に反するのですが... ですから，既に述べたセミクローズド性の効用をできるだけ損なわないように様々な方の自由参加を呼びかけることができると理想的だと思います。

今回の講演者の最年少は 30 歳代後半で，最年長は 50 歳代後半でした。ただし，参加者の最年少は 20 歳代，最年長は 70 歳代（?）でした。最年長の参加者は，イタリア応用数理学会長の Boffi 氏で，ご高齢ということもあって，会場の施設での宿泊ではなく，会場外のホテルへの宿泊でしたが，毎日，電車とタクシーで集会に参加されていらっしゃったのには驚くばかりです。また，最年少の参加者というのは，無理をいって会期中の事務局のお手伝いをお願いした斎藤保久君（大阪府大・院）と向草世香さん（九州大・院）のお二人です[12]。お二人には，単に事務局のお手伝いばかりでなく，この研究集会に若い活気を添えていただき，研究集会にとっ

[8] 宿泊費，食費，懇親会費，お茶代の実費相当。ただし，宿泊については，部屋数が限られているので，予めの予約は必須だったため，当日参加で宿泊を申し込まれた場合，利用が可能かどうかは？でしたが。

[9] 当日参加者に対する参加費はお茶代程度のものが設定されていました。

[10] 実際には，プログラムがゆったりと作られていましたから時間超過する講演はありませんでした。

[11] もちろん，このことが研究集会における交流や議論の成果の質を左右するとは限りませんが。

[12] お二人には，これまた無理をいって，この研究会への参加感想文を JAMB Newsletter へ投稿することをお願いしました［本報告書に引き続けて掲載］ので，この報告記と併せて読んでいただければ幸いです。

て大きな貢献でした。しかも，飛び込みでそれぞれの研究の話を（英語で）参加者の方々に聞いてもらうというハプニングもあって，参加者の方々もお二人の若い活気を喜ばれたことと確信しています。

この研究集会の次回は，２年後にイタリアで開かれることになっています。ただし，毎回，テーマがその都度決められますので，次回は，数理生物学に関わるものかどうかはわかりません。しかしながら，小さいながらも，このような日本の研究者と海外の研究者との親密な学術交流を図る機会というのは，大きな国際会議を開催するのとは異なる実りが期待できると思います。とりわけ，これからは，「日本の」～学の発展にとらわれない，国際感覚をもった若い研究者が育つことが日本の研究界が目標とすべき大切な要点の一つではないかと思いますので，このような研究集会が日本でも開かれることは非常に望ましいことではないでしょうか。

■

# 参加記

齋藤 保久（大阪府立大学大学院工学研究科）
向 草世香（九州大学理学部生物学教室）

上記の研究集会は２０００年１１月１３日（月）から１６日（木）までの４日間、オックスフォード大学キャサリンズカレッジ神戸インスティチュートにて行われました。オーガナイザーは広島大学の三村昌泰先生と瀬野裕美先生。我々は両先生の手伝いという形で、この国際会議に参加させていただきました。参加者はイタリア人７名、日本人１８名の計２５名で、参加者のほぼ全員が講演されました。

この会議の行われた４日間は、どの瞬間も大変刺激的で貴重なものでした。その中で特に我々２人にとって有意義であった、１５日の夕刻の出来事について述べたいと思います。我々は手伝いの身のため公式に講演することは出来ませんでしたが、１５日の夕刻に幸運にも（非公式ではありますが）参加者の方々に我々の研究内容を聴いていただける機会をもつことができました。

１５日の昼過ぎ、齋藤は参加者の一人であった静岡大学の竹内康博先生に「せっかく来ているのだから君たち（向、齋藤）も発表させてもらえるようにお願いしてみたら。多分 Banquet の始まる前に時間はあるはずだから」と言われました。今から述べる出来事は、この一言がきっかけでした（今回に限らず、今までに幾度も竹内先生の一言がきっかけで、齋藤は良い経験をさせていただいております）。事実、この会議のプログラムには時間的にゆとりがありました。早速、我々２人で相談し、講演したい旨を瀬野先生に伝えました。瀬野先生の返事は「僕が君たちに公式に研究発表の場を与えることは無理。でも君たちが勝手にやるのなら良い。Break Time には何をしたっていいわけだから、ジャック講演をしたらどう？」というものでした。ここで言う“ジャック講演”とは、講演の招待を受けていない者が講演者の邪魔をしないように講演時間外に講演を行うことを言います。ジャック講演は我々２人にとって全く初めてのことなので、少々怖じ気づきましたが、実行することを決意しました。後で知ったことなのですが、瀬野先生は私たちのジャック講演のことをイタリア語でＯＨＰシートに書いて、イタリア人参加者の方々には事前に伝えていてくれました。我々が気づかないところでサポートしてくれていたのです。いやはや、心の大きな方です、瀬野先生は。

