BIOMATH 2012

International Conference on
Mathematical Methods and
Models in Biosciences
Sofia, June 2012

and School for Young Scientists

Edited by R. Anguelov and S. Markov

CONFERENCE BOOK

This volume contains a collection of abstracts of scientific papers contributed to BIOMATH 2012 — an International Conference on Mathematical Methods and Models in Biosciences held at the Bulgarian Academy of Sciences in Sofia, June 17–22, 2012. Included is also a list of participants with their addresses, as well as information about the associated School for Young Scientists on 17th June, 2012.

Publ. House "Vanio Nedkov"
Electronically published on 8 June 2012

ISBN 978954-9462-78-4

BIOMATH is an international conference devoted to recent research in biosciences based on applications of mathematics as well as mathematics applied to or motivated by biological applications. It is a multidisciplinary meeting forum for researchers who develop and apply mathematical and computational tools to the study of phenomena in the broad fields of biology, ecology, medicine, biotechnology, bioengineering, environmental science, etc.

The conference continues a tradition of scientific meetings on Biomathematics held in Sofia since 1990. It is supported by several research units of the Bulgarian Academy of Sciences including:

- Institute of Biodiversity and Ecosystem Research (IBER)
- Institute of Biophysics and Biomedical Engineering (IBPBME)
- Institute of Chemical Engineering
- Institute of Information and Communication Technologies (IICT)
- Institute of Mathematics and Informatics (IMI)
- Institute of Mechanics
- Institute of Microbiology
- Institute of Molecular Biology
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and also by

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- South-West University "N. Rilski"
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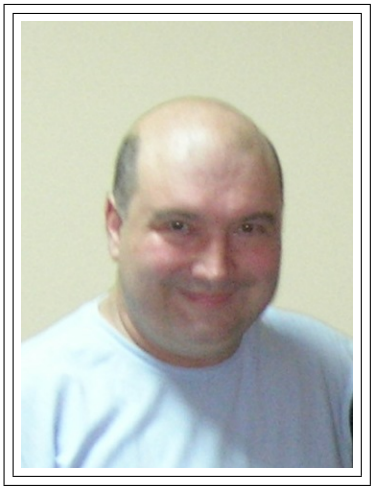
Obituary: Antony Popov (1962-2012)



It is with a deep sorrow that we inform you about the sudden death at the age of 49 of our colleague Associate Professor Dr. Antony Popov, member of the Department "Information Technologies", Faculty of Mathematics and Informatics, Sofia University.

Over the past three years we at the Department of Biomathematics worked together with Dr. Antony Popov on a research project supported by the National Science Fund of the Bulgarian Ministry of Education, Youth and Science on "Computer Simulation and Innovative Model-Based Study of Bioprocesses". Tony took an active part in this project together with his doctoral students. Scientists from our department have joint publications with Dr. Tony Popov and participated as lecturers in the Master Program of "Bio-Medical Informatics" lead by him since its inception about ten years ago. Tony created and supervised this Master Program with much enthusiasm and invested a lot of effort. In the Program he brought together as lecturers specialists from different fields: mathematics, computer science, bio-physics, bio-engineering, biology and medicine. Many students enrolled and benefited from this program. Tony was very happy and proud of his students' success and supported them whole-heartedly. Their success was his success. The high quality of their projects and diploma works bares also testimony for his hard work and enthusiasm. Tony was also the main organizer of the School for Young Scientists at the International Conference on Biomathematics "BIOMATH". He organized

almost single-handedly the School in 2011 and planned the scientific program for this year School on the 17th June 2012. Now, when he is not among us, we have deep appreciation for the tremendous job he did. We distributed the work Tony was doing by himself between five colleagues in order to fulfill the tasks which Tony would have done alone, unnoticed by us.

Tony was a very good mathematician, a specialist on Image Analysis and Image Processing. In this broad field he employed successfully various mathematical theories and tools, not previously related, such as mathematical morphology, interval analysis, fuzzy sets, rough sets, etc. Mathematical morphology by itself is an intersection point of several classical mathematical subject areas like geometry, set theory, topology, analysis and statistics. It requires a scientist with broad knowledge in all these fields, who is a true professional mathematician such as Tony Popov. He is the pioneer in Mathematical Morphology in Bulgaria and author of several excellent papers in this area.

We will always remember Tony as a very polite, responsive, modest and trusted colleague with a very tender heart. He was for us an example of a true gentleman. Goodbye, Tony! We shall miss you very much! We shall keep you in our memory!

From the colleagues of Department of Biomathematics
Institute of Mathematics and Informatics
Bulgarian Academy of Science

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1 Welcome Message from the Organisers

The BIOMATH is a series of international biomathematical conferences held in Bulgaria. Several academic and university units contributed to the organization of BIOMATH 2012 and are acknowledged in the preamble of this book. Further, we are grateful to all members of the Program and Organizing Committees for their active help. We thank also to all participants for their contribution to the success of this Conference. We warmly welcome all participants to BIOMATH 2012 who come from abroad. We are happy to meet colleagues from Algeria, Australia, Cameroon, Canada, China, France, Georgia, Germany, Greece, Hungary, India, Iran, Italy, Japan, Kazakhstan, Pakistan, Romania, South Africa, Serbia, Spain, Taiwan, Tunisia, Turkey, Ukraine, United Kingdom, United States of America, Uzbekistan.

A special session of BIOMATH 2012 is dedicated to Blagovest Sendov on the occasion of his 80th birthday. Prof. Sendov is one of the pioneers of biomathematics in Bulgaria. He supported the development of biomathematical research in the Bulgarian Academy of Sciences throughout his career. He is an active supporter of the BIOMATH series of conferences and currently chairs the Program Committee.

We hope to be able to turn the BIOMATH meetings into an annual event continuing a tradition of scientific meetings on biomathematics held at the Bulgarian Academy of Sciences since 1990. The last year BIOMATH 2011 conference held 15–18 June 2011 in Sofia was truly an international meeting that gathered researchers from four different continents and 16 different countries. We pay special attention to the publication of the presented scientific communications. Selected papers presented at the international conference BIOMATH-95 were published in vol. 32(11) of the Elsevier Journal Computers & Mathematics with Applications, as well as in vol. 2(2) of J.UCS. The BIOMATH 2011 Conference was dedicated to the memory of Dr Roumen Tsanev — a prominent biologist and a pioneer of biomathematical modeling in Bulgaria. From the presented about 70 scientific lectures at BIOMATH 2011 a selection of 19 scientific papers focused on mathematical, numerical and computational tools with particular attention on differential equation models and their numerical analysis is published in Volume 64 of the Elsevier Journal Computers

& Mathematics with Applications. Another selection of 14 papers focusing on biotechnological processes is in the process of publication in the Journal "Biotechnology & Biotechnological Equipment". For this year's issue of BIOMATH we have contracted total of five journals for possible publication of special issues with papers from selected talks at the conference.

For the Organizing committee:

Roumen Anguelov
Dept. Mathematics and Applied Mathematics
University of Pretoria
Pretoria 0002, South Africa
roumen.anguelov@up.ac.za

Svetoslav Markov
Institute of Mathematics and Informatics
Bulgarian Academy of Sciences
"Acad. G Bonchev" St. Block 8, 1113 Sofia, Bulgaria
smarkov@bio.bas.bg

2 Welcome Address of the President of the Bulgarian Academy of Sciences

On behalf of the Governing bodies of the Bulgarian Academy of Sciences I would like to welcome the eminent speakers and delegates who have come from all over the world to the 2012 International Conference on Mathematical Methods and Models in Bioscience.

The Bulgarian Academy of Sciences has a long tradition of research in Biomathematics and in supporting the development of this field. It begins with the works of the Professors Roumen Tsanev and Blagovest Sendov in the seventies of the last century. Short after, the Academy established the first research unit of Biomathematics in the Center of Biology. Following the success of this unit similar units were established in several other research centers. Currently, many institutes of the Academy have incorporated Bio-mathematical research directions like biomechanics, biophysics, bioinformatics, biotechnology, bioengineering, mathematical modeling in biosciences such as molecular biology, neuroscience, ecology, plant science, etc. Nine Academy Institutes contribute to the organization of BIOMATH 2012, which testifies to the interdisciplinary character of the conference.

The BIOMATH is a series of international biomathematical conferences held in Bulgaria. We are indeed honoured to have so many distinguished scientists in this field at the Academy. There are about 70 participants from the five continents and about 30 countries gathered here today, making this conference a truly international one.

I am happy to welcome the many young researchers participating in the conference. It is remarkable that many of the participants from abroad, bear Bulgarian names. Special thanks to all of them and particularly to those who already work in foreign countries but still have Bulgaria in their minds.

Last but not least, I would also like to acknowledge the efforts of the Organizing Committee headed by the Professors Anguelov and Markov for organizing this successful event.

In closing, may I wish to all delegates a successful conference comprising informative sessions, fruitful discussions, and new scientific contacts. I hope between the scientific activities you will also be able to enjoy our city and our country.

Acad. Nikola SABOTINOV, D.Sc.
President of the Bulgarian Academy of Sciences

Sofia, 18th June 2012

3 Foreword

The vast diversity of topics that appear in this booklet is indicative of how mathematical biology is permeating more and more branches of science. The field now ranges from very technical mathematical and computational advances required to analyse models arising from biology to directly applicable field and clinical studies. As the biological sciences present totally novel challenges, traditional differential-equation approaches in applied mathematics have had to extend to incorporate stochasticity, hybrid systems and multiscale analysis, but in non-standard ways, due to the inherent complexity of biological systems. At the same time, advances in computation now mean that more biologically realistic models can be computed but, as realism grows these advances are still not sufficient, resulting in the need to develop new numerical techniques. In short, biology has hugely stimulated the fields of mathematics and numerical analysis.

It is fair to say that most biologists still view mathematics with an air of scepticism, with mathematical modelling being more readily accepted in areas where it has been demonstrated to lead to scientific insight, such as in ecology and certain branches of physiology, not forgetting the role that statistics and bioinformatics have played at the gene and protein level. However, a growing number of biologists are now interacting with mathematicians and, indeed, seeking out active collaboration so that we are seeing a paradigm shift in applied mathematics where the *real* application is being emphasized. This requires a new generation of mathematicians who have a breadth of scientific knowledge as well as a depth of mathematical expertise and the challenges faced by this younger cohort in our mainly discipline-bound university structure need to be recognised and overcome.

Despite all these difficulties, the subject area is so exciting that it is attracting more and more young people and so the future is very bright. At the same time, in these economically harsh times, funding is being directed into interdisciplinary areas which presents many opportunities for mathematicians.

I am sorry that I cannot attend the conference. I hope you have a very enjoyable and fruitful time.

Philip K. Maini

4 Blagovest Sendov – Pioneer of Mathematical Modeling in Bulgaria: Contributions to Biomathematics and Interval Analysis

Svetoslav Markov
Institute of Mathematics and Informatics
Bulgarian Academy of Sciences

Prof. Blagovest Sendov, Full Member of the Bulgarian Academy of Sciences, turned 80

In February 2012 Prof. Blagovest Sendov turned 80. I first met him in 1963 as a student in mathematics at the Faculty of Physics and Mathematics at Sofia University. I was fascinated by his lectures in Numerical Methods. His first lecture was devoted to Mathematical modeling. On some real life situations Prof. Sendov revealed to us the philosophy of science. This lecture was crucial in my orientation in mathematical research. I was deeply impressed and I started to collect materials for a book based on the ideas of Professor Sendov, which I published later on. During the years to follow mathematical modeling became my main subject of interest. Thanks to Prof. Sendov, I was equipped with many useful ideas, tools and insights that helped me in my mathematical occupations and applications to real world problems. Prof. Sendov's "philosophy" included a deep understanding of the mechanisms of the underlying real processes, the mathematical description of these processes using contem-

porary mathematical theories and the solution of the formulated mathematical problems using advanced numerical and computational tools.

An important area of mathematical applications is the area of biology. Prof. Sendov has remarkable achievements in the field of mathematical modeling in biology, for which I wish to briefly mention below. I also wish to mention his contributions to an advanced tool for mathematical modeling known as Interval analysis, which is tightly related to his main subject of interest "Approximation theory" [24].

Prof. Sendov possesses the enormous ability to formulate difficult tasks and problems that need years of efforts to be resolved. At the weekly seminar of "Mathematical modeling" he used to pose such difficult problems and to make us young collaborators enthusiastic about working on them. He never pressed anybody of us to work on something particular, but he waited that everybody chooses a theme of interest by himself.

1. The contributions of Prof. Blagovest Sendov to biomathematics

In the period 1965–1971 Prof. Sendov collaborates actively with Dr Roumen Tsanev, an excellent molecular biologist, and also a very competent mathematician. In the summer of 1965 Prof. Sendov and Dr. Tsanev begin jointly work on the hypothetical mechanisms for cellular proliferation, differentiation and carcinogenesis, suggested by Dr. Tsanev. The two scientists wanted to establish whether a mechanism for cellular activity based on interrelated genes is logically possible to function. They decided to use the newly installed computer in the Institute of Mathematics at the Bulgarian Academy of Sciences to study a model of cellular activity based on a network of genes interrelated on the basis of equations describing the synthesis of mRNA, controlled by DNA-protein interactions and programming the ribosomes for the synthesis of proteins. During the next several years both have many discussions on the formulation of a suitable mathematical model. Prof. Sendov tries many formulations and performs multiple computer experiments.

The results of an active collaboration with long discussions and computer experiments led to several modifications of the models, which were reported in a series of joint papers [1]–[10]. These papers are devoted to modeling of different biological objects such as epidermis and liver, or different processes such as cellular activity, cellular differen-

tiation and carcinogenesis. The main result of these investigations (keeping in mind that the eukaryotic cells have to undergo cytodifferentiation) was that this process has to be controlled by an independent information, which is not necessarily semantically connected to the genetic information. This independent information was postulated as an epigenetic code. This mathematical model of living cells in a multicellular organism, based on the existence of an epigenetic code, was able to explain uniformly the processes of embryonic development, cytodifferentiation, vegetative reproduction, somatic embryogenesis, carcinogenesis and even the emergence of new forms of natural selection. All this is explained in [10] with more than 300 references to experimental results showing agreements with the results of their mathematical model.

During several years a great number of scientific papers are published, amongst them four papers in the Journal of Theoretical Biology, a survey paper in "Uspehi Mathematicheskih Nauk" and a monograph in Russian.

The studies of Sendov and Tsanev can be subdivided into four steps. The first step was to construct a mathematical model of living cells, based on the concept of Jacob and Monod for the existence of conjugate operons, working as a flip-flop. An operon has two states: repressed as inactive and derepressed as active. The mathematical realization of such flip-flop is by formulating a well-known set of nonlinear differential equations. The interaction between the different cells in an organism and the role of the nuclear membrane are important for eukaryotic cells. To this end a special variable for the diffusion through the membrane has been introduced. This variable depends on the functional state of the cell. It is known that when the eukaryotic cell enters in the mitotic cycle, the diffusion through its dissolved membrane stops. So they added to the system of differential equations, describing the activity of a cell, some additional differential equations with discontinuous right-hand side. The goal of this first model was to find out if it is possible to choose the constants in the mathematical model of a system of synchronized cells, which divide and interact between themselves by the substances going through the membranes, in such a way that they reach a homeostasis. The result of the computer experiment is that the model is adequate under a

suitable choice of the parameters of the model. The results obtained were in good agreement with the reaction of real tissues, such as the epidermal tissue, which was studied extensively by Dr Tsanev.

On the second stage a model of non-synchronized cells imitating the liver was constructed [11]. This model demonstrated a very good agreement with the experimental data, especially the reaction after "partial hepatectomy". All this was achieved on the basis of the idea for repression and derepresion.

The third stage was to model the mechanism of cytodifferentiation. Here the two scientists introduce the mechanisms of blocking and deblocking of the operons. In this situation, every operon has four different states: repressed-blocked, repressed-deblocked, derepressed-blocked and derepressed-deblocked. Only in the state derepressed-deblocked, the operon is active. To test these mechanisms, they constructed a mathematical model of a set of cells, which interacted between themselves. Every cell in the model has eight operons, one mitotic, responsible for the division of the cell, and seven functional operons. Every operon, when active, produces substances which may repress or deblock another operon. This interconnection between the operons is prescribed in the model by a matrix and represents the meaning of the epigenetic code. In other words, the existence of an epigenetic code means that the operons in a cell form a genetic network. Different types of cells in a organism have the same genetic information and differ by the difference in the set of blocked operons.

To define the interaction between the cells, a special geometrical arrangement of the cells has been proposed and the place of a new cell produced after division is prescribed. To make it simple, a population of cells called "Cylindros" has been created. To avoid the three dimensional geometry, an infinite cylinder is considered and a plane intersection of it is studied. Thus the Cylindros was a ring of two-dimensional cells on the plane with an interior space in the middle. The diffusion of all substances produced in the cells was possible only in the middle space and between the neighbor cells. In this way, the interaction between different cells was fulfilled. After division of a cell, the two new cells stayed on the same place on the ring as neighbors.

Choosing a particular matrix for the genetic net in the Cylindros, all important behaviors as embryonic development, cytodifferencia-

tion, vegetative reproduction, somatic embryogenesis and carcinogenesis have been demonstrated.

From mathematical point of view, the Cylindros was a system of ordinary differential equations of first order with discontinuous right hand sides and the number of the equations in this system depended on the time.

On the fourth stage of the study Prof. Sendov analyzes this system of ordinary differential equations for stability in respect to the number of the equations [11]–[12]. He shows that if the system is not stable, which means that the number of the equations goes to infinity, this case can be physiologically interpreted as cancerogenesis.

The collaborative work of Sendov and Tsanev is a typical example of tight interaction between the two sciences biology and mathematics. From one side biology benefits from mathematics, from the other side mathematics also benefits, as novel interesting problems and suitable tools for their solution appear. Such a tool is the analysis of Hausdorff-continuous functions and interval analysis. The contributions of Prof. Sendov to Hausdorff approximations is well-known. Here I would like to mention some of his contributions to interval analysis.

2. The contributions of Prof. Blagovest Sendov to interval analysis.

At many places in Sendov-Tsanev models partially continuos functions of one variable appear, that is functions which are continuous in certain subintervals of their domain and have "jumps" in between, the simplest such function being the Heaviside step function. The interest of Prof. Sendov to such functions is well-known. It can be assumed that this interests of him led him to numerous results around these functions, in particular to the integrated "Theory of Hausdorff Approximations" developed by him. An important role in this theory is played by the so-called Hausdorff continuous functions, which are a special case of interval functions. In this way the theory of Hausdorff aproximations is tightly related to interval analysis. Such relations have been found during the years and I shall briefly mention how this happend.

Incidentally, the first difficult problem that was given to me by Prof. Sendov in my diploma work about finding an algorithm for the Hausdorff approximation of the Heavyside step function (function "jump"). At that time we tried to perform numerical computations

related to this problem [13]; then jointly with N. Dimitrova in [14]. Later on the problem was successful solved by K. Ivanov and V. Totik [15].

The investigations in the field of interval analysis were initiated by Prof. Sendov during 1976-1980. Interval functions have often been discussed in relation to Hausdorff approximations at Sendovs seminar on Approximation Theory held regularly in the Institute of Mathematics since 1964. Numerical computations related to the best polynomial Hausdorff approximations of certain interval functions require special attention to round-off errors. In 1975 Sendov, who was my PhD supervisor, gave me reprints of papers by T. Sunaga, H. Ratschek and G. Schroeder on interval arithmetic and differentiation of interval functions. I was very impressed by these papers, especially by the famous paper by T. Sunaga, which I studied thoroughly and later on wrote a review of this extraordinary paper [16].

In the years to follow 1975 Prof. Sendov actively worked in the field of interval analysis and published several papers on so-called S-limit and S-derivative of interval functions — terms that are tightly related to the theory of Hausdorff approximations, [17]–[19].

In this papers Sendov established a theory for analysis of interval functions. His studies have been continued by some his many collaborators and during the years a lot of scientific papers have been published. Here I would like to mention some of the developments about the relations between Hausdorff-continuous functions and interval analysis obtained in the past decade thanks to a new property established in 2004 by Roumen Anguelov.

