# BIOMATH 2013

**International Conference on**
**Mathematical Methods and**
**Models in Biosciences**
**Sofia, 16–21 June 2013**

*and School for Young Scientists*

**Edited by R. Anguelov and E. Nikolova**

**CONFERENCE BOOK**

This volume contains a collection of abstracts of scientific papers contributed to BIOMATH 2013 — an International Conference on Mathematical Methods and Models in Biosciences held at the Bulgarian Academy of Sciences in Sofia, June 16–21, 2013. It also includes a list of participants with their addresses and a list of papers from the BIOMATH series of conferences published in peer-reviewed journals.



Electronically published on 12 May 2013

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:

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- Institute of Biophysics and Biomedical Engineering (IBPBME)
- Institute of Chemical Engineering
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# Contents

# 1 Welcome Message from the Organisers

The BIOMATH is a series of international biomathematical conferences held in Bulgaria. Several academic and university units contribute to the organization of BIOMATH 2013 and are acknowledged in the preamble of this book. Further, we are grateful to all members of the Program and Organizing Committees as well as to the International Steering Committee 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 2013 who come from abroad. We are happy to meet colleagues from different countries. The authors of the talks to be presented at the conference come from Belgium, Bulgaria, Cameroon, Canada, Czech Republic, Denmark, France, Germany, Georgia, Hungary, India, Israel, Lebanon, Morocco, Nigeria, Poland, Romania, Russia, South Africa, Spain, Sweden, United Arab Emirates, United Kingdom, USA.

Two special sessions "Microbial dynamics" and "Modelling under Uncertainty" are foreseen at BIOMATH 2013, see Section 4. The sessions are dedicated to Svetoslav Markov on the occasion of his 70th birthday. He is an enthusiastic supporter for Biomathematics in Bulgaria and a main organizer of the BIOMATH series of conferences.

The BIOMATH meetings are already established as an annual event continuing a tradition of scientific meetings on biomathematics held at the Bulgarian Academy of Sciences since 1990. BIOMATH 2011 (15–18 June 2011) and BIOMATH 2012 (17–22 June 2012) were truly international meeting that gathered researchers from four different continents over 20 different countries. We pay special attention to the publication of the presented scientific communications. Selected papers presented at the BIOMATH International Conference were published in the following special issues:

- International Journal of Computers & Mathematics with Applications **32** (11) (1996), BIOMATH-95.
- Journal of Universal Computer Science **2**(2) (1996)
- International Journal of Computers & Mathematics with Applications 64(3) (2012), BIOMATH 2011
- Journal of Biotechnology and Biotechnological Equipment 26(5) (2012) (Bioinformatics section)

- Special issue of the International Journal of Computers & Mathematics with Applications comprising papers from BIOMATH 2012 is in an advanced stage of preparation.

Full list of all research articles from previous BIOMATH conferences is given in Section 5.

**For the Organizing committee:**

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# 2 KEYNOTE TALKS

## 2.1 Viral Escape from CD8+ T Cells: Evidence for a Lytic Effector Mechanism?

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*Keywords: SIV and HIV infection, a cellular automata model, escape from CD8+ T cell surveillance.*

Recent evidence suggests that, in SIV and HIV-1 infection, CD8+ T cells mediate antiviral control predominantly via non-cytolytic mechanisms. This is in apparent conflict with the observation that SIV and HIV-1 variants that escape CD8+ T cell surveillance are frequently and reproducibly selected.We use a cellular automata model that describes spatial and temporal HIV-1 dynamics to address the question 'Is the observation of escape variants evidence that CD8+ T cells kill HIV-1 infected cells?'

## 2.2 Linear Regression Modeling and Validation Strategies for Structure-Activity Relationships

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*Keywords: quantitative structure-activity relationships (QSARs), linear regression analysis, model design, validation and diagnosis.*

Identification and development of a new active compounds is an extremely expensive (reflected in time - between 10 and 15 years [1] and costs) and difficult process without a guaranteed result [2] ($\sim$ 90% of the initial candidates fail to be produces due to their toxicological properties [3]). Traditional strategies based on experiments (animal models [4]) are not anymore able to meet the actual needs in identification of new active compounds while in silico approaches such as computer-aided drug design [5], structure-based drug design [6], or virtual screening [7], are used nowadays.

Quantitative structure-activity relationships (QSARs) are mathematical relationships linking chemical structure and pharmacological activity/property in a quantitative manner for a series of compounds [8]. The approaches are based on the assumption that the structure of chemical compounds (such as geometric, topologic, steric, electronic properties, etc.) contains features responsible for its physical, chemical and biological properties [9]. The linear regression analysis is the statistical method frequently used in QSAR analysis since the main aim of the modeling is to identify a model able to predict the activity of new compounds [10].

Problems solving strategies in linear regression modeling include approaches for dealing with effective assessment of assumptions (linearity, independence of the errors, homoscedasticity, normality [11]), which seems to be broken in QSARs analyses [12,13]; effective methods for model selection [11,14,15]; efficient methods for model diagnosis [16,17]; and adequate approaches for assessment of predictive power of a QSAR model [18,19].

Here we emphasize problem solving strategies that address the main issues that arise when developing multivariate linear regression models using

real data.

Other problems not addressed here include the dealing with not normal distributed errors [20,21] and additional methods for estimation of regression parameters [22].

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## 2.3 Challenges and Opportunities in Mathematical and Theoretical Epidemiology

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Sir Ronald Ross (physician) built a novel mathematical epidemiological framework for the study of the transmission dynamics and control of human diseases, over a century ago. His model and modes of thinking are still in use. In fact, Ross like frameworks are being used in identifying transmission disease mechanisms and in evaluating and ranking competing or co-supportive population-level intervention strategies in the context of communicable, vector born, sexually transmitted diseases and a number of socially transmitted processes that can be thought of as the result of contagion mechanisms. In this presentation, mathematical model formulations in the presence of various levels of heterogeneity are introduced and used to illustrate the evolution and transmission dynamics of communicable disease like influenza or tuberculosis.

## 2.4 Pattern Formation of the Causative Agent of Pierce's Disease within Microfluidic Chambers

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*Keywords: Pierce's disease, biofilm; multiphase, pattern formation*

We develop and analyze a model of the dynamics of an important bacterial pathogen, *Xylella fastidiosa* within artificial plant xylem. The bacterium is the causative agent of a variety of diseases that strike fruit bearing plants including Pierce's disease of grapevine. Biofilm colonization within microfluidic chambers was visualized in a laboratory setting, showing robust, regular spatial patterning. The model is based on a multiphase approach that is able to capture the spacing of the pattern and points to the role of the exopolymeric substance as the main source of control of the pattern dynamics. We concentrate on estimating the attachment/detachment processes within the chamber since these are two mechanisms that have the potential to be engineered by applying various chemicals to prevent or treat the disease. The spread of similar patterns are also investigated using marginal stability.