１５日の５時１５分頃でしたか、その日の最後の講演が終わって間もなく、齋藤が次のように切り出しました。

> Un momento. per favore! (イタリア語で、「ちょっと待ってください！」) Sorry. please give us. Muko and me. a chance to talk about our studies before meeting banquet. We would like you to listen to our talks for about 30 to 40 minutes. please. First. she is talking. After that. I will talk. We are very glad if you could listen to our talks as an appetizer of the banquet. You can listen with drink if you like!

最初のイタリア語でも一笑を得ましたが、特に "We are very glad if you could listen to our talks as an appetizer of the banquet" が爆笑でした。和訳すれば「晩餐会で出る料理の前菜として我々の話を聴いていた

だければ大変うれしい」となります。International な場では、ちょっとしたジョークを入れることが必要かと思い、必死になって上の文を作りました。おかげでスムーズに我々の非公式講演に入ることができて、始めに向が "Species Coexistence by Permanent Spatial Heterogeneity" というタイトルで、次に齋藤が "Global Stabiliy for a Lotka-Volterra Competition System with Positive Delayed Feedbacks" のタイトルで英語発表を行いました。２人ともぶっつけ本番でとても緊張しましたが、話題のおもしろさはアピールできたと思います。たくさんの方から質問を頂いたのに十分に答えることができなかったのが心残りですが、何とか無事にジャック講演を終えることが出来ました。

非公式ジャック講演の後の Banquet は格別なものでした。何か大きな仕事をやり遂げた後の食事やお酒は美味しく感じます。いわんや、この Banquet に出た料理とワインの豪華なこと！この時ばかりは「超美味しいー!!」と小ギャル語連発の気分でした。参加者の皆様には、前の２日間よりも我々に興味をもっていただいた様で（だと信じています）、特にイタリア人の方々と会話がはずみ、研究の話は勿論のこと、ワインの話や日本の料理の話など、いろいろな話題で盛り上がりました。ワインで舌を満足させ、美味しい料理で腹を満たしながら、酒宴での談笑に胸をいっぱいにしました。

もしもジャック講演をやっていなければ、Banquet の楽しさは半分だったかもしれません。恥（ハジ）をローマ字で書けば「HAJI」、これをイタリア人が読めば、H を発音しないため「アジ」となります。「恥」ずかしさを抑え、勇気を奮い立たせてジャック講演をしたおかげで、Banquet での酒宴を体全身で「味」わうことができたのです。

この体験を契機に、いろんな研究分野の方々と交流を深め、お互いの研究の楽しさや面白さを分かち合いたい思っております。

三村先生、瀬野先生、良い経験をさせていただき心より感謝いたします。ありがとうございました。

■

# 第２回大久保賞受賞者決定について

第2回大久保賞受賞者としてプリンストン大学のSimon Levin教授が選ばれました。選考委員会委員長から事務局長宛への受賞者決定の経緯に関する書簡を掲載いたします。

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Professor Alan Hastings
President of the Society for Mathematical Biology
Professor Yasuji Kanno,
Secretary General of Japanese Association of Mathematical Biology

April 26, 2001

Dear Professor Hastings and Professor Kanno,

We are pleased to announce that the Second Akira-Okubo prize committee has reached a conclusion. The composition of the committee and the selection procedure we followed are detailed below.

The committee is composed of six members: Mark Chaplain, Mark Lewis, and Philip Maini from SMB, and Toshiyuki Namba, Takenori Takada, and Yoh Iwasa from JAMB who is the committee chair. We received eight nominations to seven candidates. First we discussed the selection procedure which we would follow. After carefully examining all the submitted material for each candidate and exchanging our views on the suitability of the candidates, each committee member (apart from the committee chair) voted for their top three ranked candidates awarding 3, 2 and 1 marks respectively. After the first round of voting there was an immediate consensus with all the members agreeing unanimously concerning the top two candidates. We next focused on these two people and attempted to summarize their research achievements. Having discussed both candidates in detail the committee members cast votes for their preferred candidate.