The above mentioned novel property is that the set of Hausdorff-continuous functions is complete after Dedekind with respect to the familiar order relation. Let us note that the familiar functional spaces such as the space of continuous functions, the Sobolev spaces etc, with very few exceptions, are incomplete w.r.t. the order relation. Thus, a possibility appeared to solve a number of open problems in real analysis and the general theory of PDE or to improve previous results using Hausdorff continuous functions. An important result is the introduction of algebraic operations with Hausdorff-continuous functions and their application for numerical computations.

Let us mention that Hausdorff-continuous functions form a special

class of interval functions. It is well-known that interval functions do not form a linear space. Thus it is an important fact that the algebraic operations for addition and multiplication by scalars in the set of continuous functions can be extended over the set of Hausdorff-continuous functions in such a way that they form a linear space. In several papers (jointly with Prof. Sendov) it has been shown that the space of Hausdorff-continuous functions is the largest linear space of interval functions [20]–[22]. The obtained results have been applied to numerical computations [23].

The present conference BIOMATH-2012 proves that the pioneering work of Prof. Sendov in the field of mathematical modelling is alive. The idea of the BIOMATH Conference is to become a forum for biologists and mathematicians, chemists and physicists, computer scientists and others, working together as partners in research connected with living organisms and the applications of the results to medicine, biology, ecology, agriculture and elsewhere. It is natural in such collaborations that the leading ideas come from the biologists. However, success depends on the abilities of both sides, especially when complicated mathematical models are involved.

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5 KEYNOTE & INVITED TALKS

5.1 Global Stabilization of Bioreactor Models

Neli Dimitrova, Mikhail Krastanov
Institute of Mathematics and Informatics
{nelid,krast}@math.bas.bg

Keywords: nonlinear dynamic model, adaptive output feedback, global asymptotic stabilization, extremum seeking

Dynamic modeling of wastewater treatment using anaerobic digestion has been an active research area in the last four decades. After the introduction of the Haldane model [1] to characterize the growth inhibition and later of the model with single bacterial population [3], the modeling studies have been extended and detailed in order to get closer to the complexity of the process. This results in detailed models of the anaerobic digestion process, including several bacterial populations and several substrates. As a consequence, these models are difficult to calibrate and to use for control purposes. Simpler models in turn are more effective when used in designing control and optimization strategies.

Here we consider known nonlinear dynamic models [4], [5] describing an anaerobic digestion process in a continuously stirred bioreactor. Some control laws have recently been proposed for these model like the adaptive feedback of the gaseous flow rate [5] or the controller that regulates the Biological Oxygen Demand (BOD) [4], just to mention a few. This work is devoted to the global asymptotic stabilization of the models by means of a nonlinear output feedback control law. Usually, the most crucial problem in modelling bioreactors is the formulation of reasonable expressions of the bacterial specific growth rates. The feedback control law proposed here, does not assume any analytical expressions for the growth rates. Moreover, the proposed controller feeds back only the available measurements, which is the output methane flow rate. The feedback law depends on a single parameter, the so called feedback gain, that can be tuned to stabilize the system towards a previously chosen desired operating (set) point

value. This operating point could be the acceptable level of pollution in the outflow of the bioreactor, or the maximum methane flow rate. The latter problem is solved by designing a numerical model-based extremum seeking algorithm [2]. It is also shown that the feedback is robust under model uncertainties. Computer simulations are reported to illustrate the theoretical results.

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5.2 Wentzell semigroups in mathematical epidemiology

József Z. Farkas
Department of Computing Science and Mathematics
University of Stirling, United Kingdom
jzf@cs.stir.ac.uk

Keywords: Structured populations, mathematical epidemiology, Wentzell semigroups, Wolbachia infections, stability, operator semigroups

In this talk we are going to discuss some physiologically structured population models with diffusion in the state (size) space, distributed recruitment process and Wentzell boundary conditions. We will introduce Wentzell boundary conditions first through a general linear model, and then we will analyze a nonlinear model for the spread of an infection. Individuals are structured with respect to a continuous variable which represents a pathogen load. The class of uninfected individuals constitutes a special compartment which carries mass, hence the model is equipped with Wentzell (or dynamic) boundary conditions. Our model is intended to describe the spread of infection of a vertically transmitted disease, in particular we are interested in *Wolbachia* infections in mosquito populations, hence the only nonlinearity arises in the recruitment term. Well posedeness of the model and the Principle of Linearised Stability follow from standard semilinear theory. In our main result we establish existence of non-trivial steady states to the model. Our method utilizes an operator theoretic framework with a fixed point approach.

This is joint work with Àngel Calsina (Universitat Autònoma de Barcelona) and Peter Hinow (University of Wisconsin - Milwaukee).

5.3 Size-structured populations with distributed states at birth

Peter Hinow[1]
Department of Mathematical Sciences
University of Wisconsin - Milwaukee
P.O. Box 413, Milwaukee, WI 53201-0413, USA
hinow@uwm.edu

Age-structured models have been employed successfully in population dynamics for a long time and are considerably well understood. In contrast to such models where every individual is born at the same age 0, size-structured models allow to take into account different, distributed birth sizes. "Size" here can be a quite general concept, for example mass, energy content or pathogen load in a disease model. This introduces a birth operator that takes values in an infinite-dimensional Banach space and complicates greatly the mathematical analysis. In this survey, we will describe some examples of models that we recently investigated in a series of joint papers with Jozsef Farkas (University of Stirling, United Kingdom). The emphasis will be on questions such as asymptotic growth for linear models and the existence and stability of steady states for nonlinear models.

[1]joint research with Jozsef Z. Farkas, Department of Computing Science and Mathematics, University of Stirling, Stirling, FK9 4LA, United Kingdom. The research of P.H. is partially supported by grant DMS 1016214 from the National Science Foundation of the USA.

5.4 Natural weights for uniform approximation by sequences of operators

Kamen G. Ivanov
Institute of Mathematics and Informatics
Bulgarian Academy of Sciences

Uniform approximations with weights

$$w(x) = w(\gamma_0, \gamma_1; x) = x^{\gamma_0}(1-x)^{\gamma_1} \text{ for } x \in (0,1)$$

by Bernstein Polynomials B_n are considered. It is proved that the weighted error can be characterized by an appropriate K-functional $K_w(f,t)$ only for weight powers $\gamma_0, \gamma_1 \in [-1,0]$. More precisely
Theorem. Let $\gamma_0, \gamma_1 \in [-1,0]$. There exists an absolute constant M such that for every $f \in C(w)(0,1)$ and every natural number n we have

$$\frac{1}{2}\|w(f-B_nf)\| \le K_w\left(f, \frac{1}{2n}\right) \le M\|w(f-B_nf)\|.$$

The partial case $\gamma_0 = \gamma_1 = 0$ of this statement was proved independently by Totik and by Knoop and Zhou in 1994. The above inequality is not true when $\gamma_0 \notin [-1,0]$ or $\gamma_1 \notin [-1,0]$. Furthermore, the weighted K-functional is characterized by new weighted moduli of smoothness. In order to put such statements in a more general framework we give the following
Definition. *A weight w is called a* natural weight *for approximation by a sequence Q_n of operators in a specified norm if the norm of the weighted approximation error $w(f-Q_nf)$ allows matching direct and strong inverse estimates for the widest reasonable class of functions f.*

Currently, the following natural weights for other sequences of operators are known. The weights $w(\gamma_0, \gamma_1)$, $\gamma_0, \gamma_1 \in [-1,0]$, are natural for uniform approximation by Goodman–Sharma modification of Bernstein polynomials and by a similar modification of Meyer-Konig and Zeller operators. The weights $(x/(1+x))^{\gamma_0}(1+x)^{\gamma_\infty}$, $\gamma_0, \gamma_\infty \in [-1,0]$, are natural for uniform approximation by Goodman–Sharma modification of Baskakov operators. In contrast with the other results the weights $(x/(1+x))^{\gamma_0}(1+x)^{\gamma_\infty}$ are natural for uniform approximation (and for L_p approximations, $1 \le p < \infty$, as well) by Post-Widder and by Gamma operators *for all* real γ_0, γ_∞.

5.5 Toward a more complete and more accurate picture of the molecular biology of the cell[1]

Atanas Kamburov
Max Planck Institute for Molecular Genetics, Berlin
kamburov@molgen.mpg.de

Keywords: molecular biology, molecular interactions, protein-protein interactions, pathways, interaction integration, interaction confidence

Knowledge of all molecular interactions that take place in the cell promises unprecedented insights into biological processes in health and disease. Motivated by this, various methods have been developed for the detection of functional and physical molecular interactions. Examples include the yeast-two-hybrid technology for the detection of protein-protein interactions, and the ChIP-seq technology for the discovery of gene regulatory interactions. Applications of such methods have resulted in the accumulation of large quantities of interaction data for human and for other organisms. However, the available interaction knowledge is currently fragmented and dispersed among hundreds of public databases, each of which has its specific focus, data model, and exchange formats. This hampers a systems-level understanding of cell biology, because different types of interactions are still viewed and analyzed separately as if they were not part of one integrated system.

To obtain a more comprehensive model of biological reality on the molecular level, we have developed the interaction meta-database ConsensusPathDB (http://consensuspathdb.org). It integrates different types of human molecular interactions such as protein-protein interactions, genetic interactions, metabolic and signaling reactions, gene regulatory interactions, and drug-target interactions from public databases. Currently, it consolidates more than 210,000 unique interactions and over 3,330 pathways from overall 30 interaction resources.

[1] An extended version of this talk is presented also at the School for Young Scientists.

Through regular database rebuilds it is ensured that the integrated interaction content of the meta-database stays up-to-date. Physical entities and interactions from different sources are mapped to each other in order to avoid redundancies. The integration of heterogeneous interactions results in a seamless molecular association network that reveals multiple functional aspects of genes, proteins, complexes, metabolites, etc. simultaneously. Thus, it captures the molecular biology of the cell in a more complete and less biased manner. The integrated network is modeled as a mixed bipartite multigraph, allowing for a broad flexibility in accommodating different types of associations between various molecules and with different cardinalities. The web interface of ConsensusPathDB offers various ways of utilizing the integrated database content. It features several tools for network search, visualization, and analysis. Notably, it also offers various tools for the interpretation of high-throughput gene expression and metabolomics data in the light of biological interactions and pathways. Among these are over-representation and enrichment analysis that can be conducted with user-specified genes or metabolites and are based on different definitions of functional gene/metabolite sets, ranging from predefined biochemical pathways, Gene Ontology categories, and protein complexes to network neighborhoods constructed from interaction information from dozens of resources. For example, the combination of different tools available through the web interface can aid the identification of patient-specific disease-causative genes, and at the same time can point to available drugs targeted at those genes.

A widely appreciated problem of current molecular interaction data (especially of protein-protein interactions) is the high fraction of false positives. To "de-noise" our integrated interaction database and thus to obtain a more accurate picture of cell biology, we have developed an interaction confidence scoring method called CAPPIC and a correspong computational tool called IntScore (http://intscore.molgen.mpg.de). It enables to weight interactions according to the probability that they are true, and eventually to remove interactions that are likely false positives.

5.6 Error analysis of a semidiscrete FEM for some fractional order parabolic equations

Bangti Jin, Raytcho Lazarov, Joseph Pasciak, and Zhi Zhou
Department of Mathematics, Texas A&M University,
College Station, TX 77843, U.S.A.
lazarov@math.tamu.edu

Keywords: numerical methods, fractional order parabolic equations, optimal error estimates

We consider the initial boundary value problem for the homogeneous time-fractional diffusion equation $\partial_t^\alpha u - \Delta u = 0$ $(0 < \alpha < 1)$ with initial data $u(x,0) = v(x)$ and a homogeneous Dirichlet boundary condition in a bounded polygonal domain Ω. Here $\partial_t^\alpha u$ is the left-sided Caputo fractional derivative, see, e.g. [5]. This equation is known to capture well the dynamics of anomalous diffusion (also known as subdiffusion), in which the mean square variance grows slower than that in a Gaussian process, and has found a number of applications in chemistry, biology, and engineering.

We shall study two semidiscrete approximation schemes, the Galerkin finite element (FEM) and lumped mass Galerkin FEM, by using piecewise linear functions. We establish almost optimal (with respect to the regularity) error estimates, including problems with smooth, $v \in H^2(\Omega) \cap H_0^1(\Omega)$, and non-smooth, $v \in L_2(\Omega)$, data.

For the semidiscrete Galerkin finite element method on quasi-uniform meshes $\mathcal{T}_h$ and $t > 0$ we show the following family of estimates (see, [1]):

$$\|u_h(t) - u(t)\| + h\|\nabla(u_h(t) - u(t))\| \le Ch^2 \ell_h t^{-\alpha(1-\frac{s}{2})} \|v\|_s, \ \ell_h = |\ln h|,$$

where u_h is the finite element solution and $\|\cdot\|_s$ is the norm of the Sobolev space $H^s(\Omega)$, $0 \le s \le 2$. As an approximation to the initial condition we take the orthogonal L_2-projection of v onto the finite elements space.

Further, we consider the convergence of the FEM for the case of very weak initial data, namely, $v \in H^{-s}$, dual to H^s, $0 \le s < 1$.

Such problems are of substantial interest in control and parameter identification problems, see e.g. [4]. Under additional restrictions on the finite element partitioning $\mathcal{T}_h$ we shall show the following error estimate for $t > 0$, $0 \leq s < 1$,

$$\|u_h(t) - u(t)\| + h\|\nabla(u_h(t) - u(t))\| \leq Ch^{2-s}\ell_h t^{-\alpha}\|v\|_{-s},\ \ell_h = |\ln h|.$$

Finally, we will show similar results for the lumped mass FEM method as well. However, the optimal L_2-norm error estimate is valid only under additional condition on the mesh, which in two dimensions is known to be satisfied for symmetric meshes, see, e.g. [3].

We shall also present some numerical experiments that shed insight into the reliability of the theoretical study.

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5.7 On Reliable Numerical Simulations in Biosciences

Roumen Anguelov[1], Yves Dumont[2] and Jean M-S Lubuma[1]

[1]Department of Mathematics and Applied Mathematics
University of Pretoria, Pretoria 0002 (South Africa)

[2]CIRAD, Umr AMAP 34000 Montpellier (France)

roumen.anguelov@up.ac.za; yves.dumont@cirad.fr;
jean.lubuma@up.ac.za

Keywords: Nonstandard schemes, epidemiological models, dynamical systems, advection reaction diffusion equations, integro-differential equations

Biological processes that arise in science are very complex. A lot of effort has been and is being made to build differential models that aim at elucidating these phenomena. However, these models cannot be completely solved by analytic techniques. Consequently, reliable numerical simulations are of fundamental importance in gaining some useful insights on the solutions of the differential equations. Of paramount importance for the involved dynamical systems is the design of numerical simulations that replicate their underlying dynamics such as the positivity of solutions, the dissipativity of the systems, the conservation laws, the stability of equilibria, etc. This talk is based on the Nonstandard Finite Difference (NSFD) method, which has shown great potential in producing numerical schemes that are dynamically consistent with the properties of continuous models. In a first step, we give an overview of our previous works on reliable NSFD schemes for some compartmental epidemiological models of human diseases, including vector-borne ones. In particular, we demonstrate computationally that the disease free equilibrium of each model is globally asymptotically stable under some threshold conditions on the basic reproduction number. Secondly, the study is extended to advection reaction diffusion equations for the modeling and simulation of diseases on the one hand and of enzyme kinetics on the other hand. In the process, concerns pertaining to some types of diffusion are raised. Finally, the investigation is taken one step further, namely to the

design of reliable numerical simulations for a class Volterra integral equations or integro-differential equations that arise in the modeling of the dynamics of disease transmission. In this regard, we illustrate the occurrence of the backward bifurcation phenomenon whenever the integro-differential equation formulation is used for the SIS model. The emphasis of the presentation is more on the reliability and relevance of the simulations resulting from the NSFD schemes than on the theoretical proofs of the results.

5.8 Graph-theoretic conditions for Turing instabilities in biochemical reaction networks[1]

Maya Mincheva
Northern Illinois University
mincheva@math.niu.edu

Keywords: (Bio)chemical reaction networks, reaction-diffusion systems, Turing instabilities, graphs.

Biochemical reaction networks with diffusion are usually modeled by reaction-diffusion systems of equations. We say that a *Turing instability* occurs if a spatially homogeneous equilibrium is asymptotically stable as a solution of the ordinary differential equation system and unstable as a solution of the corresponding reaction-diffusion systems of equations.

In a minimal model of two reaction-diffusion equations for the concentrations of a short-range activator and a long-range inhibitor species, it is necessary that the activator species promotes its own production, in order for Turing instability to occur for some values of the parameters. One of the weaknesses of the activator-inhibitor model is that realistic biochemical mechanisms rarely consist of only two species. We show that biochemical reaction networks with any number of species can be analyzed for the potential to display Turing instability using similar graph-theoretic conditions.

Schematically, biochemical reaction networks can be represented by different types of graphs depending on the reaction kinetics. A bipartite graph with two types of nodes representing biochemical species and reactions is used to represent mass action kinetics mechanisms. The graph-theoretic condition for Turing instability in mass action kinetics reaction-diffusion system is related to the existence of a structure in the bipartite graph referred to as a critical fragment. This type of graph-theoretic condition generalizes the positive feedback cycle and in particular the self-activator condition for Turing instability.

[1]An extended version of this talk is presented also at the School for Young Scientists.

Turing-Hopf instability arises when a spatially homogeneous equilibrium loses its stability via a single pair of complex eigenvalues. A graph-theoretic condition for Turing-Hopf instability which is a generalization of the negative cycle condition for oscillations in ordinary differential equation models will be discussed.

The graph-theoretic technique will be illustrated with concrete models from biochemistry.

This is a joint work with Marc Roussel, Department of Chemistry and Biochemistry, University of Lethbridge, Canada.

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5.9 Structural Immunology of HIV and Co-evolution Patterns in gp120 N-Glycosylation Sites

Anastas Pashov[1], Swetha Garimala[2], Thomas Kieber-Emmons[3]
[1]Institute of Microbiology, BAS, Sofia
[2]Protech Solutions, Inc., Little Rock, AR, USA
[3]University of Arkansas for Medical Sciences, Little Rock, AR, USA

The G120/gp41 complex forms the spikes on the surface of the virions of the human immune deficiency virus (HIV). As a structure that interacts with CD4/CCR5 on human T cells and initiates the viral entry in the cells, this is the main target for inhibitory antibodies. The remarkable genetic variability of HIV is especially characteristic of gp120. Thus, the antibody response to gp120 is thwarted by a constant escape by structural changes of the exposed gp120 structure as well as by shifting the position of the numerous N-glycosylation sites (or NxS/T sequons). Although the attached carbohydrate side chains remain the same in structure, their position is changed in the course of this rapid molecular evolution creating the phenomenon of the "moving glycan shield". There are two main reasons for varying the position of the glycans on gp120: - protecting the protein core from inhibitory antibodies as well as maintaining its structural stability. Casting light on the sources of the evolutionary pressures for these changes may reveal links between the intrinsic structural variability of gp120 and its antigenic properties. We approached this problem by studying the co-evolution between the gp120 amino acid positions. Mutual information was used as a measure of the correlation between the different positions and the underlying relations, thus revealed, were studied as graphs using social network software. The sequences of 2614 Clade C variants (from the Los Alamos database, http://www.hiv.lanl.gov) were aligned and the mutual information of each positions to each other was calculated and standardized relative to the entropy of the respective row and column. Only the values with z-scores greater than 6 were considered in the further analysis. The most variable positions as well as the most connected ones were found among the variable N-glycosylation sites despite the correction for entropy. This means

that in reality almost all of the mutations in gp120 are related to the position of at least some N-glycosylation sites. On the other hand, the network of co-evolving positions is interspersed with non-sequon positions, which indicates a strong structural dependence. The main component of the network contained three cliques, two of which were denser, interconnected and represented local relationships in the outer domain, particularly in V4 and V5 regions. The third one is a chain of relations between sequons at a long range and may be more related to immunological pressure. Interestingly, a broadly neutralizing anti-carbohydrate antibody 2G12 binds 3 glycans at positions belonging to this third clique and apparently its evolutionary pressure on the gp120 structure has some long range effects. The receptor binding sites were practically void of connections. A structure populated densely with hub positions is the $\alpha 2$ helix and the adjacent $\beta 14$ strand. Interestingly, this region contains an immunodominant class II epitopes and induces class II restricted CD4+ cytotoxic T cells. Apparently, the evolutionary pressure through this immunogenic region can have a deep effect on gp120 structure yet spares the (co)receptor binding sites.