## 2.5 Dynamical Self-organization in Protein Folding

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We propose that protein folding is due to a self-organization process, that can be described in terms of solitons, the paradigm self-organizers in numerous physical scenarios. We present a simple Hamiltonian energy function that supports solitons, and show how these solitons can be utilized to describe protein collapse. As an example, we consider two proteins, the myoglobin and a mainly-beta-stranded protein with PDB code 3LL1 and show how in both cases the process of collapse can be modeled, with sub-atomic precision, in terms of explicit soliton profiles.

## 2.6 The Innate Immune System: Some Theory, Experiments and Medical Implications

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Simple models of the innate immune system teach us much about the development of infections when the bone-marrow function is damaged by chemotherapy. The results depend only on robust properties of the underlying modeling assumptions and not on the detailed models. Such models may lead to improved treatment strategies for neutropenic patients [1,2,3,4].

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## 2.7 Endemic Bubbles Generated by Delayed Behavioral Response in Epidemic Models

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*Keywords: endemic bubbles, delayed response, bifurcation analysis*

Several models have been proposed to capture the phenomenon that individuals modify their behavior during an epidemic outbreak. This can be due to directly experiencing the rising number of infections, media coverage, or intervention policies. In this talk we show that a delayed activation of such a response can lead to some interesting dynamics. In the case of SIS type process, if the response is not too sharp, the system preserves global stability. However, for sharp delayed response, we can observe stability switches as the basic reproduction number is increasing. First, the stability is passed from the disease free equilibrium to an endemic equilibrium via transcritical bifurcation as usual, but a further increase of the reproduction number causes oscillations, which later disappear, forming a structure in the bifurcation diagram what we call endemic bubble.

Joint work with Maoxing Liu, Eduardo Liz, Gabriella Vas

## 2.8 On the Distribution of Transcription Times

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*Keywords: gene transcription, prokaryote, stochastic model.*

We have developed a detailed model of transcription in prokaryotes [1]. For the case where the polymerases interact rarely (i.e. when the initiation rate is sufficiently low that, on average, polymerases are well spaced), we can analytically derive expressions for the moments of the distribution of transcription times. In some cases, we are also able to obtain the distribution itself semi-numerically. For small transcription units, this distribution can be strongly non-Gaussian, displaying both a large skewness and a large excess kurtosis (i.e. a slowly decaying tail, albeit one that decays exponentially). Multi-polymerase effects are also studied by simulation. We find that the analytic model generally predicts the behavior of the multi-polymerase simulations, often quantitatively, provided termination is not rate-limiting.

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## 2.9 Mathematical Models for Chagas Disease

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*Keywords: Chagas disease, insecticide spraying, simulations*

We present mathematical and computational results for a model for the dynamics of Chagas disease. It is caused by the parasite T. cruzi that is transported by the vectors Triatoma infestans, and affects millions of humans and domestic mammals throughout rural areas in Central and South America. The chronic disease causes mortality and severe morbidity. To control the disease spread periodic insecticide spraying of the village houses is used and also bank blood screening.

The basic model for the disease dynamics consists of four nonlinear ordinary differential equations for the populations of the vectors and of infected vectors, humans, and domestic animals. It has time-dependent periodic coefficients to account for seasonality, and was developed in [1]. The main motivation for the model was to optimize the insecticide spraying schedules.

The model was extended to take into account congenital transmission in both humans and domestic mammals as well as oral transmission in domestic mammals [2]. In particular, oral transmission provides an alternative to vector biting as an infection route for the domestic mammals, who are key to the infection cycle. This may lead to high infection rates in domestic mammals even when the vectors have a low preference for biting them, and ultimately results in high infection levels in humans.

Another extension was to allow for random coefficients, reflecting the uncertainty in their values. The simulations show that the variations in some of the model parameters lead to considerable variations in the numbers of infected humans and domestic mammals.

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## 2.10 On the Well-Posedness of a Class of Mathematical Models Describing Processes in Spatially Heterogeneous Biofilm Communities

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*Keywords: biofilms; systems of degenerate parabolic equations; well-posedness*

Biofilms are dense aggregations of microbial cells encased in a slimy extracellular matrix forming on biotic or abiotic surfaces in aqueous surroundings. Such multicellular communities are a very successful life form and able to tolerate harmful environmental impacts that would eradicate free floating individual cells. Biofilms play an important role in various fields and mathematical models of biofilms have been studied for several decades. They range from traditional one-dimensional models describing biofilms as homogeneous flat layers, to more recent two- and three-dimensional biofilm models that account for the spatial heterogeneity of biofilm communities.

The prototype of the models we address is a deterministic multidimensional biofilm growth model, which was first proposed in [2]. The model describes the growth of a bacterial biofilm community consisting of only one species, and is formulated as a highly non-linear reaction-diffusion system for the biomass density and the concentration of the growth-controlling substrate. The main difficulty is to model the spatial spreading mechanism of biomass: Expansion occurs locally only where and when the biomass density approaches values close to the maximal possible cell density, and biofilm and liquid surroundings are separated by a sharp interface. While the substrate concentration satisfies a standard semi-linear parabolic equation, the spatial spreading of biomass exhibits two non-linear diffusion effects. The biomass diffusion coefficient possesses a polynomial degeneracy which is well-known from the porous medium equation and shows super diffusion. Both non-linear diffusion effects are necessary to reflect the experimentally observed characteristic growth behavior of biofilms, and the

highly irregular structure causes difficulties in the mathematical analysis. The single-species single-substrate model is in good agreement with experimental findings and was analytically studied in [3], where its well-posedness was established.

Various applications require to take further biofilm processes into account and to distinguish between multiple biomass components. The prototype biofilm model was therefore extended to model biofilms which consist of several types of biomass and account for multiple dissolved substrates. The model introduced in [1] describes the diffusive resistance of biofilms against the penetration by antibiotics. In [4] an amensalistic biofilm control system was modelled, where a beneficial biofilm controls the growth of a pathogenic biofilm. The structure of the governing equations of the multi-species models differs essentially from the mono-species model, and the analytical results for the prototype model could not all be carried over to the more involved multi-species case. In both articles, the model behavior was studied numerically and the existence of solutions was established. The question of uniqueness of solutions, however, remained unanswered in both cases.

Recently, one further multi-component biofilm model was proposed, that describes quorum-sensing in growing biofilm communities. Quorum-sensing is a cell-cell communication mechanism used by bacteria to coordinate behavior in groups. It comprises a similar structure as the previous multi-component models [1] and [4], but has the particularity that adding the governing equations for the involved biomass components we recover exactly the mono-species biofilm model. Taking advantage of the known results for the prototype model we were able to prove the existence and uniqueness of solutions and its continuous dependence on initial data in [5]. It was the first time that a uniqueness result was obtained for multi-species reaction-diffusion models of biofilms that extend the single-species model [2]. The solution theory developed in [5] can be extended to more general multicomponent models and provides a positive answer to the question of uniqueness of solutions for the models [1] and [4].