Through this procedure, we reached the conclusion that the winner of the second Akira-Okubo prize is Professor Simon A. Levin (Princeton University).

Professor Simon Levin graduated the Johns Hopkins in 1961, and received his Ph. D. from the University of Maryland in 1964, both in Mathematics. Simon Levin became a professor in Ecology and Systematics, Cornell University from 1965. Since 1992, he has been teaching at Princeton University.

Beginning with his 1974 American Naturalist paper of the coexistence of competitors in a spatially structured population, Simon Levin has helped to establish the field of spatial ecology. His modeling of the inter-tidal zones with Robert Paine illustrated the importance of disturbances forming spatial patterns and the gap dynamics of mussel beds. It is now a classic study often seen in introductory ecology textbooks.

The best cited article by Simon Levin is his MacArthur Award paper published in 1992 in Ecology. Here he presented the importance of scales in understanding ecological patterns very clearly by raising a number of ideas and examples in ecology.

More recently, his collaborations with Rick Durrett brought new concepts to bear on ecological problems by emphasizing the importance of stochastic approaches to spatial ecological processes.

Simon Levin has had a long-term interest in group formation of animals. Rules

for the behavior of individuals are translated in patterns observed in groups such as herds or swarms. However, the translation from the Lagrangian to the Eulerian framework is a great challenge. This is the field Akira Okubo pioneered.

Another area where Simon's work has been central to the development of a subject is the evolution of dispersal. Simon Levin and his colleagues established principles governing how variability leads to selection for dispersal, and explored new concepts in the field of evolutionarily stable strategies to do so.

In addition, Levin has also had made a major contribution towards the modeling of infectious diseases. His recent works includes a paper on the effect of antibiotic resistance on disease.

Recently, Simon Levin has been very influential in the area of modeling biodiversity and ecological sustainability.

Simon Levin is very talented in his ability to guide and inspire people as illustrated by a list of collaborators and students. He is also extremely flexible in the kind of mathematical formulation and type of analysis.

In addition to these research achievements, Simon Levin has been influential to mathematical ecology in many ways. He was President of the SMB from 87-89, just before his term as President of the Ecological Society of America. He was recently elected to a member of the US National Academy of Sciences.

The criteria for the prize says that the objective is to honor a scientist "for outstanding and innovative theoretical work, for establishing superb conceptual ideas, for solving tough theoretical problems, and/or for uniting theory and data to advance a biological subject". We believe that Simon Levin meets all of these criteria.

Hence we are pleased to recommend Professor Simon A. Levin as the winner of the Second Akira Okubo prize.

Best wishes,
Sincerely yours,

Yoh Iwasa
Chairman, The Second Akira-Okubo Prize Committee

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Yoh Iwasa (after May 10, 2001)
Department of Biology, Faculty of Sciences,
Kyushu University,
Fukuoka 812-8581, Japan
E-mail: yiwasscb@mbox.nc.kyushu-u.ac.jp
Fax +81-92-642-2645
Tel +81-92-642-2639
http://bio-math10.biology.kyushu-u.ac.jp/~iwasa/

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# 第17回京都賞記念ワークショップの協賛について
## （経過およびご協力依頼）

平成13年７月31日
数理生物学懇談会事務局長
菅野　泰次

科学、文明の発展などに著しく貢献した人を顕彰する第17回京都賞（基礎科学部門）に、イギリス、サセックス大学のジョン・メイナード・スミス名誉教授が選出されました。メイナード・スミス教授はご承知の通り、ESSを提唱された進化生物学界の大御所です。11月に京都において記念ワークショップが開催されるのに伴い、主催者の稲盛財団からワークショップへの協賛依頼が懇談会にあり、事務局では運営委員会にお諮りして協賛を決定いたしました。このワークショップでは受賞者の記念講演の他、日本の５名の著名研究者の講演がございます。以下に、同財団からの協賛依頼状（プログラムを含む）および事務局からの回答を掲載し、ご報告といたします。