5.10 A model of chaperone overload in aging organism

Santiago Schnell

Brehm Center for Diabetes Research
University of Michigan Medical School
Ann Arbor, MI 48105-1912, USA
schnells@umich.edu

Chaperones play fundamentals role in the folding of newly synthesized proteins and in sequestering damaged proteins in cellular proteostasis. In aging organisms, failures in proteostasis lead to increased protein damage that may, in turn, contribute to a variety of protein-based diseases, including diabetes, cancer, cataracts, Alzheimer's disease and Parkinsons disease. In this talk, we present a model of protein chaperone requirements and availability. The model allows us to study how the balance between chaperone requirement and availability induces chaperone overload in aged organisms. Chaperone overload occurs when the need for chaperones to repair damaged proteins greatly exceeds the available chaperone capacity. Our model results permit us to propose new research strategies that may ameliorate chaperone overload in protein diseases.

5.11 Understanding Phase Locking Behavior in Models of Oscillatory Signaling Pathways

Karyn L. Sutton
University of Louisiana at Lafayette
kls6479@louisiana.edu

Oscillatory signals can be found ubiquitously in nature, regulating a wide variety of physiological and cellular processes. One well-studied system is the G protein coupled receptor (GPCR)-mediated signal transduction pathway, which, among other things regulates intracellular Ca 2+ oscillations, a key second messenger for cell function. However, there is much left to be done in understanding the mechanisms involved in pathways and regulation of the circuit architecture. Under constant stimulation, several models based on distinctly different structure and regulatory mechanisms result in solutions with indiscernible differences in calcium oscillatory features. The ability to stimulate cells in a time-dependent fashion in a microfluidics device allows for the observation of key differences in entrained Ca2+ oscillations, or phase locking behavior, thereby providing a means by which to determine the likelihood or feasibility of pro- posed mechanisms in the pathways. We demonstrate the use of sensitivity analysis to gain a better understanding of recent observed differences in Ca 2+ oscillations within the cell as related to model behavior, and interpret the results of these techniques to provide a mechanism-based explanation of these differences. Finally, we brie y discuss future potential uses of inverse problem methods in an effort to determine signaling circuitry in the context of microfluidics experiments.

5.12 Multiscale analysis of composite structures with applications to biology

Claudia Timofte
Faculty of Physics, University of Bucharest, Romania
claudiatimofte@yahoo.com

The goal of this talk is to present some homogenization results for nonlinear diffusion problems in composite structures, formed by two media with different features. Our setting is relevant for modeling electrical conduction in biological tissues. We shall consider a mathematical model for the electrical conduction in a medium composed of two different conductive phases (the intracellular and extracellular spaces), separated by a dielectric interface (the cell membranes), which has a capacitive and a nonlinear conductive behavior. The electric potential verifies elliptic equations in the two conductive regions, while a dynamic nonlinear condition is imposed on their interfaces. Using the periodic unfolding method, which allows us to deal with very general heterogeneous media, we can study the evolution in time of the homogenized potential. The model will allow us to analyze the Maxwell - Wagner interfacial polarization effect. We shall also discuss a completely different model, i.e. the *bidomain model*, which governs the bioelectrical activity of the heart at a macroscopic level. Our results constitute a generalization of those contained in [1-2].

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6 Conference Sessions and Presenters

Biological Fluids, Tissues, Bones and Membranes

Cell Biology, Physiology and Pharmacokinetics

Ecosystems and Population Dynamics

Epidemiological Models

Image Processing

Microbial Growth, Enzyme Kinetics, Biotechnological and Biochemical Processes

Molecular Biology, Bioinformatics

"Acad. Blagovest Sendov 80" Advanced Mathematical Methods and Computational Tools for Biological Applications

School for Young Scientists

7 CONTRIBUTED TALKS

The Problems of Parameters Identification and Optimal Control for the Monocycle Cells Aggregation Model

V. Akimenko and Yu. Zahorodnii
akm15@meta.ua, yuzagor@ukr.net

Keywords: biomass of cells, age-structured model, transport equation, parameters identification, optimal control, cells growth.

It was concerning the age-structured model of biological cells evolution on the basis of initial-boundary problem for the hyperbolic type equations which describe transport process by age. The main parameters of the model are biomass $m(\tau, t)$ and density $h(\tau, t)$ of the monocyclic group of the cells of biological age $\tau \in [0, \tau_{max}]$ at time $t \in [0, T]$.

The model has specified biological age $0 \leq \tau_d \leq \tau_{max}$, in which a cell can divided into $\mu > 1$ subsidiary ones. It also includes the criteria of inequality of the cells density with some target distribution on age parameter $\tau \in [0, \tau_d]$ during defined interval of time. It was assigned and solved the problem of optimal control of biological cells system on the base of this criteria.

Present type of the models belongs to the bio-kinetics problems and describes the biological cells evolution processes as the process of their transport on the age parameter through stages of their birth, dividing, aging and death. For the concerned linear initial-boundary system it was obtained the analytical solution.

The problems of parameters identification and optimal control were tested on the examples of some class of parameters on the base of experimental data of the hop plants growth during three-years period.

This approach for modelling and parameter identification gives the possibility to assign and resolve practical problems for researching of biological organisms, their growth control and defining dependences from environmental factors, for examples from gamma-irradiation dose or viruses affection.

A Model for a Wood Frog Population

Nofe Al-Asuoad[1], Roumen Anguelov[2], Keith Berven[3], and Meir Shillor[1]

[1] Department of Mathematics and Statistics
Oakland University, Rochester, MI 48309
nalasuoa@oakland.edu, shillor@oakland.edu

[2] Department of Mathematics and and Applied Mathematics
University of Pretoria, Pretoria, South Africa
roumen.anguelov@up.ac.za

[3] Department of Biological Sciences
Oakland University, Rochester, MI 48309
berven@oakland.edu

We present a novel model for the dynamics of a population of Wood Frogs. The model is in the form of a system of impulsive differential equations for each developmental stage (larvae, juvenile, and mature). It also takes into account the differences in the growth of the early, middle, and late stages within the juvenile population. Then we present a computer algorithm for the problem and some illustrative examples. The model and the simulations provide a means to evaluate and predict the survival rate of the colony. The model and the simulations are motivated by over 20 years of data collecting of a specific Wood Frogs colony in Michigan, USA. It is seen that the results agree qualitatively with the observed data.

Impact of phenol and its substituted derivatives on the degradation kinetics of filamentous yeast *Trichosporon cutaneum*

Plamena Zlateva[1], Maria Gerginova[2], Zlatka Alexieva[2*]
[1]Institute of System Engineering and Robotics,
[2]Institute of Microbiology, Bulgarian Academy of Sciences
*Corresponding author: zlatkama@yahoo.com

Keywords: phenol, phenol derivatives, Haldane kinetic model, Trichosporon cutaneum

The purpose of the present study was to determine the level of influence of the kind of phenolic substrates utilized by *Trichosporon cutaneum* R57 on the kinetics of degradation processes. The comparison of some kinetic parameters demonstrated that the kinds of substrate as well as the number of substitution groups specify the degradation rates of the process. The compounds used as substrates in this study are as follow: phenol, resorcinol, hydroquinone, 3-nitrophenol, 2,6-dinitrophenol, 2-chloro phenol and p-cresol. The strain *Trichosporon cutaneum* was cultivated in a minimal medium supplemented with each one of the phenolic compounds as a sole carbon and energy source. The specific degradation rates (Qs) were described by a Haldane kinetic model. The unknown model parameters were estimated using the mathematical optimization procedure for direct search. The search for the optimal values of the kinetic constants was constrained within boundaries predetermined on the basis of the process knowledge and experimental data. The results obtained demonstrated that degradation rates varied greatly in the experiments carried out. The level of biodegradability depended on the different structure and toxicity of compounds used as carbon substrates, in this case. The most toxic chlorinated phenols were characterized with the smallest Qs values while the highest value of this parameter was observed for low toxic hydroxylated phenols. The relationship between chemical structure and levels of degradation of toxic chemical contaminants provides an approach for predicting and evaluating the effectiveness of microbial destructors in the development of biotechnological processes involved in cleaning the environment.

Injectivity and Exact Inversion of Ultrasound Operators in the Spherical Geometry

Gaik Ambartsoumian
The University of Texas at Arlington
gambarts@uta.edu

Keywords: Radon transform, ultrasound operators, inversion, imaging, tomography

In ultrasound tomography an emitter sends acoustic waves through the body, and the reflections of these waves are registered by a receiver. These data measured for various locations of emitter and receiver are then used to reconstruct the acoustic reflectivity function, which represents an image of the interior of the body. Mathematically this procedure is equivalent to the inversion of an operator, which puts into correspondence to the image function the measured reflections at available receiver locations. The talk discusses the injectivity of ultrasound operators in the spherical geometry of data acquisition, and exact inversion procedures derived for several setups in this geometry.

Interval Structures in Real Analysis
Contribution of Blagovest Sendov to the Theory of Interval Functions

Roumen Anguelov[1,2] and Svetoslav Markov[1]
[1]Institute of Mathematics and Informatics, Bulgarian Academy of Sciences
University of Pretoria, South Africa

Keywords: H-continuous functions, S-continuous functions, ...

The contribution to science is often measured by the impact of one's work on future developments in terms of providing new direction, establishing a new theory or whole new field. The work of Blagovest Sendov on Interval Analysis can definitely be measured in such terms. Interval structures were first introduced by Sunaga they got popularity after intervals were introduced in practical applications leading to the design of the so called validated numerical method. The beginning of this development is associated with R Moore who is also often credited as founder of Interval Analysis. While the main preoccupation of the researches was the numerical computations - algorithms, reliability, speed - Blagovest Sendov saw a different aspect in this new development, namely, the spaces of interval valued functions. This new direction gave a new understanding of Interval Analysis (probably closer to its name) as Analysis of Real Interval Valued Functions with associated concepts of order, limit, algebraic operations, calculus, etc. Naturally, as in all areas of Analysis, the spaces of functions with particular topological, order or algebraic structure are essential role players. The topic of Interval Computations and Interval Analysis was introduced in Bulgaria via a series of meetings and publications initiated by Blagovest Sendov. During this early time of development of the interval ideas in Bulgaria he also defined two of the most important functional spaces, namely the space of S-continuous interval functions and the space of H-continuous interval functions. These two spaces are essential tools in the Sendov's Theory of Hausdorff Approximations, [1]. However, future developments showed their importance for other areas of Mathematics like Real Analysis and the General

Theory of PDEs not to mention the Interval Analysis itself. It turned out that

- The space of H-continuous functions is the largest linear space of interval functions;
- The H-continuous functions provide a constructive completion of the set of continuous functions in many respects, e.g. in terms of order, [2], algebraic structure (rational completion), topological processes (order convergence structure);
- The solutions of large classes of nonlinear PDEs can be assimilated with H-continuous functions.

We believe this is only the beginning of this new development with many interesting properties of these spaces yet to be explored, e.g. the fact that the unit ball of the space of S-continuous functions is compact, the interval values of H-continuous functions as shock fronts of waves.

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Generalized net model of the withdrawal reflex observed in the upper limb

Simeon Ribagin, Vihren Chakarov, Krassimir Atanassov
Inst. of Biophysics and Biomedical Engineering
Bulgarian Academy of Sciences
Acad. G. Bonchev Str., Block 105, Sofia-1113, Bulgaria
sim_ribagin@mail.bg, vihren@clbme.bas.bg, krat@bas.bg
and
Anthony Shannon
Faculty of Engineering & IT, University of Technology
Sydney, NSW 2007, Australia
tshannon38@gmail.com, Anthony.Shannon@uts.edu.au

In a series of papers the Generalized Net (GN) models of the human body and its systems are described in general. The present paper is devoted to the GN-modeling of the withdrawal reflex observed in the upper limb. With the present model, we describe the local signs produced by the painful stimulus and analyze the underlying neuronal mechanisms. The model involves structures of the hand and wrist, elbow complex and the pathway of the painful impulse from the sensory structures of the hand to the spinal cord and back to the reacting muscles producing the actual movement. The model is constructed in a simplified form. The purpose of the present paper is to give an example of GN-modeling of an involuntary movement in the upper limb.

Sensitivity analysis and parameter estimation of leukopoiesis model with two delays

Gergana Bencheva
Institute of Information and Communication Technologies
Bulgarian Academy of Sciences
gery@parallel.bas.bg

Keywords: Delay differential equations. Sensitivity analysis. Immune reconstitution.

A mathematical model for leukopoiesis has been proposed in [1], consisting of a system of ordinary differential equations with two delays. Its parameters are estimated for white blood cells produced from myeloid progenitor cells. It is shown in [2] that the same model is applicable also for reconstitution of white blood cells produced from lymphoid progenitors but with different parameter values. For certain parameter values the numerically obtained behaviour of B cells is in agreement with the clinical data. The aim in the current study is to extend the results in [2] with a detailed sensitivity analysis and estimation of the model parameters for T, B and NK cells and their subpopulations. A free Sensitivity Analysis Tool (SBML-SAT) based on Matlab and Systems Biology Markup Language is used for this purpose.

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Mathematical Modelling of Lipopeptide Microbial Production by Cells of *Bacillus subtilis* Immobilized in Biofilm

V. Beschkov[1], Ts. Sapundzhiev[1], O. Chtioui[2], K. Dimitrov[2], F. Gancel[2], I. Nikov[2]

[1]Institute of Chemical Engineering, Bulgarian Academy of Sciences
Sofia 1113, Bulgaria

[2]ProBioGEM Laboratory, University of Lille Nord de France
59655 Villeneuve d'Ascq Cedex, France

Industrial microbial processes are frequently accomplished with cells immobilized on solid supports as biofilm. The thickness of this film varies in time because of the microbial growth and cell accumulation. This fact leads to undesired effects of shortage in substrate supply for the cells being closer to the solid support.

In the present study this effect is studied mathematically by a model based on the second Fick's law for molecular diffusion and the kinetics of microbial growth described by the Monod equation. As a case study the unsteady production of the lipopeptide fengycine by the bacteria *Bacillus subtilis*, immobilized on a plane solid surface is considered.

A system of second order partial differential equations, coupled with the Monod kinetics for the microbial growth is chosen to describe the process. The mass transfer between the bulk fluid and the solid support is taken into account by the boundary condition for the continuity of the mass fluxes on the interphase between the biofilm and the adjacent fluid. The system was solved by the dynamic simulator 20-sim (Dutch production software) rendering the partial differential equations to ordinary ones by discretization on the time coordinate. Comparison with available experimental data for fengycine production in a bioreactor with rotating discs was made. The results of this modeling could be used for studying the real process and for evaluation of kinetic parameters from experimental data by identification procedure.

On Pelican extinction and related eco-epidemiological instability: A new outlook

Sabyasachi Bhattacharya[1,*], Priti Kumar Roy[2],
Sourav Rana[1], Nikhilesh Sil[3]
[1] Agricultural and Ecological Research Unit,
Indian Statistical Institute,
203, B. T. Road, Kolkata 700108, India.
[2]Center for Mathematical Biology and Ecology,
Department of Mathematics, Jadavpur University,
Kolkata 700032, India.
[3] Narula Institute of Technology,
81, Nilgunj Road, Agarpara, Kolkata 700109, India.
*sabyasachi@isical.ac.in

Ecology of Salton Sea in the light of Pelican extinction and related epidemio- logical instability are well studied through a seminal paper by Chattopadhyay and Bairagi (Ecological Modeling, 2001). A series of extension through more sophisticated model building approach under both deterministic and stochas- tic setup have been introduced by the common group of authors, in several articles (Ecological Modeling, 2003; Environmetrics, 2001). We propose a more realistic discrete time extension of their three component continuous models consisting of susceptible fish population, infected fish population and their predator (the Pelican population) with Theta-logistic growth (Sibly et. al., 2005, Science) in prey. Numerical simulations for a hypothetical set of parameter values for the proposed model are presented to illustrate the an- alytical findings and the outcome has been compared with the existing case.

Viral Dynamic Model of antiretroviral therapy including the integrase inhibitor Raltegravir in patients with HIV-1

Dimitra Bon[1,3], Christoph Stephan[1]
Oliver T. Keppler[1,2], Eva Herrmann[1]
[1]University Hospital Frankfurt, Germany
[2] University Hospital Heidelberg, Germany
[3]bon@med.uni-frankfurt.de

Keywords: HIV, mathematical modeling, integrase inhibitor treatment

Combination antiviral therapies consisting of reverse transcriptase inhibitors, protease inhibitors and an integrase inhibitor, have been developed to suppress HIV below the limit of detection[2]. In this presentation, we introduce a mathematical model for the effect of different combination treatment regimens on the dynamics of HIV RNA and CD4 T-cell counts [1,3,4]. We will especially focus on modeling the treatment effect of the integrase inhibitor-Raltegravir [5]. The model consists of a system of ordinary differential equations and the parameters were chosen or estimated in order to agree with clinical data of a recent clinical trial [6]. All the numerical simulations were calculated with Matlab.

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The effect of water level in a prey-predator interaction: A nonlinear analysis study

S.M.Bouguima and N.Chiboub Fellah
Department of Mathematics
Faculty of Sciences
University of Tlemcen-Algeria
email adress:bouguima@yahoo.fr

Keywords: water level, prey-predator interaction, periodic solution, coincidence degree

Water level may influence local community dynamics. We examine how seasonal variations in water level affect the outcome of prey-predator interactions in Parloup Lake in the south of France.We propose a new model to describe the annual cycle of persitence by using continuation theorem of coincidence degree.Our Model reads as follows.

$$\begin{cases} \frac{dG(t)}{dt} = -\min\left(\frac{r(t)G(t)}{B(t)+D}, \gamma_B\right) B(t) + \gamma_G G(t) - m_G (G(t))^2 \\ \frac{dB(t)}{dt} = \tau_B \min\left(\frac{r(t)G(t)}{B(t)+D}, \gamma_B\right) B(t) - m_B B(t) \end{cases} \tag{1}$$

where G is the density of the prey and B is the density of the predator.The quantity r is the accessibility function of the prey.Under suitable conditions on the parameters, we establish the existence of a positive , and periodic solution.

Reconstruction of a dynamical transmission of tuberculosis model from real data

S. Bowong[1,†,2], D. P. Moualeu[2,*], J. J. Tewa[3,*], J. Kurths[4],
[1] University of Douala, PO Box 24157 Douala, Cameroon
[2] University of Yaounde I, PO Box 812 Yaounde, Cameroon
[3] National Advanced School of Engineering, P.O. Box 8390, Yaounde, Cameroon
[4] Postdam Institute for Climate Impact Research, A 31, 14412 Potsdam, Germany

Keywords: Epidemiological models, Tuberculosis, Season pattern, Parameter estimation, States reconstruction.

This paper deals with the problem of estimating the unknown parameters and underlying variables of a tuberculosis (TB) model from real data of Cameroon. We first present a numerical study to estimate the unknown parameters of a tuberculosis model with seasonality. Simulation results are in good accordance with the seasonal variation of the reported new cases of active TB in Cameroon. We also propose a method to estimate the underlying variables from real data of TB in Cameroon. We show that the system is observable with respect to the output, hence, a differential parametrization of the output and its time derivatives can be obtained. Based on this fact, we proceed to form an extended system, which allows us to propose, in a first stage, a high-gain observer to estimate the output time derivatives and then, in the second stage to estimate the underlying variables. In order, to validate the observability result, simulation studies are performed to predict the evolution of TB in Cameroon.

[2]UMI 209 IRD/UPMC UMMISCO, Bondy, France and Project-Team GRIMCAPE, LIRIMA, University of Yaounde I, Cameroon

Equiangular surfaces and self-similar surfaces in biology

Khristo N. Boyadzhiev

The logarithmic spiral (also called equiangular spiral) is one of the most interesting curves on the plane. It is used to explain, among other things, the trajectories of insects orientating themselves by a light source [1]. A detailed account of life forms associated with this spiral can be found in [3].

There are two independent properties characterizing the logarithmic spiral: first, it is self-similar [3], and second, it is equiangular, the radius vector and the normal vector at every point cut one and the same angle.