We give an overview of the analytical results obtained for the multicomponent biofilm models in [1], [4] and [5] and present numerical simulations that illustrate the model behavior.

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## 2.11 The Algebraic Structure of Spaces of Intervals

### *Contribution of Svetoslav Markov to Interval Analysis and its Applications*

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In Interval Analysis addition of intervals is the usual Minkowski addition of sets: $A + B = \{a + b : a \in A,\, b \in B\}$. The fact that the additive inverse generally does not exist has been a major obstacle in applications, e.g. constructing narrow enclosures of a solution, and possibly one of the most important mathematical challenges associated with the development of the theory of spaces of intervals. The work on this issue during the last 50-60 years lead to new operations for intervals, extended concepts of interval, setting the interval theory within the realm of algebraic structures more general than group and linear space. This theoretical development was paralleled by development of interval computer arithmetic. Svetoslav Markov was strongly involved in this major development in modern mathematics and he in fact introduced many of the main concepts and theories associated with it. These include: extended interval arithmetic [11, 5, 10], directed interval arithmetic [13], the theory of quasivector spaces [15, 16]. His work lead to practically important applications to the validated numerical computing as well as in the computations with intervals, convex bodies and stochastic numbers [12, 14, 18]. Such advanced mathematical and computational tools are much useful under the conditions of extreme sensitivity that is often inheritably characteristic for biological processes as well as input biological parameters experimentally known to be in certain ranges [17].

One of the most important contributions to knowledge by Svetoslav Markov is in my view the embedding of the monoid structure of intervals and convex bodies into a group structure where the natural definition of multiplication by scalars is also extended in such a way that it is monotone with respect to inclusion, that is

$$A \subseteq B \Longrightarrow \gamma A \subseteq \gamma B, \quad \gamma \in \mathbb{R}.$$

The obtained structure is called a quasivector space [16]. Since the fundamental idea motivating this field is computations with sets and computing enclosures, the stated property cannot be really overemphasized. One

should note that there have been several attempts to embed the quasi-linear space of convex bodies in a more computationally convenient algebraic structure. The most well known such attempt is Radström's embedding into a linear space [19]. However, this embedding fails to preserve precisely the monotonicity property mentioned above. Hence, while the developed by Radström theory is mathematically correct and elegant, it is quite irrelevant regarding the embedded set and in fact the field of Interval Analysis or more generally the field of Set-Valued Computing. Markov's concept of quasivector space manages to capture and preserve the essential properties of computations with sets (like the stated monotonicity) while also providing a relatively simple structure for computing. Indeed, the quasivector space is a direct sum of a vector(linear) space and symmetric quasivector space which makes the computations essentially as easy as computations in a linear space.

A wide spectrum of applications is usually a testimony for the depth of an idea. The ideas of Markov have certainly wide and far reaching implications. In this talk we focus on one particular direction of development, namely the algebraic operations for interval-valued functions. I have had the privilege to have Svetoslav Markov as a teacher and as a collaborator. The algebraic structure of spaces of interval functions is the main topic of our more recent collaborative work. Jointly with Blagovest Sendov we studied the operations for Hausdorff continuous (H-continuous) function. It turned out that the linear space structure of real functions can be extended to the space of H-continuous interval functions and it is actually the largest linear space of interval functions. Hence the space of H-continuous functions has a very special place in Interval Analysis. Further, we showed that the practically relevant set, in terms of providing tight enclosures of sets of real functions, is the set of Dilworth continuous (D-continuous) interval valued function. Using an earlier idea of Svetoslav Markov of abstract construction of interval space over a vector lattice, we show in this presentation that the set of D-continuous function is a quasi-linear space of intervals of the space of H-continuous functions. Moreover, the space of H-continuous functions is precisely the linear space in the direct Markov's sum decomposition of the respective quasivector space.

Let us note that the space of H-continuous functions has applications in various areas of mathematics, e.g. Real Analysis [1, 2], Approximation Theory [20], validated computing [3, 6] as well as the general theory of PDEs [9, 7, 4]. The issue of constructing enclosures is relevant to all mentioned applications. Hence one can expect in the future development in this direction which involve the spaces of D-continuous functions and Markov's

approach to computing with them.

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# 3 CONTRIBUTED TALKS

## Identification Parameters in a Biological Model of Immune Competition : Global Optimization and Kriging Method

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*Keywords: tumor immune cells competition, inverse problem, identification parameters, global optimization, kriging method*

In this work, we study the problem of identifying parameters in the model of immune competition developed in [1,2]. Specifically, we use the approach of the inverse problem which will allow the identification of parameters from measurements of densities of two populations of cells in the proliferation case. The reformulation of the given nonlinear identification problem was considered as a parametric optimization problem using the Least Square criterion. In this work, a design procedure for global robust optimization is developed using Kriging [4] and global optimization approaches [3]. Robustness is determined by the Kriging model to reduce the number of real functional calculations of Least Square criterion. The technical of the global optimization methods is adopted to determine the global robust optimum of a surrogate model.

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# Wood Frogs Population in a Changing Environment

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*Keywords: wood frogs, population dynamics, impulsive differential equation, mathematical ecology*

We present new results for a mathematical model for the dynamics of a population of Wood Frogs, which continue the investigation begun in [1]. The model is in the form of a system of nonlinear 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 juvenile stages. We describe numerical simulations for the study of the environmental impact on the population, in particular we investigate three issues: the existence of periodic solutions for the model; the recovery of the population from 1-3 dry years in which no larvae hatch; and the dependence of the model on the system parameters. It is seen that the results agree qualitatively with the observed data, which allows us to use the model for a tentative prediction of next years development. We also present some additional mathematical and numerical issues for future study.

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# Stochastic Arithmetic as a Tool to Study the Stability of Biological Models

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*Keywords: stochastic arithmetic, CESTAC method, stability of biological models*

Stochastic arithmetic has been introduced since more than forty years by M. La Porte and Jean Vignes. It has been first proposed as an experimental statistical method called the CESTAC method to estimate the accuracy on the result of numerical program [4]. An abstract formalization of the theory called Stochastic Arithmetic has been developed and many of its algebraic properties have been studied [2]. Here a brief presentation of stochastic arithmetic, of it's main properties and of the different software existing for it's implementation are given. Then it is shown that stochastic arithmetic can be easily used to experimentally study the stability of many differential systems proposed as models for biological processes. The stability can be studied with respect to the coefficients of the model or with respect to the initial conditions. Some examples based on the Monod equation and taken from the literature are given [3], [1]. In the end it is also shown that the same method can be used to detect instabilities due to used the solver.