皆様の積極的なご参加を賜りますれば幸いでございます。

## 第１７回京都賞記念ワークショップ基礎科学部門　プログラム

日時：2001年11月12日（月）午後
場所：国立京都国際会館

シンポジウム「進化とゲーム　Evolution and Game　」

企画・司会　　巌佐　庸［（専門委員会委員）九州大学大学院理学研究院教授］

1　挨　　拶　　稲盛　豊実［稲盛財団常務理事］
2　挨　　拶　　山岸　哲［（専門委員会委員長）京都大学大学院理学研究科教授］
3　受賞者紹介　　巌佐　庸
4　受賞者講演　　ジョン・メイナード＝スミス　－　基礎科学部門 受賞者
　　「（演題未定）」
5　講　　演　　桑村　哲生［（専門委員会委員）中京大学教養部教授］
　　「動物行動学とゲーム理論」
6　講　　演　　山村　則男［京都大学　生態学研究センター教授］
　　「（演題未定）」
7　講　　演　　西條　辰義［大阪大学　社会経済研究所教授］
　　「協力の創発」
8　講　　演　　矢原　徹一［九州大学大学院　理学研究院教授］
　　「有性生殖の短期的・長期的利点－キク科直物の研究からの証拠」
9　講　　演　　小林　一三［東京大学　医科学研究所助教授］
　　「遺伝子はなぜ愛しあうのか（仮題）」

以下は、事務局への依頼状と、事務局長からの回答の書簡です。

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平成１３年７月１０日
数理生物学懇談会
事務局長　菅野泰次　殿

財団法人　稲盛財団
理事長　稲盛　和夫

第１７回京都賞記念ワークショップご協賛のお願い

拝啓　時下貴会におかれましてはますますご清栄の段慶賀に存じます。平素は格別のご高配を賜り厚く御礼を申し上げます。
さて、当財団の本年第１７回京都賞は、基礎科学部門として「生物科学（進化・行動・生態・環境）」の分野でイギリス、サセックス大学名誉教授のジョン・メイナード＝スミス教授に贈られることになりました。つきましては、今秋、メイナード＝スミス教授を京都にお招きし、京都賞授賞式関連行事として１１月１２日(月)に別紙企画書のとおり、記念ワークショップを開催する運びとなりました。このワークショップは、今後の我が国における生物科学の益々の発展を願い、参加・聴講無料で開催させて頂くもので、貴会の会員にもご興味の深い内容と存じ、是非ご協賛賜りたくお願い申し上げる次第です。　また、ご承認下さいました節は、貴会誌などに関係事項をご掲載くださいますよう併せてお願い申し上げます。なお、貴会には会計面・運営面などにおきましてご迷惑は、一切おかけ致しません。案内書等作成の都合上、ご都合の程を、８月１０日（金）までにご連絡賜れば幸甚に存じます。
以上、略儀ながら書面にてお願い申し上げます。

敬具

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財団法人　稲盛財団理事長
稲盛　和夫　殿

第17回京都賞記念ワークショップの協賛について（回答）

貴財団の高遠な活動に心から敬意を表します。
この度は、貴財団が主催する標記の記念ワークショップ基礎科学部門プログラム「進化とゲーム Evolution and Game」に関して、数理生物学懇談会に協賛のお誘いがありましたことに先ずはお礼を申し上げます。数理生物学懇談会は本プログラムの趣旨である「今後我が国における生物科学の益々の発展を願い、参加・聴講無料で開催させて頂く」に表明されている科学知識の普及と社会的奉仕の精神に強く賛同いたします。ここに協賛の意をお伝えしますと共に、数理生物学懇談会ニュース・レターおよび会員メールシステム　biomathにより、広く宣伝の労をとらせて頂くことをお約束します。
以上、略儀ながら本懇談会の回答とさせて頂きます。
敬具

平成13年７月31日
（函館市港町三丁目１番１号）
数理生物学懇談会事務局長
菅野　泰次

# 大久保賞ガイドラインについて
## 大久保賞規約の運用指針（ガイドライン）の締結について

2001年８月２日
数理生物学懇談会事務局長
菅野泰次

今夏、７月16-19日の日程で、数理生物学懇談会と SMBの合同国際会議がハワイにおいて開催され、ここで、第２回大久保賞受賞者（Simon Levin教授）の記念講演が行われました。授賞式では選考委員会委員長巌佐　庸氏による選考経過の報告に続き、楯と賞金の授与が行われる筈でしたが、両学会事務局の手違いで準備ができておらず、後日授与されることになりました。このトラブルについては事務局に大きな責任があり、シンポジウムに関係された皆様に深くお詫び申し上げます。この直後に開催された数理生物学懇談会総会では、このことが議題としてとり上げられ、大久保賞規約について SMB側と改めて調整することが取り決められました。