Now we want to explore three-dimensional surfaces with these two properties: surfaces that are self-similar and surfaces that are equiangular. It can be seen that in three dimensions the two concepts are independent (in contrast to two dimensions). There are surfaces that are self-similar and equiangular; there are self-similar surfaces that are not equiangular, and there are equiangular surfaces that are not self-similar [2]. We will give examples of all three types.

Equiangular surfaces in 3-dimensional space are described by the property: at every point on the surface the radius vector and the normal vector constitute a constant angle, independent of the point. Self-similar surfaces are characterized in a different way. A surface S in 3-space is self-similar, if it is defined by the polar equation $\rho(\theta, \varphi) = \rho_0 \exp(\mu\theta + b\varphi)$, where the angles θ and φ are spherical coordinates (latitude and longitude) and $\mu\, b$ are constants. In this case, increments in θ and φ bring to a proportional surface.

As expected, these three-dimensional analogs of the logarithmic spiral are closely associated with certain biological forms. This will be demonstrated in the presentation.

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Role of omnivory in marine plankton - Experimental and model based study

Sourav Rana, Joydeep Pal,
Joydev Chattopadhyay and Sabyasachi Bhattacharya
Agricultural and Ecological Research Unit
Indian Statistical Institute
203, B. T. Road, Kolkata- 700108, INDIA.

Omnivory may be seen as a topological connection among different feeding mechanisms i.e. herbivory and carnivory. Recent scientific studies suggest that omnivory plays a major role in species diversity. There is a considerable amount of debate on the role of omnivory-whether it is stabilizing or destabilizing factor in context of ecosystem functioning. We have collected time series data of plankton species in the Bay of Bengal for the last ten years or so and selected a guild consisting of two omnivorous zooplankton and two phytoplankton, one non-toxic species and another toxic species as the food for the zooplankton. We computed the correlation matrix for the whole guild based on the reciprocal cycles observed within the species seasonally. Based on our experimental evidences, we propose four dimensional mathematical model under three distinct cases related to different mode of feeding criteria of predator. Our results suggest that omnivory acts as a stabilizing factor among the species, depending on the density of the zooplankton members and switching mechanisms in functional feeding.

Output bounds for compartmental in-series models under parametric uncertainty

D. de Pereda, S. Romero-Vivo, B. Ricarte, J. Bondia
Universitat Politecnica de Valencia, Spain
dpereda@upvnet.upv.es

Keywords: Uncertainty, Interval simulation, Monotonicity.

Compartmental models have appeared in many different real-situations emerging from biology, economics and many other research fields. The processes there involved can be approximated as far as possible through a mathematical model. In fact, they present high variability that prevents to accurately deduce the values taken by the parameters of the corresponding model, although these values can be limited to be inside certain intervals.

Bounds on the outputs of a system should guarantee the inclusion both of the modelled dynamics and of those non-modelled in order to predict the behaviour of the system and so to improve for instance its control. By this reason, envelopes of the solutions have been investigated considerably.

In this work, the problem of obtaining tight output bounds for compartmental in-series models under parametric uncertainty is addressed. It is well-known that methods used to compute, traditionally by a monotonicity analysis [1], a solution envelope may produce a significant overestimation. Our main aim is to get an equivalent model to the initial one by performing a suitable combination of equations. In this new model the parameters monotonicity depends on the elimination rate values of the original model. If a given order relation holds for the elimination rates, output bounds are exact, i.e. no overestimations are produced. Otherwise, the method proposed allows us to obtain tighter output bounds for near-monotone systems with lower computational cost than those given by the latest techniques [1].

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Global dynamics for the spread of ectoparasite borne diseases

Attila Dénes
Bolyai Institute, University of Szeged
denesa@math.u-szeged.hu

Keywords: ectoparasite; global dynamics; Lyapunov function; persistence.

A mathematical model is introduced to simultaneously study the dynamics of ectoparasite infestation and infectious diseases spread by those ectoparasites.

The system has four potential equilibria. We identify three reproduction numbers that determine whether the infectious or the non-infectious parasites can invade the population, and whether a population already infested by non-infectious parasites can be invaded by the infection. By using Lyapunov functions and persistence theory, we show that the solutions always converge to one of the equilibria, depending on those three reproduction numbers. Hence the global dynamics is completely characterized by the reproduction numbers.

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Mathematical Modelling of Biotechnological Processes[1]

Roumen Anguelov[1,2], Neli Dimitrova[2], Svetoslav Markov[2]
[1]University of Pretoria, Pretoria 0002, South Africa
[2]Department of Biomathematics
Institute of Mathematics and Informatics
Bulgarian Academy of Sciences
"Acad. G. Bonchev" st., bl. 8, 1113 Sofia, Bulgaria
E-mail (corresponding author): nelid@math.bas.bg

Mathematics is fast becoming an essential tool for experimentation and discovery in biological processes. The practical and economical value of Mathematical Modelling is particularly apparent in fields closely related to industry like biotechnology.

Microbial growth modeling offers a large field of applications of various mathematical and computational tools together with numerous practical applications to various biotechnological processes. Our Department has recently completed a project "Computer Simulation and Innovative Model-Based Study of Bioprocesses" under contract DO 02-359/2008 with the Bulgarian Ministry of Education, Youth and Science. As part of this project all fundamental classes of Monod type microbial growth models have been investigated both theoretically and computationally with respect to their stability. In this way an essential mathematical technology for design of bioreactors and their efficient control has been developed. Other studies are related to novel classes of dynamical models considering subclasses of microbial populations accounting for their physiological state. New trends in the field of microbial growth modeling and future activities will be discussed.

[1]This talk is presented at the School for Young Scientists.

Introduction to the modelling of Plant Growth, and the Mathematical modelling of Plant-Pest Interactions[1]

Yves Dumont,
CIRAD, Umr AMAP, F-34980 Montpellier
yves.dumont@cirad.fr

Keywords: Plant Growth, Mathematical Modeling, Discrete Equation, Plant-Pest interactions, ODE, Biological Control

Plants are essential for life on Earth. They are very complex systems Despite the great importance of plants, only a small number of modellers, and applied mathematicians have been involved in the modelling, the development of mathematical tools, the simulation of plant growth, and, in general, in problems related to Agronomy or Forestry. In fact, the processes that are involved in plant growth are very complex and thus the amount of knowledges necessary to understand how a plant is growing is huge and only a multidisciplinary approach can be used to overcome the encountered difficulties. Because of these complexites it is difficult to handle them efficiently in plant growth models, and, more important, what are the essential ingredients to take into account to obtain a realistic modeling. Indeed, if we know very precisely what is going on in photosynthesis, transpiration processes,..., we didn't yet succeed in the development of macroscopic laws, like in Physics or in Mechanics. Plant growth modelling is not only challenging from the scientific point of view, but is also crucial for real applications, like, for instance, improving crop yields, developing biological tools against Pest attacks, studying the impact of climate change, time evolution of rain forests,.... Thus not only plant growth modeling is challenging but its interactions with the environment too.

The aim of this talk is to present some problems related to plants that are under study in AMAP [1,5,6]). After a brief recall on some "basic" knowledges' in Botany and in Ecophysiology, I will present some modelling approaches commonly used by Biologists and Computer Scientists (see for instance AMAPSTUDIO [2]). Then, I will

[1]This talk is presented at the School for Young Scientists.

turn to a more mathematical approach, using mimimal equations, related to the interactions between plants and insects [3,4].

CIRAD is an International Centre of Agronomic Research for Developing Countries. It is based in Montpellier (France). About 800 researchers, around the world, are working in life sciences, social sciences and engineering sciences, applied to agriculture, food and rural territories.

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Modeling and Simulations of Mosquito Dispersal

Y. Dumont[a] and C. Dufourd[b]
[a] CIRAD -Umr AMAP, Montpellier, France
[b]IRD - CRVOI, Réunion Island, France

Keywords: Mosquito spreading, Modeling, PDE, Simulations

Controlling the spreading of mosquitoes is important to lower the epidemiological risk of an epidemic. Standard vector control tools, like adulticide and larvicide, together with mechanical control, are useful [1], but cannot be always used, because, for instance, mosquito can develop resistance to insecticides. Thus it is absolutely necessary to consider new and sustainable alternatives. The Sterile Insect Method is an interesting feature: it consists of releasing sterile males that will mate with wild females such that the wild population decays under a certain threshold or goes to extinction [2, 3].

The study of wild mosquito dispersal is very important to optimize the releases of sterile males in order to have the maximum impact on the wild mosquito population. We model mosquito displacements taking into account some important environmental and entomological knowledge, like wind, attractors (breeding and blood feeding sites).... In a previous paper [4], we have only considered females in two biological stages: breeding females and blood feeding females. Here, we consider the full model with different compartments including males, immature and mature (breeding, resting and feeding) females, and the aquatic stage. The modeling leads to a very complex system of Nonlinear Partial Differential Equations. Using appropriate numerical methods, we illustrate our talk with different numerical simulations.

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Modeling the Biocontrol of an invasive plant.

A. Mathieu[a], F. Chiroleu[a], S. Quilici[a], O. Flores[a], and Y. Dumont[b]
[a]CIRAD -Umr PVBMT, Réunion Island, France,
[b] CIRAD -Umr AMAP, Montpellier, France

Keywords: Modeling, invasive plant, plant-insect interactions, biocontrol

The giant bramble, *Rubus alceifolius Poir. (Rosaceae)* is one of the most invasive plants in la Réunion. In the last decades, mechanical and chemical control have been used to limit its spreading. However, la Réunion being one of the hot spots of endemicity in the world, the use of chemical products is limited. Moreover, parts of the island are completely inaccessible. Thus, control is really limited. That is why biological control agents have been considered, like *Cibdela janthina Klug (Argidae).*

This sawfly is native from Sumatra and can cause severe damages to *Rubus alceifolius.* After some preliminary studies between 2001 and 2007, Cibdela has been released in 2008 in the South-East part of la Réunion. Since then the Cibdela population has spread through the island. The first objective has been reached: *Rubus alceifolius* has completely disappeared in some places (in particular at low altitudes), while in other places an equilibrium between Rubus and Cibdela has apparently been reached . Altogether, some unexpected situations appeared, and that is why new biological and ecological investigations have began two years ago. In this context, mathematical modeling can be a useful tool to formalize all extensive knowledges about Rubus-Cibdela interactions and to estimate the long term behavior of the bramble, when attacked by the sawfly, at different altitudes.

The aim of this talk is to present some preliminary studies about the modeling of these interactions. We will also present some theoretical results and illustrate our talk with various simulations.

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Characterization of the Discrete Pulse Transform of Images with Applications

Inger Fabris-Rotelli
University of Pretoria, South Africa
inger.fabris-rotelli@up.ac.za

Keywords: LULU, Discrete Pulse Transform, DPT, Nonlinear Decompositions, Feature Detection, brain segmentation

The Discrete Pulse Transform (DPT) for images and videos has been developed over the past few years and provides a theoretically sound setting for a nonlinear decomposition of an image or video. In [1] the theoretical basis of the DPT was presented. In this paper we now present a sound characterization of this useful nonlinear hierarchical decomposition by referring to its ability as a separator, the consistency of the decomposition, as well as the smoothing ability of the decomposition. We illustrate the strength of this decomposition on a application in brain imaging.

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Modeling of viral dynamics after liver transplantation in patients with chronic hepatitis B and D

Natalie Filmann[1,3], Ingmar Mederacke[2], Heiner Wedemeyer[2] and Eva Herrmann[1]

[1]Goethe-University Frankfurt, Germany
[2]Hannover Medical School, Germany
[3]filmann@med.uni-frankfurt.de

Keywords: Infectious diseases, hepatitis B and D, viral dynamics, PK/PD

Viral kinetic models have become an important tool for understanding the main biological processes behind the dynamics of chronic viral diseases and optimizing effectiveness of anti-viral therapy [1]. We analyzed the dynamics of hepatitis B and D coinfection (HBV/HDV) and the pharmacokinetics/pharmacodynamics of the reinfection prophylaxis (=polyclonal antibodies) after liver transplantation. Therefore we developed a mechanistic model consisting of a system of ordinary differential equations. This model was fitted by analyzing the kinetics of HBV/HDV-viremia after liver transplantation in patient data and correlated with the reinfection prophylaxis dosing schemes [2]. The results suggest that this modeling approach may help to optimize reinfection prophylaxis.

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A Realistic Neuron Shape Development in Realistic Cellular Tissue Environment

Jordan Genoff
Technical University of Sofia at Plovdiv
jgenoff@tu-plovdiv.bg

Keywords: realistic neuron development, realistic neuron shape, realistic neuron morphology

Realistic neuron spatial shape development has proven to be a highly complex research topic in biology. There exist several computational modeling methodologies with their mathematical foundations and software implementations for this subject. Though each of them approaches the problem in its individual and original way, they all have a basic common feature - they are neuron-centric, i.e. it is assumed that the neuron shape develops as a result of morphological changes mostly caused by intracellular processes. A significant number of these processes are initiated as reactions to extra-neuronal biochemical or mechanical impacts, but the latter are usually considered in a generalized or, in the best case, probabilistic manner. The incontrovertible fact that neurons are not alone in space and their neighboring cells are not transparent at all is somehow disregarded.

This paper proposes the idea that the exact geometric configuration of the surrounding cells plays a highly important role in the specific shape development of every single neuron. A modeling approach is suggested that aims at detailed investigation of how neuron growth cones are supervised by the neighboring cells and their contact properties. A Cellular Potts Model (CPM) is chosen as a simulation implementation technique. However, which is another contribution in the paper, CPM is utilized in an unusually hard parameter and input data setup, which reveals some avoidable drawbacks of this model.

A Multi-Layered Hidden Markov Model with Entropy Gradient

Jordan Genoff
Technical University of Sofia at Plovdiv
jgenoff@tu-plovdiv.bg

Keywords: hidden markov model, multi-layer stochastic model, sequential data mining

An extension of the classical hidden Markov model (HMM) for sequential data probabilistic modeling is presented. A multi-layer structure is derived as a special case of a Dirichlet process. The proposed recursive procedure assumes the hidden state chain of a given (outer) layer as the observation sequence of the next (inner) layer. The three canonical problems of HMM are formulated according to the extension and their solutions are proposed. Special attention is paid to the third problem - model parameters estimation or learning. The idea to gradually increase/decrease the Markov chain entropy across consecutive layers is introduced and embedded into parameters estimation. Analysis of entropy gradient reveals deeply hidden properties of the sequential data source - either completely i.i.d. stochastic or entirely deterministic nature of the most inner layers. Further investigation is directed towards maneuvering with model order. The multi-layered HMM is experimentally tested on synthetic sequential data, various types of coding DNA and finally - on various types of non-coding DNA.

Molecular Dynamics study of structural and electrostatic features of MHC class II-peptide complexes at different protonation states

D. Grancharov*, B. Atanasov, L. Litov, P. Petkov
University of Sofia "St. Kliment Ohridsky"
*dgrancharov@phys.uni-sofia.bg

MHC class II molecules play important role in the creation of the immune response by presenting antigenic peptides on the cell surface of APC to be processed by T-helper cells. It is widely accepted that acidic environment hosts the process of formation of such MHC class II-peptide complexes and that they undergo conformational changes during their journey to neutral pH. In the current study we use Molecular Dynamics and electrostatic calculations to get insight into specific interactions that take place at the atomistic level of this system. We propose a complete electrostatic model of the neutral to low pH transition for the MHC molecule in which we modify the charge state of the system and thereby account for the acidic properties of the medium. The preliminary results confirm suggestion of pH-dependent conformational changes with functional consequences.

Calculating All Positive Values of IRR in InADeS Using Sendov's Method

Angel Golev, Nikolay Kyurkchiev, Nikolay Pavlov, Asen Rahnev
Faculty of Mathematics and Informatics, University of Plovdiv
236, Bulgaria Blvd., 4003 Plovdiv, Bulgaria
angelg@uni-plovdiv.bg, nkyurk@uni-plovdiv.bg,
nikolayp@uni-plovdiv.bg, assen@uni-plovdiv.bg

Keywords: IRR, Sendov's method, InADeS.

The internal rate of return (IRR) is one of the most popular methods for investment appraisal. A peculiar characteristic of IRR is that there might be several values for IRR for certain cash flows. Therefore, the IRR is associated with two major problems how to determine all possible values for IRR, and how to select the most appropriate one.

This paper describes how we use Sendov's method for simultaneous approximate calculation (localization) of all positive roots of an algebraic polynomial in Investment Analysis and Decision Software (InADeS). An algorithm is developed to calculate all positive values of IRR for a cash flow.

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Mathematical Modelling Regulatory Mechanisms of Molecular-Genetic Systems

B.N.Hidirov
Institute of Mathematics and Information Technologies
regulatorika@yahoo.com

Keywords: molecular-genetic systems, chaos, hepatitis viruses

Attained successes in biology during last century allow to create mathematical and computer models for quantitative studying regulatory mechanisms functioning (regulatorika) molecular-genetic processes in living systems. This work deals with researching regulatorika of cell's molecular-genetic systems based on the notion of regulatory system "orasta", consisting of operator-regulator ("or") and active system with time average ("asta").

Functional-differential equations of molecular-genetic systems regulatorika (E-MGS) are developed using approaches by Bl.Sendov, B.Goodwin, M.Eigen with taking into account temporal relations, presence of combined feedback and cooperative character of processes in cell's regulation loops.

We use developed E-MGS modifications (E-MGSA and E-MGSB) for the quantitative analysis of interconnected activity between liver cells (hepatocytes) and hepatitis viruses (A and B accordingly). Results have shown there are three regimes with domination of hepatocyte molecular-genetic system (α), hepatitis virus dominance (β) and symbiotic coexistence (γ). At E-MGSB the attractor stability can be broken with arising the irregular solutions and "black hole" effect. This implies presence of unpredictable behavior and sharp destructive changes when hepatocyte is infected by hepatitis B viruses. Possibility for quantitative prediction coming the listed regimes and their features allows to establish molecular-genetic bases of infection pathogenesis, to realize diagnostics and forecasting main stages of disease current caused by hepatitis A and B viruses infection

Discrete equations and nonlinear phenomena in biology

B.N.Hidirov, M.Saidalieva, M.B.Hidirova
Institute of Mathematics and Information Technologies,
Academy of Sciences of Uzbekistan, Tashkent,Uzbekistan
regulatorika@yahoo.com

Keywords: discrete equations, regulatory mechanisms, dynamic chaos

As usual, quantitative analysis of functioning regulatory mechanisms (regulatorika) of living systems on different organization levels leads to studying characteristic solutions of the nonlinear discrete equations of regulatorika. General analysis of these equations using the methods for quantitative analysis, studying dynamics of Lyapunov number, Kolmogorov entropy, Lamerey diagrams shows varied behavior of solutions in the basin of positive attractor: stable stationary solutions, Poincare type limit cycles, dynamic chaos and collapsed solutions with transition into attraction field of trivial attractor ("black hole" effect). Construction of appropriate parametric portrait has allowed to research conditions for qualitative alteration of the solutions when changing the parameters values.

Analysis of parametric portrait for discrete equations of regulatorika has shown presence of small regions with normal behavior of solutions (r-windows) in the field of the dynamic chaos. This area borders upon areas of Poincare type limit cycles and "black hole".

Applications of considered nonlinear discrete equations of regulatorika for the quantitative studying origin and developments mechanisms of HIV/AIDS on cellular communities level of immune system, viral hepatitis type B on molecular-genetic level of hepatocyte and hormonal regulation of programmed cell death (apoptosis) on cellular level of the thyroid gland have allowed to define some regularities of these diseases course and to consider questions of possible ways of treatment.

Exploring family relations between international patent applications

Peter Hingley
European Patent Office
phingley@epo.org

Keywords: Censored binomial, genetics, patents, random assignment.

In the international system for granting patents for inventions, first patent filings (FF) can be followed by subsequent filings (SF) at other patent offices within one year. Each such group of related filings constitutes a patent family. In terms of the average $\#SF$ per FF (ϕ) and the average $\#FF$ per SF (θ), the following identity holds for links L within all families [1] :-

$$\#L = \#FF.\phi = \#SF.\theta.$$

Let r be the number of FF that do lead to SF. Tests are developed as to whether the observed r is in agreement with a random process for making SF, conditional on the given set of FF one year earlier. An exact expression for the random distribution of r can be used for small sized data sets [2]. Its behaviour and also the behaviour of a normal approximation to a censored binomial distribution for r are assessed. The approach is stimulated by the Wright-Fisher model in population genetics and possible parallel applications to other biological processes are sought, such as to growth of cells in cancer.