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# An SIRS Stochastic Model with Warning Signals

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*Keywords: computer virus, epidemiology, infections, quasi-stationarity, extinction time, hazard time*

Epidemiological models have been proposed to study the spread of computer viruses. To deal this subject, there exists a mathematical approach based on deterministic models defined in terms of differential equations. Other mathematical approach is based on stochastic models that employ Markov chains, branching and diffusion processes,... The model proposed here belongs to this last approach. It is a stochastic susceptible-infected-removed-susceptible ($SIRS$) model, where immune computers send warning signals to reduce the propagation of the virus among the rest of computers in the population. An analysis of the quasi-stationary distribution, the number of infections, the extinction time and the hazard time is performed for this model. Eventually, some numerical results for these characteristics are presented.

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# A Model of Biological Transport and Askey-Wilson Polynomials

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The asymmetric simple exclusion process is considered as the fundamental model of nonequilibrium physics. It has very important applications, among others, for modeling biological transport phenomena.

The open model has the intriguing feature that the bulk properties in the steady state strongly depend on the boundary processes. In this work the model is studied within an approach based on a tridiagonal Askey-Wilson algebra that is generated by the boundary operators. The infinite dimensional representations of the boundary algebra are defined in terms of the Askey-Wilson polynomials and are implemented for the exact solvability of the model in the steady state.

# Modified Multi-Population Genetic Algorithms for Parameter Identification of Yeast Fed-batch Cultivation

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*Keywords: multi-population genetic algorithms, genetic operators, fermentation process*

In this investigation two new modifications of standard multi–population genetic algorithm have been developed. Modifications differ from each other in the sequence of execution of main genetic operators selection, crossover and mutation. The main idea of both modifications is the operator selection to be executed between the operators crossover and mutation, or between mutation and crossover, respectively. Newly elaborated modifications of multi-population genetic algorithms together with the standard one have been investigated for a parameter identification of yeast fed-batch cultivation. Obtained results have been compared and newly proposed modifications have been shown as accurate as the standard one multi-population genetic algorithms even proved to be faster.

# Numerical Analysis in Size-Structured Population Models with Dynamical Environment

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*Keywords: size-structured models, numerical integration; convergence* We will study the numerical integration of a nonlinear model that describes the dynamics of size-structured populations feeding on a dynamical food-source. Such models are determined by the next equations:

$$u_t + (g(x, S(t))\, u)_x = -\mu(x, S(t))\, u, \quad 0 < x < x_M(t),\ t > 0, \tag{1}$$

$$g(0, S(t))\, u(0,t) = \int_0^{x_M(t)} \alpha(x, S(t))\, u(x,t)\, dx\ , \quad t > 0, \tag{2}$$

$$u(x,0) = \phi(x), \quad 0 \le x \le x_M(t), \tag{3}$$

$$S'(t) = f(t, S(t), I(t)), \quad t > 0, \qquad S(0) = s_0, \tag{4}$$

$$I(t) = \int_0^{x_M(t)} \gamma(x, S(t))\, u(x,t)\, dx, \quad t > 0. \tag{5}$$

where $x_M(0) = x_M$ and $x_M(t)$ represents the characteristic curve that begins at the maximum size. The integration of (1)-(5) is made by means of a suitable method for the coupled problem. We will analyse the consistency, stability and convergence properties of the numerical scheme. Special attention is devoted to the requirements imposed to the quadrature rule. Also, we will analyse the behaviour of such numerical scheme in the integration of the dynamics of *Daphnia magna*, feeding on a dynamical algal population [1].

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# Asymptotic Preserving Scheme from Kinetic to Macroscopic Scale for Multicellular Growing Systems

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*Keywords: kinetic theory, multicellular systems; asymptotic limits, asymptotic preserving schemes, micro-macro decomposition.*

In this work, we develop a numerical method to solve a model for Kinetic Theory of Active Particles (in brief KTAP) which is able to capture a macroscopic models of biological system of two populations cells. The asymptotic preserving (AP) schemes are based on the micro/macro decomposition technique, which applies to general collision operators. We also present several numerical tests to illustrate the efficiency of our approach.

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# Numerical Study of a Chemotaxis System with Non-Linear Boundary Conditions

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*Keywords: finite volume method, non-linear boundary conditions, haematopoietic stem cells migration*

A mathematical model for haematopoietic stem cells migration towards their niche in the bone marrow has been proposed in the literature. It consists of a chemotaxis system of partial differential equations (PDEs) with non-linear boundary conditions and an additional ordinary differential equation on a part of the computational boundary. Various classical numerical methods applied directly to this system may lead to numerical instabilities and loss of the positivity property of the solution, as illustrated in [1]. Finite volume method with appropriate flux limiter and time integration scheme can be used to ensure positivity and nonoscillatory nature of the numerical solution. The non-linear boundary conditions require specific approximation (proposed in [2] for the considered system of PDEs) of the unknown functions when the finite volumes close to the boundary are treated. The aim in the current study is to extend the theoretical results in [2] with numerical experiments and analysis of the properties of the numerical method. Ongoing results for various sets of parameters (e.g. chemotactic sensitivity function, flux limiter, time/space mesh size) will be presented.

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# Numerical Evaluation of Immobilized Cell Contribution in Bioreactors

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Immobilized microbial cells can grow and detach from their carrier and grow independently as free ones in the liquid media. The present work proposes a numerical approach for evaluation the contribution for certain microbial conversions of immobilized cells and the free ones separately. For this purpose experimental data are required.

This approach consists in mathematical models considering the microbial growth both of the free and immobilized cells, the cell detachment from the carrier and the kinetics of substrate consumption and product formation. The mathematical models are based on ordinary differential equations for cells attached to solid supports and of partial ones for entrapped cells. The cell release into the broth is taken into account introducing a cell detachment rate factor.

Four different processes are considered: biodegradation of 1,2-dichloroethane by bacteria (*Klebsiella oxytoca*), fixed on activated carbon; the same substrate by *Xanhobacter autotrophicus*, entrapped in polyacrylamide gel; the production of cyclodextrin glucanotransferase by free and immobilized cells of *Bacillus circulans*; the lactic acid fermentation by cells of *Lactobacillus rhamnosus* immobilized in polyacrylamide gel.

The cell detachment factor for each process could be evaluated from experimental data using the proposed models in an identification procedure. It is shown that in different cases the cell detachment factor could be different and the contribution of the immobilized and the free cells may vary depending on the microbial culture.

# A Phenomenological Model for the Adaptative Biomechanical Response of Growing Tree

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*Keywords: trees, growing structure, beam theory, quasi-static evolution, existence, energetic solutions*

Modelling the shape evolution of growing trees requires to account for the interaction between growth and adaptative biomechanical response to its environment. Trees develop growth strategies to ensure light and nutrient capture as stability. These strategies are linked with the branching process and shape evolution of the exisiting branches or stem. Unlike growth of bones and soft tissues where the change in volume originates from the insertion of new particles within the continuum, growth in trees is modeled by the addition of new material points on an existing deformed structure. Most of the existing models adopt an incremental approach and propose the equilibrium of the growing structure to be reached at each time $t$ after growth has occurred, thus separating growth and mechanical effects. Guillon *et al.* [1, 2] have origninally proposed a new formalism to model the time-space continuous growth of rod with applications to tree-like structures. The purpose of this work is to advance some thermodynamically consistent constitutive relations describing the biomechanical response of the continuously radially growing section. In particular, we introduce an internal variable which aims at accounting for the adaptative structure of the (growing) woody stem section. We present an existence analysis for both the constitutive relation problem and the quasi-static evolution problem.