７月23日から SMBの Mark Lewis会長と日本側の大久保賞選考委員の間で Eメールによる協議が行われました。日本側の交渉代表者には難波利幸氏になっていただきました。この交渉の末、従来の規約を補足する３項目からなる運用指針（ガイドライン）がLewis会長から提案されました。その骨子は (1)両学会はそれぞれの負担で受賞者の招待講演を行うこと、授賞式を執り行うまでの (2)選考委員会と事務局の役割を明文化したこと、および (3)大久保賞の内容は楯と賞金であり、これについてのみ大久保賞基金を支出すべきこと、からなっています。特に強調されるのは、受賞者講演は両学会の負担で行うべきことを文言として明文化した点であります。

ニュースレター NO.25に述べられている大久保賞設置準備委員会報告によれば、この招待講演の規定は、1997年のJAMB総会において元々規約に記載することが了承されていたものの、SMBの執行部の交代により削除された経緯があります。今回 Lewis会長から再び明文化する提案がありましたので、日本側としては異議なしと考え、運営委員会の皆様にお諮りし協約締結いたしました。会員の皆様のご理解とご承認をお願いする次第です。

最後に、この指針を取り決めるに当り、 SMBとの交渉を一手に引き受けて下さいました難波利幸氏、および巌佐　庸氏、高田壮則氏の選考委員の皆様に心よりお礼を申し上げ、ご報告といたします。

以下に、大久保賞規約運用指針（ガイドライン）について SMBとの合意文書を掲載します。なお、大久保賞規約についてはニュースレター NO.25をご参照下さい。

## GUIDELINES FOR AKIRA OKUBO PRIZE

July 2001

These guidelines are in addition to the existing rules governing the Akira Okubo Prize.

[1] Okubo Prize winner is expected to give a talk to both the SMB and JAMB, with the Societies covering the respective costs. In the event of a joint talk to the Societies, the cost should be split between SMB and JAMB.

[2] Because (i) there are three members on each of the JAMB and SMB parts of the Okubo Prize Committee, (ii) the rules specify that one from each part of the Committee should be replaced each year, and (iii) the Okubo Prize is awarded every other year, there will be one individual in each of the JAMB and SMB parts of the Okubo Prize Committee that serve in

both a current and previous Award process. This leads to continuity in the award process. These individuals, should be sure to inform the Secretary Generalof the JAMB or President of the SMB when it is time to specifythe Chair of the Okubo Prize Committee and start the nomination process.

[3] Once the recommendation for the Prize winner has been made by the Okubo Prize Committee, the Chair of the Okubo Prize Committee should ask the Secretary General of the JAMB and President of the SMB to write a congratulatory letter to the candidate and should prepare the plaque and cash prize. Money to pay for the plaque and cash prize is to come from the Akira Okubo Prize Fund, administered by theTreasurer of the SMB.

以上

## 編集後記

７月１６日～１９日、ハワイで開催されたSMB, JAMB合同数理生物学国際会議の要旨を掲載しました。数理生物に関係したある程度まとまった規模の国際学会はそれほど多くはないのかもしれません。日本とアメリカを合わせると、数理生物学研究者のかなりのシェアーを占めるでしょう。会議では口頭発表・ポスター発表を合わせて１７０を越える発表がありました。トピックスは、生態学・免疫学・分子生物学・細胞生物学・バイオインフォマティック等々と多岐にわたりました。一方、広島大学の瀬野さんから、昨年行われた日本応用数理学会とイタリア応用数学会の共同研究集会についての報告をいただきました。小ぢんまりとした濃密な討論の場として成功をおさめたようです。参加できなかった方々が、本号の記事から、刺激と情報と得ていただければと思います。（西村）

ニュースレター編集局・事務局
菅野泰次 kanno@fish.hokudai.ac.jp
西村欣也 kinya@fish.hokudai.ac.jp（投稿受付）
岸道郎 kishi@salmon.fish.hokudai.ac.jp
（入会受付）
松石隆 matuisi@fish.hokudai.ac.jp
高田壮則 takada@dc.htokai.ac.jp
原登志彦 t-hara@orange.lowtem.hokudai.ac.jp
〒041－8611 函館市港町３－１－１
北海道大学大学院水産科学研究科内
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