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Growth in a Turing Model of Cortical Folding

Monica K. Hurdal and Gregory Toole
Department of Mathematics
Florida State University, Tallahassee, FL, USA
mhurdal@math.fsu.edu

Keywords: cortical folding, morphology, neurobiology, Turing system

The brain's cerebral cortex is folded into many gyri (hills) and sulci (valleys). Little is known about how the cortex folds or why the folds are located where they are. We have developed a spatio-temporal mathematical model of cortical folding to address this question. Our model utilizes a Turing reaction-diffusion system on an exponentially growing prolate spheroidal domain. This domain approximates the shape of the lateral ventricle (LV) during cortical development. The Intermediate Progenitor Model (IPM) of cortical folding states that regional patterning of self-amplification of intermediate progenitor cells (IPCs) in the subventricular zone of the LV corresponds with the formation of cortical folding. As self-amplification of IPCs is genetically controlled via chemical gradients, a Turing system is a logical choice to create a mathematical representation of the IPM. A growing domain model of cortical folding may be more realistic than previous static domain models of cortical folding since it incorporates the growth that inherently occurs as the brain develops. By comparing patterns generated by our growing prolate spheroid Turing system with those generated by a static prolate spheroid Turing system, we show that the addition of growth causes a significant change in system behavior; the system produces transient patterns instead of converging to one final pattern. Our model illustrates the importance of including growth in a model of cortical folding and can be utilized to explain certain human diseases of cortical folding.

Multiple Objective Optimisation of Batch Cultivation of *Saccharomyces cerevisiae* in Mixing Systems

Tatiana Ilkova, Olympia Roeva, Mitko Petrov
Institute of Biophysics and Biomedical Engineering - BAS
105 Acad. G. Bonchev Str., Sofia 1113, Bulgaria
tanja@biomed.bas.bg, olympia@biomed.bas.bg,
mpetrov@biomed.bas.bg

Keywords: Multiple objective optimisation, Saccharomyces cerevisiae, Batch cultivation, Mixing systems, Rotation speed

Multiple objective optimisation is a natural extension of the traditional optimisation of a single objective function. On one hand, if the multiple objective functions are commensurate, minimizing single objective function, it is possible to minimize all criteria and the problem can be solved using traditional optimisation techniques. On the other hand, if the objective functions are incommensurate or competing, then the minimization of one objective function requires a compromise in another objective function. The competition between multiple objective functions is a key distinction between the multiple objective optimisation and traditional single objective optimisation. In our investigations we discussed the problems of multiple objective optimisation of a batch cultivation of the *Saccharomyces cerevisiae* in different mixing systems (impulse and vibromixing) for searching the maximal rotation speed, initial conditions, and amplitude is developed. The multiple objective optimisation problems are transformed to a single objective function with weight coefficients. The applied multiple objective optimisation of the process has shown vast increase of their productivity, respectively decrease in the residual substrate concentration. This result leads to a higher economical effectiveness for each of them at a smaller outlay.

Green Fluorescent Protein based drug response data modeling and analysis[1]

Ivan Ivanov

Department of Veterinary Physiology and Pharmacology,
Texas A&M University
Institute for Applied Mathematics and Scientific Computations,
Texas A&M University
IIvanov@cvm.tamu.edu

We focus on comparing and modeling of the effects of anti-cancer drugs on cell lines. The ability to quantify and compare the effects of a newly developed drug to a range of already available anti-cancer agents is critical when evaluating its potential application. Using a specific Green Fluorescent Protein (GFP) technology developed at TGen, researchers have been able to track various reporter genes from the same cell population for an extended period of time (50 hours). Such dynamic gene expression data forms the basis for drug similarity comparisons. We present a novel time series alignment algorithm that can reliably identify mechanistic similarities in drug responses.

[1]This talk is presented at the School for Young Scientists.

Towards modelling the chemical control in Mal secco Citrus disease management

Khaled Khanchouch[1], Mohamed Rabeh Hajlaoui[2], Hakan Kutucu[3]
[1]University of Tunis, Tunisia
khanchouchkhaled@yahoo.fr
[2]Laboratory of Biotechnology Applied to the Agriculture
National Institute of Agronomic Research, Tunisia
hajlaoui.rabeh@iresa.agrinet.tn
[3]Izmir Institute of Technology, Turkey
hakankutucu@iyte.edu.tr

Mal secco citrus disease is a devastating pathogen in lemon orchards [1]. There are great efforts to control this threat in the regions where the causal agent Phoma tracheiphila is installed and strict regulations in many others countries to prevent its introduction [2]. Selection of the effective chemicals capable to reduce the effect of the pathogen in the infected plants should be based on an efficient model allowing describing precisely the development of the disease in the chemical treated plants. In this study a polynomial model is adopted to evaluate the fungicide activity of Dithane M 45. The model offers to test the fungicide at any concentration of its active molecule, from 0 to 1000 ppm. Results obtained by the mathematical model are in concordance with those of the experimental essays at the tested concentrations. Using the mathematical model it's possible to determine the lowest concentration of the active molecule which gives the highest fungicidal effect. Application of this model reduces significantly the utilization of the over useless doses of the fungicide and thus limit its toxic spread in the environment.

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An influence of age and sex on the elastic mechanical behavior of human abdominal fascia

M. Kirilova, D. Pashkouleva, V. Kavardzhikov
Institute of Mechanics, Bulgarian Academy of Sciences
M.Kirilova@imbm.bas.bg

Keywords: human fascia, elastic properties

The investigations of mechanical properties of human abdominal layers are a basis for the improvement of hernia meshes. This knowledge is necessary for successful matching of properties of tissues and their synthetic substitutes. The purpose of this study is to characterize elastic mechanical properties of human abdominal fascia according to its age, sex and direction of loading.

Twenty nine samples from fascia transversalis (FT) and 55 samples from umbilical fascia (UF) have been cut along the fibers direction or perpendicular to them. The specimens were divided in groups according to their localization, age, sex and direction of loading. The tensile tests were performed. From the obtained stress - stretch ratio curves the following mechanical parameters were determined for both fasciae: mean values of the maximum tensile stress, stretch at maximum stress, maximum stretch ratio and secant modulus at 5% - $E_{(5)}$.The comparison between the defined parameters was accomplished by means of t-test.

The influence of age on the elastic mechanical properties of UF was determined. The differences between mechanical properties of fascia transversalis according to sex are not statistically significant but there exists statistically significant differences between maximum stretch ratio and maximum tensile stress calculated for men and women from umbilical fascia.

The results highlighted age and sex dependency of elastic mechanical behavior of the umbilical fascia. Further experiments with fascia transversalis are necessary to prove the obtained results about this type of fascia.

The spread of influenza on long distance travel networks

Diána H. Knipl
Bolyai Institute, University of Szeged
knipl@math.u-szeged.hu

Keywords: influenza modeling, long distance travel networks, delay differential equations

National boundaries never hindered infectious diseases to reach distant territories; however, the speed at which an infectious agent now can propagate around the world has signicantly increased in the last 50 years. We introduce an SEAIR-based model for long distance travel networks, which describes the dynamics of a pandemic on regions connected by air transportation. Due to the high connectedness of several distant places, we include the possibility of transmission of the disease during travel, which is modeled by an age structured system where age is the time elapsed since the start of the travel. The model is equivalent to a large system of delay differential equations, we examine basic properties of the system. We detail the method of the calculation of the reproduction number, and parametrize the model with influenza and real air traffic data.

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Numerical modelling of Electro-Thermo-Convection and Heat Transfer in 2D cavity

Dantchi Koulova
Institute of Mechanics, Bulgarian Academy of Sciences

We study numerically the combined effects of an electric field and a thermal gradient simultaneously applied to a horizontal dielectric liquid layer. When the electric potential and/or temperature is large enough (above the typical thresholds of the thermo or electro-convective phenomena) a convective motion appears. At sufficient high applied voltage the ion injection from the electrode into the liquid of low conductivity induces an electric space charge and electro-convective motion of the liquid. This motion increases the electric charge transfer between the electrodes and consequently the heat exchange. Therefore the heat transfer in the flow may increase significantly. Such a complex phenomena are described by the Navier-Stokes equations (conservation of mass and momentum), the energy equation (with Boussinesq assumption), the electric charge conservation and Poisson equation (Gauss theorem). This full set of coupled equations of Electro-Hydro-Dynamic (EHD) and Thermo-dynamic we solved directly in 2D rectangular cavity using a finite volume method. We first heat the liquid (at time 0) till the thermal steady state is obtained then we apply the electric potential and injection of electric charges from the walls. The different cases of heating and injecting are considered: heating and injecting from a lateral wall (left or right) and from the lower electrode. The heat transfer is characterized by the Nusselt number. The flow structure and Nusselt number strongly depend on the non-dimensional characteristic parameters: electrical parameter T, Rayleigh number Ra, Prandtl number Pr and mobility parameter M. The convective flow patterns are given for a 2x1 rectangular cavity where the pure thermo-convection gives rise to one or two rolls whereas the pure electro-convection gives four rolls. The development of the convective motion passing from a purely thermal convection to a purely electrical convection is investigated. The combined effect of both electric and thermal field on the flow patterns and on Nusselt number is analyzed for different parameters. We have also evaluated the heat transfer enhancement due to electro-convection. It is shown that the electrical forces increase and dominate the heat transfer.

An intelligent system for semantic mapping and merging of anatomical ontologies[1]

Peter Petrov[1,*], Milko Krachunov[1], Ognyan Kulev[1], Maria Nisheva[1], Dimitar Vassilev[2]
[1]Faculty of Mathematics and Informatics,
University of Sofia "St. Kliment Ohridski", Bulgaria
[2]Bioinformatics group, AgroBioInstitute, Sofia, Bulgaria
*Corresponding author: p.a.petrov@gmail.com

Anatomical ontologies of various species are nowadays publicly available both in scientific literature and on the web. Such ontologies typically contain several thousand terms and relations (usually from 5000 to 10000 each) but often the knowledge employed in them is huge. Having species-specific anatomical ontologies is valuable when it comes to text (literature) searching or text mining in the context of a particular species. But these ontologies do not have the necessary means to aid researchers in performing tasks like cross-species text (literature) searching or cross-species text mining, or to help them design new experiments with new (i.e. not yet tested) organisms based on information available about experiments already performed on certain (e.g. model) organisms. Often though, the experimental results about particular model organism A (e.g. mouse) may be more general and thus applicable to another organism B (e.g. rat), or at least may provide valuable insights about the design of new biological experiments to be performed with the organism B (i.e. rat in this example). This is where the process of mediating anatomical ontologies come into use. We view anatomical ontologies as directed acyclic graphs (DAGs) with their nodes denoting anatomical concepts and their edges denoting relations between these concepts. To mediate (map and merge) two or more anatomical (source) ontologies basically means: (i) to draw cross-species semantic links between the DAGs representing their ontologies; (ii) whenever possible to merge the nodes and the edges from the two input ontologies, and to promote them to a more general model thus

[1]This talk is presented at the School for Young Scientists.

generating as output a new general ontology (i.e. a super-ontology). The only informal requirement for the super-ontology is that it makes sense from the points of the two input species-specific ontologies. The informal requirement to make sense and the models employed (ontologies and DAGs) turn that problem into a task for building an intelligent anatomical ontologies integration software system. The system should be able to map two (and more) input anatomical ontologies and to merge them into a general output super-ontology. The software system solving these tasks is called AnatOM (an abbreviation from Anatomical Ontologies Merger). In this paper we give an outline of the models and the algorithmic procedures for mediating (mapping and merging) anatomical ontologies and a detailed description of the software system AnatOM which implements them.

Proper predation and treatment prevent the extinction of predator and disease propagation-conclusion drawn from a predator-prey system with disease in both populations

Kusumika Kundu[1], Krishna pada Das[2]
[1]Acharya Prafulla Chandra College, New Barrackpore, Kolkata-700131
[2]Mahadevananda Mahavidyalaya, Barrackpore, Kol-700120
[1]kusumika11@yahoo.com

Keywords: Prey, Predator, Disease in both populations, Predation, Treatment.

Disease in ecological systems plays an important role. In the present investigation we propose and analyze a predator-prey mathematical model in which both species are affected by infectious disease. The parasite is transmitted directly (by contact) within the prey population and indirectly (by consumption of infected prey) within the predator-population. We derive biologically feasible and insightful quantities in terms of ecological as well as epidemiological reproduction numbers that allow us to describe the dynamics of the proposed system. Our observations indicate that predator-prey system is stable without disease but high infection rate drive the predator population toward extinction. We also observe that predation of vulnerable infected prey makes the disease to eradicate into the community composition of the model system. Local stability analysis of the interior equilibrium point near the disease free equilibrium point is worked out. To study the global dynamics of the system, numerical simulations are performed. Our numerical analysis reveals that predation rates especially on susceptible prey population and recovery of infective predator play crucial role for preventing the extinction of the susceptible predator and disease propagation.

Global Existence and Asymptotic Behaviour of the Solutions to Boussinesq Paradigm Equation

N. Kutev, N. Kolkovska, M. Dimova
Institute of Mathematics and Informatics,
Bulgarian Academy of Sciences,
Acad. Bonchev str., bl.8, 1113, Sofia, Bulgaria

Keywords: Boussinesq equation, global existence, blow up, solitary waves

We investigate the Cauchy problem for Boussinesq Paradigm Equation

$$\begin{aligned} \frac{\partial^2 u}{\partial t^2} = \Delta u + \beta_1 \Delta \frac{\partial^2 u}{\partial t^2} - \beta_2 \Delta^2 u + \Delta f(u), \quad x \in \mathbb{R}^n, \quad t \in \mathbb{R}^+, \\ u(x,0) = u_0(x), \quad u_t(x,0) = u_1(x), \quad x \in \mathbb{R}^n, \\ u(x,t) \to 0, \quad \Delta u(x,t) \to 0, \quad |x| \to \infty, \end{aligned}$$

where $f(u) = \alpha |u|^p$, $p > 1$, α, $\beta_2 = const \neq 0$, $\beta_1 = const$.

New energy functionals are introduced and their sign preserving properties under the flow of the equation are studied. The existence of global weak solutions with supercritical initial energy is proved and their asymptotic behaviour for $t \to \infty$ is investigated.

Numerical experiments illustrate the results.

Fractional order Cole model of bioimpedance of the human skin: new results

M. Lazarević, Z. Vosika, G. Lazović
J. Simić-Krstić and Dj. Koruga
University of Belgrade, Faculty of Mechanical Engineering
Belgrade, Serbia
mlazarevic@mas.bg.ac.rs

Keywords: human skin, fractional calculus, Cole model, bioimpedance

In this paper, electrical impedance measurement data and fractional calculus have been utilized for modeling bioimpedance properties of human skin. In relation to our experimental in vivo conditions, structure and complexity of the human skin, we suggested that bio-electrical behavior of the human skin can be described by the series layer Cole model based on modified fractional distributed-order based on the Caputo-Weyl fractional derivatives. The equivalent total impedance $\underline{Z}_c(\omega)$ of this new electric circuit is given by the next equation:

$$\underline{Z}_c(\omega) = R_\infty + (R_0 - R_\infty) \int_{0+}^{1} \frac{p(\alpha)\mathrm{d}\alpha}{1 + (j \cdot \omega \cdot \tau_\alpha)^\alpha}$$

The impedance spectrum was measured in a finite frequency range up to 100kHz. Our proposed modified Cole model much better fit to experimentally curve in given frequency range in compare to existing Cole models. The fitting is done using Levenberg-Marquardt nonlinear least squares.

Climate-driven dynamics of seasonal influenza in sub-tropical region

Maria C.A. Leite
Department of Mathematics and Statistics, University of Toledo
Maria.Leite@utoledo.edu
Xiangming Xiao
Department of Botany and Microbiology and
Center for Spatial Analysis, University of Oklahoma
Meijun Zhu
Department of Mathematics, University of Oklahoma

The seasonal dynamics of influenza in the tropical and subtropical regions are not well documented and less defined [1]. Those mathematical epidemiological models developed for the temperate regions cannot predict double peaks (winter/spring, summer) of seasonal influenza in the tropical and subtropical regions. We introduce a novel approach to analyze seasonal dynamics and inter-annual variation of influenza transmission in Hong-Kong and Beijing during 1990-2009. I will discuss mathematical epidemiological models that incorporate three ecology-based response functions: response of influenza virus survival and human susceptibility to air temperature and influenza virus transmission response to specific humidity. Also, I will present numerical simulation results obtained when the mathematical models are driven by monthly air temperature and specific humidity data from the NCEP Re-Analysis data set. Interestingly, the models reproduce not only the reported double peaks of influenza A cases in subtropical-region, but also the observed temporal pattern of flu in temperate regions (one winter peak).

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A Linear Complementarity Numerical Approach to the Non-Convex Problem of Structures Environmentally Damaged and by Cable-bracings Strengthened

K. Liolios[1], S. Radev[2], A. Liolios[1] , I. Georgiev[2] and K. Georgiev[2]
[1] Democritus University of Thrace, Xanthi, Greece
kliolios@env.duth.gr, aliolios@civil.duth.gr
[2] Bulgarian Academy of Sciences
stradev@imbm.bas.bg, john@parallel.bas.bg

Keywords: Computational Structural Mechanics, Cable-braced Structures, Optimization Algorithms

Environmental actions, as well as earthquake strong excitations, can often cause significant damages to Civil Engineering structures, e.g. buildings and bridges. A main such defect is the strength degradation, causing a reduction of the loads bearing capacity. To overcome such defects, sometimes cable-like members are used as a first strengthening and repairing procedure. These members can undertake tension but buckle and become slack and structurally ineffective when subjected to a sufficiently large compressive force. Thus the problem governing conditions have an equality as well as an inequality form. This nonlinear problem of structures containing as above cable-like members belongs to the so-called Inequality Problems of Mechanics. This paper presents a computational treatment for the mathematically strict analysis of such structures, which have been environmentally damaged and by cable-elements strengthened. Concepts of the non-convex analysis are used. The cable behaviour is considered as nonconvex and nonmonotone one and is described by generalized subdifferential relations including loosening, elastoplastic - fracturing etc. effects. A hemivariational inequality approach is used for a stability criterion concerning the numerical scheme. A double discretization, in space by finite elements and piece-wise linearization of cable - behaviour, and in time by a direct time-integration method, is applied. Thus, a linear complementarity problem, with a reduced number of unknowns, is solved by using optimization algorithms. Finally, an example from Civil Engineering praxis is presented and discussed.

Epidemic Model with delay on homogenous networks

Maoxing Liu[1,2] and Gergely Rost[2]
[1]Department of Mathematics, North University of China
Taiyuan, Shanxi, P. R. China, 030051
[2]Bolyai Institute, University of Szeged
6720 Szeged, Hungary, math6@163.com

Keywords: Networks. Epidemics. Delay. Bifurcation.

During epidemic outbreaks, people may adjust their contact patterns according to the perceived risk of an infectious disease. In this paper, we assume that individuals will reduce some links when diseases are prevalent and have high risks, but with some delay. Under such assumption, we study the effect of the delay on the contact patterns within the population and the dynamics of the epidemics. We give asymptotic stability results for the disease-free equilibrium and the endemic equilibrium. We conclude that, due to the time-delayed information processing, the density of infected individuals and the topology of the network vary in time in periodic forms. Our results indicate that the delay can have important effect on the spreading of infectious diseases.