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# Distribution at Contingency of Alignment of Two Literal Sequences under Constrains

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*Keywords: literals alignment, contingency matrix, probability distribution function (PDF), cumulative distribution function (CDF)*

Sequence alignments, defined as a way of arrange DNA (deoxyribonucleic acid), RNA, (ribonucleic acid) or protein (amino-acid) sequences to identify similar regions that could reflect functional, structural or evolutionary relationships between sequences, is frequently used nowadays due to huge amount of already identified sequence of DNA, RNA, or proteins. Several algorithms were developed and implement for global or local alignments, and each having advantages and disadvantages.

Our research started from the hypothesis that the distribution of alignments could provide useful information about the chance that a certain alignment occur or not by chance. We present here a statistical approach based on distribution analysis that is able to identify the thresholds for rejecting an alignment by chance under the supposition that each literal has at least one alignment in any case. For two literal sequences, we define the alignment through the frequency of matches (with 0 meaning no alignment and n meaning perfect alignment, where n is the number of nucleotides or amino-acids in the two equal length sequences). A closed form of the probability distribution function of the alignment was obtained. We provided that the cumulative distribution function have (unfortunately) no general closed form. Anyway, a series of statistics (including mode and central moments till order 4) were obtained with closed forms. By using the formula for the cumulative probability of an alignment, for the particular case of four literals alignment, thresholds to reject the alignment by chance were obtained as follow: 70% for $n > 8$; 60% for $n > 13$; 55% for $n > 21$; 50% for $n > 39$; 45% for $n > 282$; 44% for $n \to \infty$.

# Simulation of Biotechnological Processes Using System Simulations

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*Keywords: system simulations, biotechnological processes*

System simulations are used for modeling simple and complex physical processes that can be expressed in terms of ordinary differential equations or differential algebraic equations and discrete event simulation. There are many software programs for system simulations and all of them represents the physical system in a graphical form using many components connected together.

In this paper we demonstrate how to model and run system simulations of some biotechnological processes.

# Monotone Combined Finite Volume-Finite Element Scheme for Anisotropic Keller-Segel Model

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*Keywords: chemotaxis, convection-diffusion, anisotropy, degenerate parabolic equation, combined numerical scheme, nonlinear corrections.*

The directed movement of cells and organisms in response to chemical gradients, **Chemotaxis**, has attracted significant interest due to its critical role in a wide range of biological phenomena. The Keller-Segel model has provided a cornerstone for mathematical modeling of chemotaxis. We are interested by the numerical analysis of the following degenerate Keller-Segel model,

$$(1)\ \begin{cases} \partial_t u - div(S(x)a(u)\nabla u) + div(S(x)\chi(u)\nabla v) = 0 \\ \partial_t v - div(M(x)\nabla v) = \alpha u - \beta v,\ \alpha, \beta \geq 0 \end{cases}.$$

The unknowns $u$ and $v$ are respectively the density of cells and the concentration of chemo-attractant. Heterogeneous and anisotropic tensors are denoted by $S$ and $M$. A scheme recently developed in the finite volume framework treats the discretization of the model (1) in homogeneous domains where the diffusion tensors are considered to be the identity matrix. However, standard finite volume scheme not permit to handle anisotropic diffusion on general, possibly nonconforming meshes. In the other hand, it is well-known that finite element discretization allows a very simple discretization of full diffusion tensors and does not impose any restrictions on the meshes but many numerical instabilities may arise in the convection-dominated case. A quite intuitive idea is hence to combine a finite element discretization of the diffusion term with a finite volume discretization of the other terms. Hence, we construct and we study the convergence analysis of a combined scheme discretizing the system (1). This scheme ensures the validity of the discrete maximum principle under the classical condition that all transmissibilities coefficients are positive. Therefore, a nonlinear technique is presented as a correction to provide a monotone scheme for general tensors.

# On the Modeling the Immune Response to Cancer Cells: Asymptotic Analysis

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*Keywords: kinetic theory, immune competition, active particles, asymptotic analysis, nonlinearity.* This works deals with the modeling of immune activation and the immune response to the evolution of cancer cells. A mathematical model is proposed on the basis of mathematical methods of the Kinetic Theory for Active Particles (a KTAP approach). Firstly we focussed on the mathematical framework suitable for derivation of the model. Then a qualitative analysis is carried out to prove the existence of the solution of the Cauchy problem related to the model. We pay special attention to the dynamics of tumor cells contrasted by the immune system, which activates by Cytokinin signals. We show how parameters and initial conditions influence the asymptotic behavior of the solution.
**Acknowledgements:** This work is supported by Hassan II Academy of Sciences and Technology (Morocco) project: 'Methodes mathematiques et outils de modelisation et simulation pour le cancer'.

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# Classification of Occlusal Curves Using Clustering Methods

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*Keywords: dental medicine, statistical clustering, occlusal curves, medical software*

A new method for dental prosthetics, which uses specially designed software to model occlusal curves, has been investigated. Using this software, the occlusal curves distances have been taken of 103 students from the Faculty of Dental Medicine, from 19 to 26 years of age, of which 49 women and 54 men. K-means and hierarchical cluster analysis have been performed on this same dataset. The purpose of this research is to aid and improve the existing expert classification and in general to compare software-assisted approach to human expert one.

**Acknowledgements** This work was supported by the European Social Fund through the Human Resource Development Operational Programme under contract BG051PO001-3.3.06-0052 (2012/2014).

# On the Concept of Biological Control in a Competition Chemostat Model

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*Keywords: chemostat model, competitive exclusion principle, nonmonotone response functions, distinct removal rates, global stability, biological control*

We investigate a known competition model of the chemostat with general (nonmonotone) response functions and distinct removal rates. Based on the competitive exclusion principle A. Rappaport and J. Harmand [2] established the concept of the so called biological control. The proof of the latter result is based on a theorem of B. Li [1]. Here we first propose a modification of Li's theorem and then present an extension of the biological control concept. The theoretical results are demonstrated numerically on particular examples.

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# Numerical analysis of steady state patterns in cell-based auxin transport models

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*Keywords: bifurcation analysis, pattern formation, parameter dependence.*
Cell-based models that describe the pattern formation and the flow of chemicals in plant organs are important building blocks in a multiscale simulation of a whole plant. An example of an important mechanism is the transport of the hormone auxin throughout the plant's organs because it is closely related to the growth characteristics of roots, shoots and leaves.