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On a New Class of Microbial Growth Models

Svetoslav Markov[1], Roumen Anguelov[2]
[1]Institute of Mathematics and Informatics
Bulgarian Academy of Sciences
[2]University of Pretoria, Pretoria 0002, South Africa
E-mail (corresponding author): smarkov@bio.bas.bg

Keywords: Bioreactor, Chemostat, Microbial growth, Monod model, Batch mode, Nonlinear model, System of ODE's

It has been often mentioned in the literature that Monod type microbial growth models describe adequately bio-processes appearing in bioreactors, under certain favorable conditions when micro-organisms actively produce specific enzymes for the degradation and consumption of nutrient substrates and grow at the maximum possible rate.. However, conditions in bioreactors sometimes become unfavorable, microbial growth may be inhibited and bio-technological processes may go out of control. Therefore it is reasonable to subdivide the microbial population in (at least two) classes to better describe their physiological state. In this work we study theoretically and computationally certain Monod type models. To this end several familiar bioreactor models are theoretically analyzed with respect to properties of their solutions.We then introduce and study a new class of microbial growth models oriented towards biotechnological processes. We follow an analogy with Henri-Michaelis-Menten enzyme kinetic mechanism to model a bioreactor in batch mode with decay. The models are based on systems of ODE and take into account phases of microbial growth. Some properties of these models are studied and compared to classical Monod type models. It has been shown that with appropriately chosen coefficients the proposed models are good alternatives to classical Monod type models, especially when introducing microbial phases. In addition this approach allows to assign clear biological meaning to all constants involved, in particular the growth rate constants (which are usually functions depending on the substrate in Monod models). Some hints to compute the parameters of the proposed models have been given. The presented computational experiments concern the growth of the microbial strain E. Coli on glucose substrate. .

Time scales and spatially distributed competition dynamics

M. Marvá[1], P. Auger[2,3] and R. Bravo de la Parra[1]
[1]Dpto Matemáticas, Universidad de Alcalá. 28871 Madrid, Spain
marcos.marva@uah.es, rafael.bravo@uah.es
[2]UR UMMISCO, IRD France Nord, F-93143, Bondy, France
[3]UPMC Univ Paris 06, UMI 209, UMMISCO, F-75005, Paris, France
pierre.auger@ird.fr

Keywords: competition; fast displacements; two time scales ODE.

In this work we present a two species competition model in a multi-patch environment. Namely, we consider two species populations inhabiting a serial of patches and classical competition at each patch. We also consider a free competition patch where both species grow according to a logistic equation. Individuals can move frequently form this free competition patch to any other patch, and conversely. The total carrying capacity is fixed for each species and individuals move according to Ideal free distribution (IFD), i.e. individuals prefer to remain in patches with larger local carrying capacity. A final assumption in that individual displacements are much faster than local competition, which yields a two time scales model.

We investigate the relation between the number of patches, global coexistence and total biomass maximization at coexistence equilibrium. The study of the two time scales model is done by means of approximate aggregation techniques [1], [2]. Under certain hypotheses, and based on the existence of time scales, a reduced (less dimensional) system retaining certain asymptotic information of the initial model can be derived.

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A Bivariate Correlated Destructive Model

Leda D. Minkova

Faculty of Mathematics and Informatics
Sofia University "St. Kl. Ohridski"

In this notes we define a bivariate version of the correlated destructive cure rate model. As an example we consider the bivariate Pólya - Aeppli survival model with marginal survivals, given by Borges et al. (2012). Zero correlation in the univariate case coincides with the long - term survival function. This motivates the definition of a bivariate long - term survival function. We discuss some properties of the defined model including the probability generating function, recursive relations, and conditional distributions.

Borges P., Rodrigues J. and Balakrishnan N. (2012). Correlated destructive generalized power series cure rate models and assiciated inference with an application to a cutaneous melanoma data, *Computational Statistics and Data Analysis,* **56**, 1703 - 1713.

Basic Reproduction Ratio for a Fishery Model in a Patchy Environment

Ali Moussaoui
Department of Mathematics, University of Tlemcen, Algeria
moussaouidz@yahoo.fr

Keywords: Population dynamics, Stock-effort model, Time scales, Aggregation of variables, Stability.

We present a dynamical model of a multi-site fishery. The fish stock is located on a discrete set of fish habitats where it is harvested by the fishing fleet. We take advantage of the existence of two time scales to reduce the dimension of the model and to build an aggregated model governing the habitat fish densities and the total fishing effort. Several equilibria exist, Fishery Free Equilibria (FFEs) as well as Sustainable Fishery Equilibria (SFEs). We show that the dynamics depends on a threshold which is similar to a basic reproduction ratio for the fishery. When the basic reproduction ratio is less or equal to 1, one of the FFEs is globally asymptotically stable (GAS), otherwise one of the SFEs is GAS.

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Optimization of product formation in enzymatic reactions - A mathematical approach

Sumit Nandi[*] and Priti Kumar Roy [**]

[*] Narula Institute of Technology, Kolkata-700109, India.
[**]Centre for Mathematical Biology and Ecology, Department of Mathematics,
Jadavpur University, Kolkata 700032, West Bengal, India

Keywords: Enzyme kinetics, dynamical reaction system

Enzymes play important roles in almost all biochemical reactions. The enzyme kinetics has traditionally been modeled by ordinary differential equations based on concentrations of substrate, enzyme, enzyme-substrate complex and product in the dynamical reaction system. Here we proposed a system of differential equations for enzyme-substrate reactions with a view to optimize the product by using suitable concentrations of substrate and enzyme. The approximate solutions are derived using singular perturbation method utilizing outer and inner solutions. We also computed numerical solutions for model equations graphically which is based on analysis of the results of enzymatic dynamical reaction system.

SEVERAL APPLICATIONS OF DIFFERENTIAL EQUATIONS TO BIOLOGICAL SYSTEMS

Ivan Jordanov[‡], Elena Nikolova[⋆], Nikolay K. Vitanov[⋆]

[‡] University of National and World Economy
Sofia, Bulgaria

[⋆] Institute of Mechanics, Bulgarian Academy of Sciences
Sofia, Bulgaria

Keywords: nonlinear dynamics, microRNA, QSSA, population dynamics migration, kinks

This work discusses two applications of ODEs and PDEs to genetic and population systems, respectively in order to describe their dynamical features. In the first part of this study dynamics of the microRNA repression on the protein translation is represented by a system of seven ordinary differential equations. We apply the method for reduction of dimensionality of dynamical systems with time hierarchy to the above-mentioned model. On the basis of this procedure the obtained quasi-stationary approximation of the original system allows us to derive analytical relationships between the steady-state (output) and the initial (input) values of all variables of the original model. These relationships are interpreted as restrictions on concentrations of the considered genetic process.

In the second part of the work the dynamics of the migration of the members of interacting populations is described by a system of two partial differential equations. We consider the migration as a diffusion process influenced by the changing values of the birth rates and coefficients of interaction between the populations. By applying an unified algebraic method to the described model we show that kink solutions of model equations are possible. We obtain an analytical solution for the density of populations.

Introduction to high-throughput RNA sequencing[1]

Dean Palejev
Faculty of Mathematics and Informatics, Sofia University
palejev@fmi.uni-sofia.bg

Keywords: high-throughput sequencing, RNA sequencing, NGS, differential expression, differential composition

Introduction to high-throughput sequencing (NGS). Alignment to genome and transcriptome. Common RNA data analysis tasks: differential expression, splice variant estimation, differential composition. Statistical tests. Examples using Tourette Syndrome data. Issues with the current data analysis methods. Open problems.

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[1] This talk is presented at the School for Young Scientists.

Position-induced phase change in a TASEP with a double-chain section (a model of biological transport)

N.Ch. Pesheva[1] and J.G. Brankov[2]
[1]Institute of Mechanics, Bulgarian Academy of Sciences
4 Acad. G. Bonchev St., 1113 Sofia, Bulgaria
[2]Bogoliubov Laboratory of Theoretical Physics, Joint Institute for Nuclear Research, 141980 Dubna, Russian Federation

Keywords: TASEP, Protein synthesis, traffic flow, non-equilibrium phase transitions, non-equilibrium statistical physics

The totally asymmetric simple exclusion processes (TASEP) has been used to model the phenomenon of protein synthesis since 1968. Here we consider a simplified stochastic model of messenger RNA synthesis along a DNA track with a double-chain defect. That is, our TASEP model is defined on an open network consisting of simple head and tail chains with a double-chain section in-between. The individual RNAP molecular motors are represented by hard-core particles jumping stochastically to a nearest-neighbor site on the right provided the target site is empty. At the bifurcation point of the network the particles choose with equal probability one of the two chains to move along, and at the merging point they have to wait for the first site of the tail chain to become empty. A RNAP molecule enter the DNA track (initiation stage) with a prescribed probability rate α from the first site of the head chain, and leaves it (termination stage) with probability rate β from the last site of the tail chain. As a result of extensive Monte Carlo simulations we have found a novel property of the model in the maximum-current phase, when $\alpha > 1/2$ and $\beta > 1/2$: upon moving the double-chain defect along the network, keeping fixed the length of both the defect and the whole network, a position-induced phase change in the defect chains takes place. This change from the maximum-density phase through shock phase to low- or high-density phase is observed in the density profile in each of the chains forming the defect. An explanation of the phenomenon is given in terms of finite-size effect on the effective injection and removal rates at the ends of the double-chain defect. The possible implications of this result for the protein synthesis, however, need still to be elucidated.

Analysis on the influence of Ca^{2+} and pH on the specific growth rate of *Acidithiobacillus ferrooxidans*

Elitsa Petrova[a] , Plamena Zlateva[b]
[a]Institute of Mechanics
Bulgarian Academy of Science
Akad.G. Bonchev Str. Block 4, 1113 Sofia, Bulgaria
ely@imbm.bas.bg
[b]Institute of System Engineering and Robotics
Bulgarian Academy of Science
Akad.G. Bonchev Str. Block 2, 1113 Sofia, Bulgaria

Keywords: specific growth rate, Acidithiobacillus ferrooxidans, pH, Ca^{2+}

Acidithiobacillus ferrooxidans are acidophilic chemolitoautothropfic bacteria, with capability to oxidize ferrous ions and used in waste water, tail gas treatment and bioleaching technologies. It forms jarosite - extracellullar solid substance which helps for solid, self-organized biofilm formation and forms sediments in cultures from suspended biomass. This work is a part from studies on influence of different regimes of cultivation on bacterial physiology. The laboratory experiments were carried out with nine modifications of nutrient medium with different pH and Ca^{2+} concentrations for studying their influence on the strain. The specific growth rates were calculated for different time intervals. The experimental data show some significant for bacterial physiology differences in studied parameters. Between 24-34 hours from cultivation, the specific growth rate decrease. In that time interval the strain is turning from lag phase to phase of logarithmic growth and Ca^{2+}, as growth factor and pH are important for the cells in that time. At pH 3; Ca^{2+}= 2,44 - 1,22 mg/l the specific growth rate do not decrease. The results obtained about the specific growth rates were statistically assessed. The assessment of the specific growth rates for important for the strain time intervals between 0 - 24-th hour, 34-48-th and 48 - 59-th hours shows, no statistically significant differences. The analysis of the results allows the choice of appropriate cultivate regime for further experiments with cells for adaptation to high substrate levels.

Unbounded Parametric Tolerable Solution Sets

Evgenija D. Popova
Institute of Mathematics and Informatics
Bulgarian Academy of Sciences
Acad. G. Bonchev str., block 8, 1113 Sofia, Bulgaria
epopova@math.bas.bg

Keywords: linear systems, dependent interval data, tolerable solution set

We consider linear systems of equations, the input data of which depend linearly on interval parameters, and a parametric *tolerable* solution set, which is defined by universal quantifiers applied to the parameters in the matrix and existential quantifiers applied to the parameters in the right-hand side. Such solution sets are considered often in control engineering.

Basing on a characterization of the parametric tolerable solution set as a convex polyhedron [1], we present necessary and sufficient conditions (in both general and computable forms) for a nonempty parametric tolerable solution set to be unbounded. For unbounded parametric tolerable solution sets, we discuss their structure and how to obtain their estimations. The results we present generalize the corresponding results of I. Sharaya [2] for nonparametric unbounded tolerable solution sets. Numerical examples illustrate the theory and the solution sets.

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Modeling survival in Chilhood Acute Lymphoblast Leukemia

K.Prodanova, N.Yorukova
Technical University of Sofia, SCACCC- Sofia

Acute lymphoblastic leukemia (ALL) is the most common malignancy diagnosed in children, representing nearly one third of all pediatric cancers. 30have a gene marker. Patients with gene marker TEL-AML (Acute Myeloid Leukemia) are subtype of ALL. TELl-AML1 is the most frequently deformation, wich is found in patient of this subtype of ALL. In this paper the survival analysis is used to determines the prognostic significance of TEL-AML1 and to models the time it takes for relapse or death. The data are from 160 patients, observed in SCACCC- Sofia for a time of 8 years. Gene marker TEL-AML1 is detected in 33 of the patients. For estimating event (relapse or death) free survival rate the KaplanMeier method is used. Time to event is calculated as the time from study entry to first event or data of last contact. The log- rank test is used for comparison of survival curves between two groups. Multivariate analysis is condacted by using Cox proportional hazards regression.

Numerical solution of the Rosenau-Burgers equation by Quintic B-Spline Collocation Method

Abdur Rashid
Department of Mathematics, Gomal University
Dera Ismail Khan, Pakistan
prof.rashid@yahoo.com

Keywords: Rosenau-Burgers equation, Quintic B-Spline Collocation Method

The Rosenau- Burgers equation arises in some natural phenomena, for example, in bore propagation and in water waves. The asymptotic behavior of the solution for the Cauchy problem to the Rosenau-Burgers equation, in particular, the stability of travelling waves and diffusion waves have been well studied in [1-4].

In this paper we introduce the collocation method using quintic B-spline for solving the Rosenau-Burgers equation. The method is based on Crank-Nicolson formulation for time integration and quintic B-spline functions for space integration. The von Neumann stability is used to prove that the scheme is unconditionally stable. Newton's method is used to solve the nonlinear block pentadiagonal system obtained. Numerical tests are performed for test problem to check the accuracy of the proposed scheme.

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Modelling of a Fed-batch Culture applying Simulated Annealing

Olympia Roeva, Tanya Trenkova
Bulgarian Academy of Sciences
olympia@biomed.bas.bg, ttrenkova@gmail.com

Keywords: Meta-heuristic algorithms, Simulated annealing, Parameter optimization, Cultivation processes, E. coli.

Mathematical forms and their parameters used to describe cell behaviors constitute the key problem of bioprocess modelling, in practical, in parameter estimation. The model building leads to information deficiency and to non unique parameter identification. While searching for new, more adequate modeling metaphors and concepts, methods which draw their initial inspiration from nature have received the early attention. In this paper a Simulated Annealing (SA) algorithm is proposed to identify the unknown parameters in a non-linear mathematical model of a fed-batch cultivation process. A set of unstructured models is suggested to model biomass growth, glucose utilization, acetate formation and oxygen consumption of a E. coli cultivation process. The non-linear model contains 5 state variables and 7 parameters. The model identification is carried out using experimental data from the E. coli MC4110 fed-batch cultivation process. In order to increase the performance of the SA algorithm the adjustments of its parameters de- pending on the considered problem is provided. The resulting non-linear model predicts adequate and with a high degree the variation of the considered state variables. Simulation results reveal that accurate and consistent estimates can be obtained using SA algorithm.

Variance calculations for quantitative real-time PCR experiments with multiple levels of replication

Susana Soto Rojo[1,2,*], Gary Glonek[1], Patty Solomon[1]
[1]The University of Adelaide, Australia
[2]Universidad Católica del Norte, Chile
[*] susana.sotorojo@adelaide.edu.au

Keywords: variance, quantitative real-time PCR, metagenomics

Heap bioleaching is an established technology for recovering copper from low-grade sulfide ores. In Chile, copper production by bioleaching has increased from 5% to more than 10% in the last decade. This reflects the relevance of this technology and the importance of further development. Only recently, genetics-based approaches have been employed to characterize mineral-processing bacteria. In these approaches data analysis is a key issue. Consequently, it is of fundamental importance to provide adequate mathematical models and statistical tools needed to draw reliable conclusions.

The present work relates to current metagenomic studies of the consortium of organisms inhabiting the bioleaching heap of La Escondida mine in Chile. These studies aim to describe and understand the relationship between the dynamics of the community and the industrial process.

A series of quantitative real-time PCR experiments were performed to quantify the microorganisms at various stages of the bioleaching cycle. In this work we address the problem of establishing the reliability of the 16S rRNA gene copy number values obtained by real-time PCR. To do so requires careful modelling and estimation of the error variance at several different levels. A relevant question that arise is: will the use of PCR and/or extraction replicates result in a significantly smaller error variance than not having replicates at all? Three different sets of data and multiple linear regression analysis per microorganism were used to estimate the relevant components of variance. It was concluded that the sampling error is the dominant source of variability for all microorganisms and that extraction replicates would produce only a modest reduction in the error variance.

Impact of Perfect Drug Adherence to Dendritic Cell and T-Cell Proliferation on Immunopathogenic Mechanism for Dynamical System of Psoriasis

Priti Kumar Roy and Abhirup Datta
Center for Mathematical Biology and Ecology,
Department of Mathematics,
Jadavpur University, Kolkata - 700032, India.
pritiju@gmail.com

Keywords: T-Cells, Dendritic Cells, Keratinocytes, Dermis, Epidermis, Cytokines, T-Cell Proliferation, Optimal Control.

Psoriasis vulgaris is a universal continual autoimmune seditious skin sickness characterized by T-Cell reconciled hyperproliferation of Keratinocytes. This group of skin chaos is illustrated by macroscopic and additionally microscopic skin discrepancy. In this research article, we put forward a mathematical representation for the Psoriasis, consisting a set of differential equations, concerning T-lymphocyte Cells, Dendritic Cells and epidermal Keratinocytes. We here integrate the T-Cell proliferation in the system dynamics. By impulsive differential equation, we have studied the effect of DC based drug therapy. We have studied the model both in absence and presence of drug. Analytically we have determined the threshold value of drug dosage and dosing interval for optimum level of disease. We have also investigated the effect of perfect adherence of drug dose on the immune cell count at the extreme cases and observed that, frequent drug dose leads the immune cells to its maximum level in the psoriatic pathogenesis.

Mathematical modeling of the liver's control mechanisms at the delta hepatitis

M. Saidalieva
Institute of Mathematics and Information Technologies
regulatorika@yahoo.com

Keywords: mathematical modeling, dynamic chaos, delta hepatitis

In the given work the mathematical and computer modeling of liver regulatorika at viral hepatitis type D on molecular-genetic level are considered.

Research objective is development of the quantitative methods and techniques for liver regulatorika and diagnostics of viral infection (viral hepatitis type D) stages using methods for mathematical modeling and information technology toolboxes. For mathematical modeling the methods of the quantitative studying regulatorika of living systems have been used.

The equations of mathematical models for regulatorika of liver cells and hepatitis D virus under delta hepatitis based on the approaches generalization by Bl.Sendov, B. Goodwin, M. Eigen, V.A.Ratner, J. Smit with taking into account cooperativity, time mutual relations and presence of the combined feedback in hepatocyte regulation system are carried out.

In the course of quantitative researches the following modes of considered process have been received: clarification, symbiosis, auto-oscillations and irregular fluctuations (chaos), sharp destructive changes ("black hole" effect) which define various clinical forms of disease.

The developed quantitative methods based on the mathematical modeling liver regulatorika at molecular-genetic levels, allow to predict coming chaotic, repeating changes and "black hole" effect in liver under hepatitis D virus infection. This gives the chance to diagnose coming unpredictable changes phase in liver regulatorika and beginning cirrhosis using computer calculations

Completely monotone, Bernstein functions and convexity

Hristo Sendov

The University of Western Ontario, Canada

We extend a construction by J. Borwein and O. Hijab, by showing how every completely monotone (resp. Bernstein) function on $(0, \infty)$ can be extended to a symmetric convex (resp. concave) function on $\mathbb{R}^n_{++}$. Since every completely monotone function is a Laplace transform of a measure on $[0, \infty)$ properties of that measure determine properties of the symmetric convex function. Similarly, the Lévy–Khintchine representation defines a Lévy measure corresponding to every Bernstein function. In parallel, we investigate how concavity properties of the Lévy measure determine properties of the symmetric concave function.

This is a joint work with Ričardas Zitikis, the University of Western Ontario.

Identification of the parameters of the Michaelis-Menten model of tissue respiration by use of exact solutions to the diffusion-consumption equation for tissue slice and half-space

R. Ivanova[1] and G. Simeonov[2]
[1]Dept. of Biomechanics, Institute of Mechanics, BAS
[2]Dept. of Fluid Mechanics, Institute of Mechanics, BAS
rumjana_ivanova@abv.bg, gsimeonov48@yahoo.co.uk

Keywords: tissue respiration, Michaelis-Menten model, parameter identification, diffusion-consumption equation, exact solutions

The identification of the parameters of the Michaelis-Menten model of tissue respiration is based on data from Warburg-type experiments in which the full oxygen uptake of the tissue under study is measured together with the oxygen tension of the suspending medium. The proposed algorithm of identification uses exact analytical solutions to the diffusion-consumption equation with sink term representing Michaelis-Menten kinetics of oxygenation for a tissue slice and a half-space, obtained by the authors [1,2]. The algorithm is applied to estimation of the tissue respiration parameters in two cases: slices of skeletal muscle tissue [3] and six albino-rat tissues (kidney, heart, liver, brain, diaphragm, lung) [4]. The presentation reports a further development of the authors' work [5] where an aproximation to the Michaelis-Menten model, the so called zero- to first-order kinetics model, was used.

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Noise discovering and correction in NGS data using artificial neural networks

Valeriya Simeonova*, Antony Popov
Faculty of Mathematics and Informatics, Sofia University, Bulgaria
*Corresponding author: v.n.simeonova@me.com

Keywords: NGS data, noise discovery, noise correction, quality scores, predictors, training, AINN

The quality of next-generation sequencing data is still a problem in nowadays bioinformatics. There are different types of errors, but what is the common is the fact that when we look to a specified base it is not correct. The proposed approach for estimating if a base is correct or not, is based on an idea that it is predictable if the base is wrong or right. The architecture of the artificial neural network is universal, so it can be used with data from different NGS platforms (Sanger, Illimina, 454), for different types of sequencing (WHS, WXS, EST). Just the training set follows the alignment procedure. The architecture supports two main tasks: • To discover if a base is not correct, i.e. is there an error • To predict what should be the correct base value for discovered wrong ones. As predictors are used 14 parameters - several of them are just identifier for the type of specie set, the current number of the short read, the current number of the base position, sequencing platform identifier of sequencing type. The other part of predictors are based on quality scores of NGS data, and a group of two predictors - base value which is presented as boolean identifier if the base is wrong or not, and the type error - based on alignment (if it is insertion/deletion or a conflict between 2 bases). The following limitation is set up: 1000 short reads at all. Pre statistics are done for each data set. Based on distribution of different statistics 1000 short reads are picked up. This set is aligned to the reference sequences, leading to no more than 400 000 rows in the training set. Using this approach for different species but with the same sequenator, will correct the errors caused by the sequenator. The strategy: sequencing a small genome/transcriptome and sequencing not a small genome/transcriptomon the same sequenator will lead to more sequenced genomes/transcriptoms and needed calibration for the current sequencing machine.

Improvement of *in vitro* micropropagation effciency of Golden Root by QSAR[1]

Valeriya Simeonova[1,*], Krasimira Tasheva[2], Georgina Kosturkova[2]
[1]Faculty of Mathematics and Informatics, Sofia University, Bulgaria
[2]Institute of Plant Physiology and Genetics, BAS, Sofia, Bulgaria
*Corresponding author: v.n.simeonova@me.com

Keywords: Rhodiola rosea, in vitro development, multiplication coefficient, QSAR, AINN

Rhodiola rosea (Golden root) is an endangered medicinal plant with phytoconstituents and antioxidant potential known to effect positively various physiological functions, including cognition, working ability, cardioprotection, etc. The objectives of the study was to analyze the components of the system for its improvement by bioinformatics methods. For this purpose results (like percentage, number and size of buds, shoots, plants, calli, roots and other parameters) from the biological experiment were used for initial data. Quantitative structure activity relationship model (QSAR) is an effective way to obtain results with less empirical data but conserving the accuracy and data trend. This method was used to analyze, predict and improve plant growth and development in in vitro conditions and for the optimization of some parameters as combination of ingredients in the cultivation medium, concentrations of phytoregulators, illumination, temperature, etc. The architecture of training table was constructed in two levels of predicting first level provided us with much more on times predicted base data while the second level of predicting used the results from the first one. As we had two different processes before and after rooting, they corresponded to the predicting levels. According to the fact that QSAR is a representative of regression models, we are showing how to combine artificial neural networks results with graphical analysis for multidimensional data in studying the *in vitro* data of golden root. The unusual applying of Rose of winds diagram was proposed as the most appropriate way for visualize the data. The proposed analysis helped us to understand how to cultivate in vitro Golden root more efficiently in less time and more rapid manner, using less materials and resources.

[1]This talk is presented at the School for Young Scientists.

Solving the string selection problem using optimization tools

Majid Soleimani-damaneh
School of Mathematics, Statistics and Computer Science
College of Science, University of Tehran, Tehran, Iran
School of Mathematics, Institute for Research in Fundamental Sciences (IPM), P.O. Box: 19395-5746, Tehran, Iran
soleimani@khayam.ut.ac.ir

Keywords: Molecular biology; Optimization; Closest String Problem (CSP).

In recent years many optimization models have been provided showing that a large number of biological problems can be formulated as optimization problems; see, e.g., [1,2,3]. A known class of computational problems in molecular biology is the consensus string problem, to which belongs the problem of string selection via comparison. In this paper, we deal with this problem, and it is shown that it can be modeled as a discrete multiobjective optimization model. Some novel definitions, based upon the Pareto optimality notion, are introduced and zero-one optimization models are given to solve them. It can be seen that defining and modeling the problem using Pareto optimality leads to more useful sequences in the set of optimal solutions.

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Mathematical problems in the theory of bone poroelasticity

Merab Svanadze[1] and Antonio Scalia[2]
[1]Ilia State University, Tbilisi, Georgia
e-mail: svanadze@gmail.com
[2]University of Catania, Italy
e-mail: scalia@dmi.unict.it

Keywords: Bone poroelasticity. Vascular porosity. Lacunar-canalicular porosity. Boundary value problems.

The concept of porous media is used in many areas of applied science (e.g., biology, biophysics, biomechanics) and engineering. The double porosity model would consider the bone fluid pressures in the vascular porosity and lacunar-canalicular porosity.

This paper concerns with the dynamical theory of poroelasticity for solid with double porosity. The system of equations of this theory based on the equations of motion, conservation of fluid mass, the effective stress concept and Darcy's law for material with double porosity. This theory is straightforward generalization of the earlier proposed theories of consolidation with double porosity. Some basic results of the classical theories of elasticity are generalized and the following results are obtained: the fundamental solution of the system of equations of steady vibrations is constructed, the Green's formulae in the considered theory are obtained, the representations of Galerkin type and general solutions are obtained, the formulae of integral representations of regular vector and regular (classical) solutions are obtained, and finally, the uniqueness and existence theorems of the internal and external basic boundary value problems are proved by means of the boundary integral method and the theory of singular integral equations.

On the Varga's Theorem for entire functions

Milko D. Takev

Faculty of Mathematics and Informatics, Sofia University
5 J. Bourchier, 1164 Sofia, Bulgaria
takev@fmi.uni-sofia.bg

In 1968 Varga proved a necessary and sufficient condition for a function f to be entire of order p, using the best uniform approximation of the function with polynomials of nth degree. In this article we prove an analogous theorem using the nth modulus of smoothness of f.

Predator-prey model with prey harvesting, Holling response function of type III and SIS disease

Jean Jules Tewa[†,a,d], Ramses Djidjou Demasse[b,d], Samuel Bowong[c,d]
[a] National Advanced School of Engineering, University of Yaounde I,
[b] University of Yaounde I, Faculty of Science,
[c] University of Douala, Faculty of Science,
[d] UMI 209 IRD&UPMC UMMISCO and GRIMCAPE team,
[†] Correspondance : (+237) 77.71.13.69, tewajules@gmail.com

The populations of prey and predator interact with prey harvesting. When there is no predator, the logistic equation models the behavior of the preys. For interactions we use the generalized Holling response function of type III : $\phi(x) = \dfrac{m\,x^2}{a\,x^2 + b\,x + 1}$, where m and a are positive constants, b is an arbitrary constant. This function models the consumption of preys by predators. It is well known that with this function, the predation rate of predators increases when the preys are few and decreases when they reach their satiety (a predator increases his searching activity when the prey density increases). Our goal is to analyze the influence of a SIS infectious disease in the community. The epidemiological SIS model with simple mass incidence is chosen, where only susceptibles and infectious are counted. We assume firstly that the disease spreads only among the prey population and secondly that the disease is present in the two populations of the community. There are many bifurcations as : Hopf bifurcation, heteroclinic bifurcation, nilpotent bifurcation and saddle-node bifurcation. The results indicate that either the disease dies out or one population disappears and individuals of the other population eventually become infected. For some particular choices of the parameters however, there exists endemic equilibria in which both populations survive.

Intrinsic protein disorder and Ewing's sarcoma

Roumiana Todorova
IBFBMI-BAS, Acad G Bonchev Str, Bl 21
1113 Sofia, Bulgaria
todorova@bio21.bas.bg

Intrinsically disordered regions are important elements of cancer-associated proteins that necessitates the understanding of how these regions contribute to the development of cancer. Predictors were used to estimate the protein disorder of native EWS and its oncogenic fusions EWS/FliI, EWS/ATF1, EWS/ZSG, EWS/ERG, EWS/WT1, EWS/CHOP, EWS/CHN. A difference in the CTD was detected between the wild type protein and its oncogenic fusions, due to the different C-terminal content. Comparing, the EWS oncogenic fusions show similar Intrinsic disorder in the EAD, the NTD (AA 1-264). Finally, the oncogenic function is related to a decreased IPD in the CTD, due to the fused partner, a TF. The different isoforms shown similar profiles, shifted with some amino acids, due to translocations. The disordered region found in (AA 132-156) of EAD consisted of the longest region free of Y motifs. The IQ domain (AA 258-280), a Y-free region, flanked by two Y-boxes, is also disordered by all used Predictors. The EWS functional regions RGG1, RGG2 and RGG3 are predominantly disordered. This is consistent with the finding that the particular AA composition of the EAD creates an enabling structure with several critical Tyr residues dispersed in a polar/neutral environment, favoring hydrogen bonding interactions and flexibility. The regions surrounding the breakpoint in the oncogenic fusions are significantly more disordered. EWS-FLI1 participates in protein-protein interactions on the basis of its intrinsic disorder, rather than protein interaction domains. Summarizing, the data from the ID predictions, using several Predictors, have shown a relationship between the functional characteristics of proteins, their structure and amino acid composition, dictating the intrinsic disorder and preventing from forming singular, fixed structures. The relationship function-structure-disorder could be used in the design of potential antitumor agents against the EWS fusions related tumors.

Bio-Inspired Synchronization Problems in Cellular Automata

Hiroshi Umeo
Univ. of Osaka Electro-Communication
umeo@cyt.osakac.ac.jp

Keywords: Cellular Automaton, Firing Squad Synchronization Problem

Synchronization of large-scale networks is an important and fundamental computing primitive not only in parallel and distributed computer systems but in nature-based biological systems. We study a synchronization problem that gives a finite-state protocol for synchronizing cellular automata. The synchronization in cellular automata has been known as firing squad synchronization problem since its development, in which it was originally proposed by J. Myhill in the book edited by Moore [1964] to synchronize all/some parts of self-reproducing cellular automata. The problem has been studied extensively for more than fifty years [1, 2]. It is defined as follows: given a one-dimensional array of n identical cellular automata, including a *general* at one end that is activated at time $t = 0$, we want to design the automata such that, *at some future time*, all the cells will *simultaneously* and, *for the first time*, enter a special *firing* state. The problem has been referred to as achieving a *macro-synchronization* in *micro-synchronization* system and *realizing a global synchronization using only local information exchange*. In this paper, we present a survey on recent developments in designing optimum- and non-optimum-time synchronization algorithms and their implementations for one- and two-dimensional cellular arrays. Several simple, state-efficient mapping schemes are proposed for embedding one-dimensional firing squad synchronization algorithms onto two-dimensional arrays. The discussions are made from a viewpoint of biological systems, including fault-tolerance, self-replication, self-reproduction, self-repairing and growing nature-based systems.

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Upstream finite volume scheme for a bone healing model

Alexandre UZUREAU, Mazen SAAD, Yves COUDIÈRE
Laboratoire de Mathématiques Jean Leray
alexandre.uzureau@univ-nantes.fr

Approximately $5 - 10\%$ of the 5.6 million fractures occurring annually in the United States develop into non-unions or delayed unions. In Europe, 1.5 million bone grafts are carried out to treat this fractures. Understanding the bone healing is fundamental to treat these complex clinical cases.
We are interested in the modelling and the simulation of the bone regeneration. Many phenomenons are involved in the healing process. We propose a model based on the one developed in [1] including four quantities: the mesenchymal stem cells, the osteoblasts, the bone matrix and the osteogenic growth factor. The evolution of these quantities is governed by a coupled reaction-cross diffusion system with nonlinear terms.
We propose a numerical scheme based on an implicit finite volume method constructed on an orthogonal mesh [2]. We show that the solution of our numerical scheme is physically admissible (nonnegative) and we derive nonstandard energy estimates to ensure that the concentrations are bounded. Moreover, we prove the convergence of the numerical scheme towards a weak solution.
Two numerical simulations are performed based on the proposed scheme with Voronoi meshes: long bone fractures and skull fractures in rats. This model simulates successfully the progress of the mineralization front.

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Waves and statistical distributions connected to a system of competing populations

Nikolay K. Vitanov ⋆, Zlatinka I. Dimitrova ‡
⋆ Institute of Mechanics, Bulgarian Academy of Sciences
vitanov@imbm.bas.bg
‡ Institute of Solid State Physics, Bulgarian Academy of Sciences

Keywords: population dynamics, nonlinear PDEs, fluctuations, probability description

We discuss the dynamics connected to interacted spatially distributed populations. Two cases are considered:

⊙ Migration waves for the case of negligible fluctuations of the environment

⊙ Probability distributions of the density of members of the populations for the case of influence of fluctuations on the spatial-temporal dynamics

For each case the correspondent nonlinear differential equation or system of nonlinear differential equations are treated analytically (where possible) or numerically. The obtained results are discussed from the point of view of methodology for solving nonlinear differential equations and from the point of view of the population dynamics.

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Lagrangean approach to HP folding

Nicola Yanev
Faculty of Mathematics and Informatics
Sofia University, Bulgaria
choby@math.bas.bg

Keywords: Protein folding, HP model, integer programming, Lagrangean duality

One of the most widely studied protein structure prediction models is the hydrophobic-hydrophilic (HP) model, which explains the hydrophobic interaction, tries to maximize the number of contacts among hydrophobic amino acids. In order to find a lower bound for the number of contacts, a number of heuristics have been proposed, but finding the optimal solution is still a challenge. In this talk, we focus on creating a new integer programming model capable to: provide tractable input for mixed-integer programming solvers, to be general enough and to allow Lagrangean relaxation capable to provide small duality gap when branch&bound is used for exact solving. Computational experiments using benchmark problems show that our formulation achieves these goals.

The Wave of Invasion in a Diffusive Predator-Prey Model with Holling Type Functional Response

Chi-Ru Yang
National Center for Theoretical Sciences, Taiwan
cryang@math.cts.nthu.edu.tw

Keywords: Traveling wave; Predator-prey; Wazewski Theorem; LaSalle's Invariance Principle; Lyapunov function

In this work we investigate the existence of traveling wave solutions for a class of diffusive predator-prey type system whose each nonlinear terms can be separable as a product of suitable smooth functions satisfying some monotonic conditions. Applying the methods of Wazewski Theorem and LaSalle's Invariance Principle, we obtain the existence results. Our results can apply to various kinds of ecological models.

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On the Influence of Structurally-Steady Mappings on Predator-Prey Model

Janar Yermekbayeva
L.N.Gumilyov Eurasian National University
erjanar@gmail.com

Keywords: D-factor,compensator effect, control law, structurally-steady mappings, bifurcation values, compensatory control mechanism

Predator-prey, competition, foodchain models with constant parameters often approach a steady state in which the species coexist in equilibrium. Bifurcations endanger the existence of particular species in the foodchain. The critical values at which bifurcations occur enable one to asses the effect of perturbations. Complex models are necessary for an adequate description of ecosystem. To understand the bifurcation mechanisms in ecosystems, simpler models are needed. In this work we propose a predator-prey model.
We study the influence of the D-factor on the dynamics of predator-prey population and propose the term "the compensator effect". Vaccination is a biological analogue of the compensator effect.

$$\frac{\partial x_1}{\partial t} = px_1\Big(1-\beta x_1-\frac{x_2}{1+x_2^2}\Big)+(x_2^3-3x_2x_1^2++k_1(x_1^2+x_2^2)-k_2x_2-k_3x_1)$$

$$\frac{\partial x_2}{\partial t} = cx_2\Big(-\alpha-x_2+\frac{\gamma x_1^2}{1+x_1^2}\Big)+(x_1^3-3x_1x_2^2-+k_1(x_1^2+x_2^2)-k_2x_1-k_3x_2)$$

We use a simple model to explore the effect of epidemiological flashes and the optimal vaccination policy; define bifurcation values. We propose compensatory control mechanisms as one-,two-and three-parametrical structurally-steady mapping, presented as the D-factor, which shows the possibility of stabilization of the population at the set level.

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8 LIST OF CONTRIBUTORS

42 Vitalii Akimenko
Faculty of Cybernetics
Taras Shevchenko National University of Kyiv, Kyiv, Ukraine
akm15@meta.ua

43 Nofe Al-Asuoad
Department of Mathematics and Statistics, Oakland University
Rochester, MI 48309, USA
nalasuoa@oakland.edu

44 Zlatka Alexieva
Institute of Microbiology
Bulgarian Academy of Sciences
zlatkama@yahoo.com

45 Gaik Ambartsoumian
Univ. of Texas at Arlington
gambarts@uta.edu

46 Roumen Anguelov
30 Dept. Mathematics & Applied
43 Mathematics, Univ. of Pretoria
88 Pretoria 0002, South Africa
59 roumen.anguelov@up.ac.za

68 B. Atanasov
University of Sofia "St. Kliment Ohridsky", Bulgaria

48 Krassimir Atanassov
Inst. of Biophysics and Biomedical Engineering, BAS
Acad. G. Bonchev St., Bl. 105
Sofia-1113, Bulgaria
krat@bas.bg

P. Auger 89
UR UMMISCO, IRD France Nord, F-93143, Bondy, France
UPMC Univ Paris 06, UMI 209, UMMISCO, F-75005, Paris, France
pierre.auger@ird.fr

Gergana Bencheva 49
Institute of Information and Communication Technologies
Bulgarian Academy of Sciences
gery@parallel.bas.bg

Keith Berven 43
Department of Biological Sciences
Oakland University, RochesterMI 48309, USA
berven@oakland.edu

Venko Beschkov 50
Inst. of Chemical Engineering
Bulgarian Academy of Sciences
Sofia 1113, Bulgaria
bioreac@bas.bg

Sabyasachi Bhattacharya 51
Agricultural and Ecological Research Unit, Indian Statistical Institute, 203, B. T. Road, Kolkata - 700108, India 56
sabyasachi@isical.ac.in

Dimitra Bon 52
University Hospital Frankfurt
Germany bon@med.uni-frankfurt.de

57 J. Bondia
Universitat Politecnica de Valencia, Spain

53 S.M.Bouguima
Department of Mathematics
Faculty of sciences
University of Tlemcen
B.P.119, Tlemcen 13000
Algeria
bouguima@yahoo.fr

54 Samuel Bowong
111 Faculty of Science
University of Douala
PO Box 24157 Douala
Cameroon
sbowong@gmail.com

55 Khristo N. Boyadzhiev
Department of Mathematics
Ohio Northern University
Ada, Ohio, USA
k-boyadzhiev@onu.edu

95 J.G. Brankov
Bogoliubov Laboratory of Theoretical Physics
Joint Institute for Nuclear Research
141980 Dubna, Russian Federation

89 R. Bravo de la Parra
Dpto Matemáticas, Universidad de Alcalá. 28871 Madrid, Spain
rafael.bravo@uah.es

48 Vihren Chakarov
Inst. of Biophysics and Biomedical Engineering,
Bulgarian Academy of Sciences
Acad. G. Bonchev St., Bl. 105
Sofia-1113, Bulgaria
vihren@clbme.bas.bg