Based on experimental evidence, a number of cell-based auxin transport models were developed. Due to the intercellular transport of chemicals, these models are complex dynamical systems with a large set of endogenous and exogenous parameters. The models share underlying mathematical principles w.r.t. steady state pattern formation which plays a central role in the growth and development of plant organs. This calls for a uniform computational approach. In our research we focus on computer simulations of general cell-based transport models and more specifically we use numerical bifurcation analysis to study the steady state patterns. It indicates how the stability of patterns is lost or gained as the system parameters change. Bifurcation analysis of ODEs is widespread in biology and various numerical tools produce bifurcation diagrams. However, these automatic tools do not work for large scale problems, such as biological patterning. Indeed, realistic simulations of large tissues that take multiple interacting chemicals into account give rise to very large and sparse systems of coupled ODEs. We analyze recent large scale transport models with new mathematical and computational tools that enable quantitative prediction of the bifurcations that appear at the macroscopic level in these models. This allows us to predict the patterns and self-similar solutions that appear during organ growth and to see how their stability changes as endogenous parameters are modified or as externally applied changes are enforced. We use these methods to compare the model output with observed data such as the auxin distribution and venation patterns in leaves in order to get a better understanding of the processes that regulate organ development in plants.

# Deriving Insect Population Characteristics from Trap Data

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*Keywords: insect trap, active area of a trap, advection-diffusion equation*

Setting up traps is a common way of establishing the presence of a species of insects and its population density. Deriving estimates of population density from trap data typically requires knowledge of the properties of the trap, e.g. active area, strength of attraction, as well as some properties of the population, e.g. diffusion rate, [2]. These parameters are seldom exactly known, [1], and also tend to vary in time, e.g. as a result of changing climatic conditions. We propose using a set of traps in such a configuration that they have different rate of trapping the insects. The properties of the traps and the characteristics of the population, including its density, are simultaneously estimated from the streams of captured insects in these traps. The basic model is an advection-diffusion equation where the traps are represented via suitable advection term defined on the active area of the trap. The values of the unknown parameters of the model are derived by solving an optimization problem. The robustness of the method is demonstrated by numerical simulations.

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# Mathematical Analysis of a Size Structured Tree-Grass Model in Savanna Ecosystems

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*Keywords: savanna, modeling, qualitative analysis, numerical simulation*

Several continuous competition-based models have been developed to study the possible coexistence of trees and grass in savanna ecosystems according to environmental parameters such as climate or fire regime. In those models fire intensity is a fixed parameter. Here, we model fire intensity through an increasing function of grass biomass and let fire return-time vary according to climate types. (For instance, in Africa, in moist savannas fire occurs every 1-2 years, while in dry savannas it is every 3-10 years.) Following [1], we also consider a tree-grass compartmental model that distinguishes small trees (like saplings) that are sensitive to fire from tall trees that are not. On those bases, we model the savanna vegetation dynamics through three state variables (biomass of grass and of the two classes of woody plants) involved in a system of three interrelated, non-linear equations. We carry out a qualitative analysis that highlights three ecological thresholds namely, the destruction ratio of trees due to causes which are different of fire, the survival ratio of grass after the "predation" of trees and the survival ratio of trees after fire. These thresholds summarize the dynamics of the system. Finally, we develop a non-standard numerical scheme [2], and show some numerical simulations to illustrate our analytical results.

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# Modelling Fire as Discrete Events in Some Tree-Grass Interaction Models with Explicit Soil Water Resource

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*Keywords: Savannah, tree-grass interaction, fire, water, impulsive model, nonstandard numerical schemes, periodic solution*

Savannah is a grassland ecosystem characterized by various trees density. It occurs in areas with annual rainfall from 300 to 1800 mm. If rainfall plays an important role in this savannah ecosystem, big fire events also can disturb the whole dynamics. Several continuous competition-based models have been proposed to explain different tree-grass patterns, taking into account fire events (see for instance [1] and references therein). We first consider a tree-grass model, but instead of considering continuous fire forcings, we consider fire as discrete events and derive an impulse differential system. A qualitative analysis show that a periodic equilibrium can exist as well as local and global equilibria, according to some threshold parameters. Then, we consider an eco-hydrological model recently published [1], that takes into account rainfall through a soil moisture equation. We perform a mathematical analysis and develop a nonstandard numerical scheme, that is able to preserve all qualitative properties of the model. Finally, using appropriate numerical schemes [3], we perform several numerical simulations. We conclude and present further possible developments.

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# The C-Root Model.

**From Mosquito Dispersal to Root Growth.**

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*Keywords: Root growth modelling, soil models, PDE, simulations*

Plant root system plays a very important role in plants life. Indeed, the main functions of a root system are anchorage and uptake of water and nutrients. Following several and numerous experiments, various models have been developed, most of them are based on the complete and explicit representation of the root system, like Architectural models or Functional and Structural Models. These models are very complex (many parameters) and are appropriate only at the plant level. At the crop level, these models are no more suitable because of computational limitations .... That is why density based models, describing the evolution of root densities in space and in time have been developed. In [2], a continuous model has been proposed, and applied to simulate the growth of a single horizontal Eucalyptus root. This model, called C-Root, is based on an Advection-Diffusion-Reaction family-like equations, like those considered to study mosquito dispersal [1]. Each operator in the model is related to a root growth process, such as primary growth, branching and mortality. The aim of this talk is to present the C-Root model as well as new simulations on various root systems. Since root growth is not only endogeneous but may depend on abiotic interactions, we discuss further investigations to couple our model to water and soil nutrients models [3].

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# Foot-and-Mouth Disease Virus, Epithelial Cell Death and PDE Models

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*Keywords: infection, virus, PDE, epithelium, interferon*

Foot-and-mouth disease virus (FMDV) is a highly infectious animal virus that affects cloven-hoofed animals (including cattle, sheep and pigs). Because FMDV is a serious global socio-economic threat, it has been studied extensively for many decades. However, there are still several significant knowledge gaps in the pathogenesis of the disease. In particular, the predilection for certain epithelial tissues to develop vesicular lesions is currently unexplained. For example, epithelial cell lysis is extensive in the epithelial tissue of the bovine tongue, which results in the development of vesicular lesions. Nevertheless, the epithelium of the dorsal soft palate (DSP) does not show similar signs, even though it is a primary infection site of FMDV. The factors which influence epithelial cell death and the development of lesions are the focus of this work, which is one of the few modelling studies on the within-host dynamics of FMDV.

With the aim of identifying potential determinants of FMDV-induced epithelial cell lysis in cattle, a spatially explicit 1D PDE model was developed to investigate the roles played by bovine epithelial thickness and cell layer structure. Numerical investigations demonstrated that these two factors alone do not explain the formation of lesions and, consequently, additional biological complexity is essential to explain the bifurcation in epithelial cell behaviour. Detailed exploration of parameter space offered an insight on the importance of potential differences in viral replication and receptor distribution between epithelia and between epithelial cell layers. The 1D epithelial tissue model has been subsequently expanded to a 3D structure, to facilitate the study of the size, as well as the occurrence of lesions, while greater biological realism has been added to the model by incorporating the antiviral activity of interferon to allow its effects on the FMDV dynamics in epithelium to be explored.

# Reconstruction of a Function from its Elliptical Radon Transform

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*Keywords: circular Radon transform, elliptical Radon transformm, reconstruction, bistatic regime, backprojection algorithm*

The talk discusses the fundamental question of image reconstruction in bistatic regime in which the measurements represent line integrals over a family of ellipses with foci at the source and receiver locations. An integral transform, the elliptical Radon transform is introduced and used to model the data. This talk presents some new numerical results about the inversion of the elliptical Radon in 2D. A new approximate inversion formula is presented in the case of circular acquisition geometry when the source and the receiver are rotating around the origin at a fixed distance from each other. We demonstrate the efficiency of the suggested algorithm by presenting a computational implementation of the method on a numerical phantom. This novel algorithm can be efficiently implemented as a numerical method in several bistatic imaging modalities e.g. in biomedical imaging.

# Replica Exchange MD Investigation of the Conformational Space of Prion Proteins

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*Keywords: prion proteins, replica exchange molecular dynamics, conformational space*

Prion proteins are found on the surface of nerve cells. Their function is not fully understood yet, but they are related to the etiology of certain rare deseases, like CJD, GSS, Kuru, FFI etc [1]. Prions exist in a native (PrP) and in a highly infective pathological form (PrPSc scrapie form). PrPSc proteins can transform native prions into scrapie forms, aggregate and thus lead to cellular death. Experimental insights on the scrapie form suggest a higher fibrilar beta-structure content, in contrast to the mostly globular alpha-helical native form [2]. However, the 3D structure of PrPSc is still unknown. The present study aims at identification of scrapie form candidates, investigating the prion conformational space by means of replica exchange molecular dynamics. Thus, a conformation of a chicken prion protein is constructed with beta-structure content in agreement with the experimental data.

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# Correlated Probit Model for Multiple Side Effects in Cancer Radiotherapy

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*Keywords: EM algorithm, correlated probit model, polymorphism XRCC3 codon 241 ($C > T$)*

In the period from 2006 to the beginning of 2008 121 women with cervical or endometrial cancer were followed at Medical Academy - Sofia. Normal tissue is affected as a result of radiation treatment. This leads to different types of normal tissue reactions. In this work we focused on early (starting from the first day of radiotherapy to 3 months after it) skin and early urogenital normal tissue reactions. We were interested in the strength of association between both types of tissue reactions on the one hand and associations between them and genetic factors on the other hand. We used univariate and multivariate statistical models to assess the effects of predictor variables on normal tissue reactions: a separate probit model for each type of reactions and a joint correlated probit model for both type of reactions. We established that there was a relationship between skin reactions and polymorphism XRCC3 codon 241 ($C > T$) and that skin and urogenital reactions were weakly statistically associated. For fitting the correlated probit model we proposed an extension of the EM algorithm. For the implementation of the algorithm we created functions in the free software environment for statistical computing and graphics **R**. We present a simulation study to confirm the reliability of the presented algorithm.

**Acknowledgements:** This work was supported by the European Social Fund through the Human Resource Development Operational Programme under contract BG051PO001-3.3.06-0052 (2012/2014).

# Exponential Stability for Differential Equations with Random Impulses at Random Times

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*Keywords: impulsive differential equations, random moments of impulses, p-moment exponential stability.*

The modeling of real world phenomena in which the state of the investigated process changes instantaneously at uncertain moments, requires application of impulsive differential equations with impulses occurring at random times. The investigations of such kind of differential equations combine ideas of qualitative theory of differential equations and probability theory. In this paper the statement of differential equations with randomly occurring impulses is given and p-moment exponential stability of the solutions is studied.

# Pattern Formation and Cross-Diffusion for a Chemotaxis Model

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*Keywords: reaction-diffusion system, chemotaxis, cross-diffusion, Turing's principle. pattern formation.*

Chemotaxis is the feature movement of cell or an organism along a chemical concentration gradient. The mathematical analysis of chemotaxis models show a plenitude of spatial patterns such as the chemotaxis models applied to skin pigmentation patterns, that lead to aggregations of one type of pigment cell into a striped spatial pattern. The analysis of pattern formation can be traced to a seminal paper by Turing [1], who established that a reaction-diffusion system can generate stable nonuniform patterns in space if the components of the system interact with each other.

Our motivation is the numerical simulations of the pattern formation for a volume filling chemotaxis model. In [2], the effect of volume filling is expressed through a nonlinear squeezing probability. We investigate pattern formation using Turing's principle and the standard argument used by Murray [3]. Next, we introduce an implicit finite volume scheme; it is presented on a general mesh satisfying the orthogonality condition [4,5]. The originality of this scheme is the upstream approach to discretize the cross-diffusion term. Finally, we present some numerical results showing the spatial patterns for the chemotaxis model.

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# Computational Study of a Bioreactor Model with Microbial Growth Phases and Spatial Dispersal

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*Keywords: continuously stirred bioreactor model, reaction diffusion equations, travelling wave solutions*

We consider a batch mode bioreactor model proposed in [1]. The model is developed using the fact that the bacterial growth undergoes several phases: lag, log, stationary and death phase [1],[2]. First we modify the model by introducing additional (the so-called transport) terms to describe continuously stirred bioreactor dynamics. Then we extend the model by adding diffusion terms to the equations [3]. The latter reaction diffusion equations are studied numerically. Thereby, solutions in the form of travelling waves are found.

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# Computation of the Equilibrium Point for Discrete-time Linear Stochastic Systems

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The linear optimal control problem of linear systems subject to Markov jumps and/or multiplicative noises is considered and the computation of an optimal control strategy is commented. This kind of models has found many applications in engineering and finance as, for instance, in nuclear fission and heat transfer, population models and immunology, portfolio optimization (O. Costa, de Oliviera, Optimal mean-variance control for discrete-time linear systems with Markovian jumps and multiplicative noises, Automatica 48(2012), 304–315), etc., and several results related to the control of these systems have already been derived. The challenge of the applications is that the weighting matrices in the linear quadratic models are assumed to be singular or indefinite.

The realization of the optimal control strategy depends on the stabilizing solution of some appropriate systems of Riccati-type coupled equations, i.e. a set of generalized discrete-time algebraic Riccati equations has to be solved. The LMI approach for computing the stabilizing symmetric solution of this system is studied. We construct two new modifications of the standard LMI approach and we show how to apply these new modifications to the investigated problem. Computer realizations of all modifications are compared. Numerical experiments are given where the new LMI modifications are numerically compared. Based on these experiments the main conclusion is that the new LMI modifications are faster than the standard LMI approach.