Joydev Chattopadhyay 56
Agricultural and Ecological Research Unit, Indian Statistical Institute
203, B. T. Road, Kolkata - 700108
India joydev@isical.ac.in

F. Chiroleu 63
CIRAD -Umr PVBMT
Réunion Island, France

O. Chtioui 50
ProBioGEM Laboratory
University of Lille Nord de France
59655 Villeneuve d'Ascq Cedex
France

Yves Coudière 114
Laboratoire de Mathematiques Jean Leray, Universite de Nantes
France

Diego de Pereda 57
Universitat Politecnica de Valencia, Spain
dpereda@upvnet.upv.es

Attila Dénes 58
Bolyai Institute, University of Szeged
Hungary
denesa@math.u-szeged.hu

50 K. Dimitrov
ProBioGEM Laboratory
University of Lille Nord de France
59655 Villeneuve d'Ascq Cedex
France

21 Neli Dimitrova
59 Institute of Mathematics and Informatics
Bulgarian Academy of Sciences
nelid@math.bas.bg

115 Zlatinka I. Dimitrova
Institute of Solid State Physics
Bulgarian Academy of Sciences

83 M. Dimova
Institute of Mathematics and Informatics, Bulgarian Academy of Sciences, Acad. Bonchev str., bl.8, 1113, Sofia, Bulgaria

111 Ramses Djidjou Demasse
Faculty of Science
University of Yaounde I
P.O. Box 8390, Yaounde
Cameroon

62 Claire Dufourd
IRD - CRVOI, Réunion Island
France

62 Yves Dumont
63 CIRAD, Umr AMAP
30 34000 Montpellier, France
60 yves.dumont@cirad.fr

64 Inger Fabris-Rotelli
University of Pretoria
South Africa
inger.fabris-rotelli@up.ac.za

József Z. Farkas 23
Department of Computing Science and Mathematics
University of Stirling, UK
jzf@cs.stir.ac.uk

N.Chiboub Fellah 53
Department of Mathematics
Faculty of sciences
University of Tlemcen
B.P.119, Tlemcen 13000
Algeria

Natalie Filmann 65
Goethe-University Frankfurt
Germany
filmann@med.uni-frankfurt.de

O. Flores 63
CIRAD -Umr PVBMT
Réunion Island, France

F. Gancel 50
ProBioGEM Laboratory
University of Lille Nord de France
59655 Villeneuve d'Ascq Cedex
France

Swetha Garimala 34
Protech Solutions, Inc., Little Rock, AR, USA

Jordan Genoff 66
Technical University of Sofia 67
at Plovdiv, Plovdiv, Bulgaria
jgenoff@tu-plovdiv.bg

86 I. Georgiev
Institute of Information and Communication Technologies
Bulgarian Academy of Sciences
Acad. G. Bonchev Str. 8
1113 Sofia, Bulgaria
john@parallel.bas.bg

86 K. Georgiev
Institute of Information and Communication Technologies
Bulgarian Academy of Sciences
Acad. G. Bonchev Str. 8
1113 Sofia, Bulgaria
john@parallel.bas.bg

44 Maria Gerginova
Institute of Microbiology
Bulgarian Academy of Sciences

101 Gary Glonek
The University of Adelaide
Australia

69 Angel Golev
Faculty of Mathematics and Informatics
University of Plovdiv
236 Bulgaria Blvd.
4003 Plovdiv, Bulgaria
angelg@uni-plovdiv.bg

68 Damyan Grancharov
University of Sofia "St. Kliment Ohridsky"
dgrancharov@phys.uni-sofia.bg

76 Mohamed Rabeh Hajlaoui
Laboratory of Biotechnology Applied to the Agriculture, National Institute of Agronomic Research, Tunisia
hajlaoui.rabeh@iresa.agrinet.tn

Eva Herrmann 52
Goethe-University and University Hospital 65
Frankfurt, Germany

Bahrom Hidirov 70
Dep. Regulatorika 71
Institute of Mathematics and Information Technologies
Academy of Sciences of Republic of Uzbekistan, F.Khodjaeva 25
Tashkent, Uzbekistan
regulatorika@yahoo.com

M.B.Hidirova 71
Dep. Regulatorika
Institute of Mathematics and Information Technologies
Academy of Sciences of Republic of Uzbekistan, F.Khodjaeva 25
Tashkent, Uzbekistan
regulatorika@yahoo.com

Peter Hingley 72
European Patent Office
Erhardtstr. 27
80469 Munich, Germany
phingley@epo.org

Peter Hinow 24
Department of Mathematical Sciences
University of Wisconsin - Milwaukee
P.O. Box 413, Milwaukee, WI

53201-0413, USA
hinow@uwm.edu

73 Monica K. Hurdal
Department of Mathematics
Florida State University
Tallahassee, FL, USA
mhurdal@math.fsu.edu

74 Tatiana Ilkova
Institute of Biophysics and
Biomedical Engineering, BAS
105 Acad. G. Bonchev Str.
Sofia 1113, Bulgaria
tanja@biomed.bas.bg

75 Ivan Ivanov
Department of Veterinary
Physiology and Pharmacology,
Texas A&M University
IIvanov@cvm.tamu.edu

25 Kamen Ivanov
Institute of Mathematics and
Informatics
Bulgarian Academy of Sciences
Acad. G. Bonchev St, Block 8
1113 Sofia, BULGARIA
kamen@math.bas.bg

105 R. Ivanova
Dept. of Biomechanics
Institute of Mechanics, BAS
Sofia, Bulgaria
rumjana_ivanova@abv.bg

28 Bangti Jin
Department of Mathematics
Texas A&M University
College Station, TX 77843, U.S.A.

Ivan Jordanov 93
University of National and World
Economy, Sofia, Bulgaria

Atanas Kamburov 26
Max Planck Institute for Molec-
ular Genetics, Berlin, Germany
kamburov@molgen.mpg.de

V. Kavardzhikov 77
Institute of Mechanics
Bulgarian Academy of Sciences
Acad. G. Bontchev Str., Bl. 4
Sofia 1113, Bulgaria

Khaled Khanchouch 76
University of Tunis, Tunisia
khanchouchkhaled@yahoo.fr

Oliver T. Keppler 52
University Hospital Frankfurt
University Hospital Heidelberg
Germany

Thomas Kieber-Emmons 34
University of Arkansas for Med-
ical Sciences, Little Rock, AR,
USA

M. Kirilova 77
Institute of Mechanics
Bulgarian Academy of Sciences
Acad. G. Bontchev Str., Bl. 4
Sofia 1113, Bulgaria
M.Kirilova@imbm.bas.bg

Diána H. Knipl 78
Bolyai Institute, University of Szeged
Hungary
knipl@math.u-szeged.hu

83 N. Kolkovska
Institute of Mathematics and Informatics, Bulgarian Academy of Sciences, Acad. Bonchev str., bl.8, 1113, Sofia, Bulgaria
natali@math.bas.bg

84 Dj. Koruga
University of Belgrade
Faculty of Mechanical Engineering, Belgrade, Serbia

107 Georgina Kosturkova
Institute of Plant Physiology and Genetics, BAS, Sofia, Bulgaria

79 Dantchi Koulova
Institute of Mechanics
Bulgarian Academy of Sciences
Acad. G. Bonchev Srt, bl.4
1113 Sofia, Bulgaria
dantchi@imbm.bas.bg

80 Milko Krachunov
Faculty of Mathematics and Informatics, University of Sofia, Sofia, Bulgaria

21 Mikhail Krastanov
Institute of Mathematics and Informatics
Bulgarian Academy of Sciences
krast@math.bas.bg

80 Ognyan Kulev
Faculty of Mathematics and Informatics, University of Sofia, Sofia, Bulgaria

82 Kusumika Kundu
Acharya Prafulla Chandra College, New Barrackpore
Kolkata-700131, India
kusumika11@yahoo.com

J. Kurths 54
Postdam Institute for Climate Impact Research
A 31, 14412 Potsdam
Germany

N. Kutev 83
Institute of Mathematics and Informatics, Bulgarian Academy of Sciences, Acad. Bonchev str., bl.8, 1113, Sofia, Bulgaria

Hakan Kutucu 76
Department of Mathematics
Izmir Institute of Technology, Turkey
hakankutucu@iyte.edu.tr

Nikolay Kyurkchiev 69
Faculty of Mathematics and Informatics
University of Plovdiv
236 Bulgaria Blvd.
4003 Plovdiv, Bulgaria
nkyurk@uni-plovdiv.bg

Mihailo Lazarević 84
University of Belgrade
Faculty of Mechanical Engineering, Belgrade, Serbia
mlazarevic@mas.bg.ac.rs

Raytcho Lazarov 28
Department of Mathematics
Texas A&M University
College Station, TX 77843, U.S.A.

lazarov@math.tamu.edu

84 G. Lazović
University of Belgrade
Faculty of Mechanical
Engineering, Belgrade, Serbia

85 Maria C.A. Leite
Dept. Mathematics & Statistics
University of Toledo
maria.Leite@utoledo.edu

86 A. Liolios
Democritus University of Thrace
Dept. Civil Engineering
GR-671 00 Xanthi, Greece
aliolios@civil.duth.gr

86 Konstantinos Liolios
Democritus University of Thrace
Dept. Environmental Engineering
GR-671 00 Xanthi, Greece
kliolios@env.duth.gr

68 Leandar Litov
University of Sofia "St. Kliment Ohridsky"
Leandar.Litov@cern.ch

87 Maoxing Liu
Department of Mathematics
North University of China
Taiyuan, Shanxi, P. R. China, 030051
math6@163.com

30 Jean M-S Lubuma
Department of Mathematics and Applied Mathematics
University of Pretoria
Pretoria 0002, South Africa
jean.lubuma@up.ac.za

Svetoslav Markov 12
Institute of Mathematics and 88
Informatics 46
Bulgarian Academy of Sciences 59
Acad. Georgi Bonchev St, Bl. 8
1113 Sofia, BULGARIA
smarkov@bio.bas.bg

M. Marvá 89
Dpto Matemáticas, Universidad de Alcalá. 28871 Madrid, Spain
marcos.marva@uah.es

A. Mathieu 63
CIRAD -Umr PVBMT
Réunion Island, France

Ingmar Mederacke 65
Hannover Medical School
Germany

Maya Mincheva 32
Northern Illinois University
mincheva@math.niu.edu

Leda D. Minkova 90
Faculty of Mathematics and Informatics, Sofia University
Sofia, Bulgaria
leda@fmi.uni-sofia.bg

D. P. Moualeu 54
University of Yaounde I
PO Box 812 Yaounde
Cameroon

Ali Moussaoui 91

Department of Mathematics
University of Tlemcen
Algeria
moussaouidz@yahoo.fr

92 Sumit Nandi
Narula Institute of Technology
Kolkata-700109, India
sumitnandi5@gmail.com

50 I. Nikov
ProBioGEM Laboratory
University of Lille Nord de France
59655 Villeneuve d'Ascq Cedex
France

93 Elena Nikolova
Institute of Mechanics
Bulgarian Academy of Sciences
Sofia, Bulgaria

80 Maria Nisheva
Faculty of Mathematics and
Informatics, University of Sofia,
Sofia, Bulgaria

82 Krishna pada Das
Mahadevananda Mahavidyalaya
Barrackpore, Kol-700120
India

56 Joydeep Pal
Agricultural and Ecological Research Unit, Indian Statistical Institute
203, B. T. Road, Kolkata - 700108
India

94 Dean Palejev
Faculty of Mathematics and
Informatics, Sofia University
palejev@fmi.uni-sofia.bg

Joseph Pasciak 28
Department of Mathematics
Texas A&M University
College Station, TX 77843, U.S.A.

D. Pashkouleva 77
Institute of Mechanics
Bulgarian Academy of Sciences
Acad. G. Bontchev Str., Bl. 4
Sofia 1113, Bulgaria

Anastas Pashov 34
Institute of Microbiology, BAS,
Sofia
ansts@yahoo.com

Nikolay Pavlov 69
Faculty of Mathematics and
Informatics
University of Plovdiv
236 Bulgaria Blvd.
4003 Plovdiv, Bulgaria
nikolayp@uni-plovdiv.bg

N.Ch. Pesheva 95
Institute of Mechanics
Bulgarian Academy of Sciences
4 Acad. G. Bonchev St.
1113 Sofia, Bulgaria
nina@imbm.bas.bg

P. Petkov 68
University of Sofia "St. Kliment
Ohridsky"

Mitko Petrov 74
Institute of Biophysics and

Biomedical Engineering, BAS
105 Acad. G. Bonchev Str.
Sofia 1113, Bulgaria
mpetrov@biomed.bas.bg

80 Peter Petrov
Faculty of Mathematics and
Informatics, University of Sofia,
Sofia, Bulgaria
p.a.petrov@gmail.com

96 Elitsa Petrova
Institute of Mechanics
Bulgarian Academy of Science
Akad.G. Bonchev Str. Block 4
1113 Sofia, Bulgaria
ely@imbm.bas.bg

97 Evgenija D. Popova
Institute of Mathematics and
Informatics
Bulgarian Academy of Sciences
Acad. G. Bonchev str., block 8,
1113 Sofia, Bulgaria
epopova@math.bas.bg

98 Krasimira Prodanova
Technical University of Sofia
SCACCC- Sofia
kprod@tu-sofia.bg

63 S. Quilici
CIRAD -Umr PVBMT
Réunion Island, France

86 S. Radev
Institute of Mechanics
Bulgarian Academy of Sciences
Acad. G. Bonchev str. 8
Sofia 1113, Bulgaria
stradev@imbm.bas.bg

Asen Rahnev 69
Faculty of Mathematics and
Informatics
University of Plovdiv
236 Bulgaria Blvd.
4003 Plovdiv, Bulgaria
assen@uni-plovdiv.bg

Sourav Rana 51
Agricultural and Ecological Re- 56
search Unit
Indian Statistical Institute
203, B. T. Road, Kolkata - 700108
India.

Abdur Rashid 99
Department of Mathematics
Gomal University
Dera Ismail Khan, Pakistan
prof.rashid@yahoo.com

Simeon Ribagin 48
Inst. of Biophysics and
Biomedical Engineering,
Bulgarian Academy of Sciences
Acad. G. Bonchev St., Bl. 105
Sofia-1113, Bulgaria
sim_ribagin@mail.bg

B. Ricarte 57
Universitat Politecnica de
Valencia, Spain

Olympia Roeva 100
Institute of Biophysics and 74
Biomedical Engineering, BAS
105 Acad. G. Bonchev Str.
Sofia 1113, Bulgaria

olympia@biomed.bas.bg

101 Susana Soto Rojo
The University of Adelaide
Australia
susana.sotorojo@adelaide.edu.au

101 Patty Solomon
The University of Adelaide
Australia

57 S. Romero-Vivo
Universitat Politecnica de
Valencia, Spain

87 Gergely Rost
Bolyai Institute, University of Szeged
6720 Szeged, Hungary
math6@163.com

102 Priti Kumar Roy
51 Centre for Mathematical Biology
92 and Ecology, Department of Mathematics, Jadavpur University
Kolkata, India Pin - 700032
pritiju@gmail.com

114 Mazen Saad
Ecole Centrale de Nantes
44322 Nantes, France
mazen.saad@ec-nantes.fr

103 M. Saidalieva
71 Dep. Regulatorika
Institute of Mathematics and Information Technologies
Academy of Sciences of Republic of Uzbekistan, F. Khodjaeva 25
Tashkent, Uzbekistan
regulatorika@yahoo.com

Ts. Sapundzhiev 50
Inst. of Chemical Engineering
Bulgarian Academy of Sciences
Sofia 1113, Bulgaria

Antonio Scalia 109
University of Catania
Italy
scalia@dmi.unict.it

Santiago Schnell 36
Brehm Center for Diabetes Research University of Michigan Medical School Brehm Center 5132
1000 Wall Street Ann Arbor, MI
48105-1912 USA
schnells@umich.edu

Hristo Sendov 104
The University of Western
Ontario, Canada
hssendov@stats.uwo.ca

Anthony Shannon 48
Faculty of Engineering & IT,
University of Technology
Sydney, NSW 2007, Australia
tshannon38@gmail.com
Anthony.Shannon@uts.edu.au

Meir Shillor 43
Department of Mathematics and
Statistics, Oakland University
Rochester, MI 48309, USA
shillor@oakland.edu

Nikhilesh Sil 51
Narula Institute of Technology,
81, Nilgunj Road, Agarpara
Kolkata 700109, India

105 Georgi Simeonov
Dept. of Fluid Mechanics
Institute of Mechanics, BAS
Sofia, Bulgaria
gsimeonov48@yahoo.co.uk

106 Valeriya Simeonova
107 Faculty of Mathematics and
Informatics, Sofia University
Bulgaria
v.n.simeonova@me.com

84 J. Simić-Krstić
University of Belgrade
Faculty of Mechanical
Engineering, Belgrade, Serbia

108 Majid Soleimani-damaneh
School of Mathematics, Statistics and Computer Science
College of Science
University of Tehran, Iran
soleimani@khayam.ut.ac.ir

52 Christoph Stephan
University Hospital Frankfurt
Germany

37 Karyn L. Sutton
University of Louisiana at Lafayette
Louisiana, USA
kls6479@louisiana.edu

109 Merab Svanadze
Ilia State University
Tbilisi, Georgia
svanadze@gmail.com

110 Milko D. Takev
Faculty of Mathematics and
Informatics, Sofia University
5 J. Bourchier, 1164 Sofia
Bulgaria
takev@fmi.uni-sofia.bg

Krasimira Tasheva 107
Institute of Plant Physiology and
Genetics, BAS, Sofia, Bulgaria

Jean Jules Tewa 111
National Advanced School of En- 54
gineering and Faculty of Science
University of Yaounde I
P.O. Box 8390, Yaounde
Cameroon
tewajules@gmail.com

Claudia Timofte 38
Faculty of Physics, University of
Bucharest
Romania
claudiatimofte@yahoo.com

Roumiana Todorova 112
IBFBMI-BAS
Acad G Bonchev Str, Bl 21
1113 Sofia, Bulgaria
todorova@bio21.bas.bg

Gregory Toole 73
Department of Mathematics
Florida State University
Tallahassee, FL, USA

Tanya Trenkova 100
Institute of Biophysics and
Biomedical Engineering, BAS
105 Acad. G. Bonchev Str.
Sofia 1113, Bulgaria
ttrenkova@gmail.com

113 Hiroshi Umeo
University of Osaka
Electro-Communication
Japan
meo@cyt.osakac.ac.jp

114 Alexandre Uzureau
Laboratoire de Mathematiques Jean
Leray, Universite de Nantes
44321 Nantes, France
alexandre.uzureau@univ-nantes.fr

80 Dimitar Vassilev
Bioinformatics group,
Agrobioinstitute, Sofia
jim6329@gmail.com

115 Nikolay K. Vitanov
93 Institute of Mechanics
Bulgarian Academy of Sciences
vitanov@imbm.bas.bg

84 Z. Vosika
University of Belgrade
Faculty of Mechanical
Engineering, Belgrade, Serbia

65 Heiner Wedemeyer
Hannover Medical School
Germany

85 Xiangming Xiao
Department of Botany & Microbiology, Center for Spatial Analysis, University of Oklahoma

116 Nicola Yanev
Faculty of Mathematics and
Informatics, Sofia University
Bulgaria
choby@math.bas.bg

Chi-Ru Yang 117
National Center for Theoretical
Sciences, Taiwan
cryang@math.cts.nthu.edu.tw

Janar Yermekbayeva 118
L.N.Gumilyov Eurasian National
University, Astana, Kazakhstan
erjanar@gmail.com

N.Yorukova 98
Technical University of Sofia
SCACCC- Sofia

Yu. Zahorodnii 42
Cybernetics Department, Kyiv National University of Taras Shevchenko, Kyiv
yuzagor@ukr.net

Zhi Zhou 28
Department of Mathematics
Texas A&M University
College Station, TX 77843, U.S.A.

Meijun Zhu 85
Department of Mathematics
University of Oklahoma

Plamena Zlateva 44
Institute of System Engineering 96
and Robotics, Bulgarian Academy
of Science, Akad.G. Bonchev St.
Bl. 2, 1113 Sofia, Bulgaria
plamzlateva@abv.bg

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