# Upscaling from Discrete to Continuous Mathematical Models of two Interacting Populations

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*Keywords: individual movement, Chemotaxis, upscaling*

Populations interact in a wide variety of ways: through cooperation, competition, or predation. In this work we consider two interacting populations, individuals and a stimulus. Individuals move in response to the stimulus population while the stimulus only diffuses. Both populations grow while the stimulus population is being depleted by the individuals. In order to account for the random nature of the system, an individual-based model (IBM) is first developed and then upscaled into a continuous partial differential equation (PDE) model by considering transition probabilities of the individuals at each site. Finally, a set of numerical experiments is presented showing very good agreement between the IBM and the PDE model.

# Turing Instability of a Chemical System with Reactants Binding to a Substrate

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*Keywords: Turing instability, substrate binding, Turing parameter space*

Relevance of Turing mechanism for biology has been questioned due to not allowing pattern formation when the diffusion constants of the two reacting chemicals are identical. The idea that binding of the activator to a substrate may effectively reduce its diffusion rate and thus destabilize a system that would otherwise be stable was formulated in an article by Lengyel and Epstein [2], where the authors reduce the original system of three linear partial differential equations to a two-dimensional reaction-diffusion system that they analyse. We question relevance of this analysis due to lack of connection between the original and the reduced model and suggest that analysing the reduced model actually does not yield any possibilities beyond the standard setting. Nevertheless, our analysis of the three dimensional system shows that one can indeed relax the standard conditions on diffusion constants that are necessary for Turing instability, in particular allow identical diffusion coefficients. Another question that we raise is whether one can relax the condition on the effective diffusion rates in the three- or four-dimensional model. This idea is supported by a previous result of Klika, Baker, Headon and Gaffney [1] that one can significantly reduce the necessary conditions for Turing instability by adding more reactants into the system. Furthermore, the approach of studying the full four-dimensional system allows relaxing the kinetic contraints, for example by permitting two activators to generate a pattern.

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# On a Bivariate Poisson Negative Binomial Risk Process

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*Keywords: ruin probability, compound birth process, bivariate negative binomial distribution*

In this paper we define a bivariate counting process as a compound Poisson process with bivariate negative binomial compounding distribution. We investigate some of its basic properties, recursion formulas and probability mass function. Then we consider a risk model in which the claim counting process is the defined bivariate Poisson negative binomial process. For the defined risk model we derive the joint distribution of the time to ruin and the deficit at ruin as well as the ruin probability. We discuss in detail the particular case of exponentially distributed claims.

**Acknowledgements:** This work was supported by the European Social Fund through the Human Resource Development Operational Programme under contract BG051PO001-3.3.06-0052 (2012/2014).

# On the asymptotic stabilizability of a nonlinear bioprocess model

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*Keywords: asymptotic stabilizability, bioprocess model, bioreactor.*

A nonlinear model of a bioprocess is considered. Assuming that the model parameters are unknown but bounded, the global asymptotic stabilizability of the control system is studied. The performance of the approach is illustrated via numerical simulations.

# On Some Multipoint Methods Arising from Optimal in the Sense of Kung–Traub Algorithms[1]

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*Keywords: solving nonlinear equations, order of convergence, optimal algorithm, efficiency index*

In this paper we will examine self-accelerating in terms of convergence speed and the corresponding index of efficiency in the sense of Ostrowski–Traub of certain standard and most commonly used in practice multipoint iterative methods using several initial approximations for numerical solution of nonlinear equations due to optimal in the sense of the Kung–Traub algorithm of order 4, 8 and 16. Some hypothetical iterative procedures generated by algorithms from order of convergence 32 and 64 are also studied (the receipt and publication of which is a matter of time, having in mind the increased interest in such optimal algorithms). The corresponding model theorems for their convergence speed and efficiency index have been formulated and proved.

[1]This article is dedicated to the 70th anniversary of Prof. Dr. Svetoslav Markov.

# Simulation Model of a Tropical Foliar Epidemic Disease at Plant Scale: Case of Black Sigatoka on Banana

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*Keywords: black sigatoka, foliar epidemic, disease model, stochasticity, Bayesian inference.* Black sigatoka (BS), caused by the fungal pathogen *Mycosphaerella fijiensis*, is considered as the most destructive foliar disease of banana and plantains. Controlling BS is essential to the export production because of the important damages caused to fruit quality. The main current control consists in frequent aerial fungicide applications and deleafing, which is not a safe and durable solution. To overcome this practice, CIRAD has set up a banana breeding program to create BS partial resistant varieties. However evaluation of resistances efficacy puts constraints in time (long crop cycle) and space (numerous experimentals plots to set up). To help in resistant hybrid selection, a mechanistic simulation model of BS was designed. This model aims to better understand the pathosystem and to identify the most effective resistance components. The model was developed in discrete time at plant scale. It describes, without spatialization and in optimal climatic conditions, the development of the lesions during several crop cycles. Two sub-models are defined: the first one describes simply the growth of the banana in a deterministic way (9 parameters); the second one describes the complete and detailed epidemic cycle by integrating stochasticity (12 parameters). Infectious cycle data were collected in both controlled and natural infestation conditions on susceptible and resistant cultivars. Data used for the model calibration were collected over a period of three months on the same kind of cultivars. The estimation of the model parameters was realized in a bayesian framework using MCMC (Markov Chain of Monte Carlo) methods such as the Metropolis-within-Gibbs algorithm. First result of sensitivity analysis allow to quantify the epidemiological impact of each resistance components.

# Calculating Binding Free Energies of Variants of hIFN-$\gamma$ and their Extracellular Receptor

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*Keywords: Human Interferon Gamma, Free Energy Calculations, Binding Free Energy*

Cytokines play an important role in cellular communication and in modulation of the cellular immune responses. A computational protocol is presented that allows the prediction and analysis of the effect of particular mutations in the cytokine molecules on the interactions with their receptors. It is based on the theory developed by B. Jayaram and D. L. Beverige [1] and relies on collecting statistical data from molecular dynamics simulations. The protocol was first tested on a native cytokine receptor complexes against experimental data such as association/dissociation constants or binding free energies on a particular cytokine receptor system, namely the human interferon gamma (hIFN$\gamma$) human interferon gamma receptor (hIFN$\gamma$R) complex.

**Acknowledgements:** Financial support from Grant DMU03/23/12.12.2011 of the Bulgarian National Science Fund is acknowledged.

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# Nonstandard Discretizations in Cancer Modeling

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*Keywords: cross-diffusion equations; nonstandard finite difference method; cancer growth*

Diffusion equations have been extensively studied in biosciences, contrary to cross-diffusion equations, which are more challenging from both the mathematical analysis and numerical analysis point of view. Yet, they arise naturally in cancer modeling, as seen from the book mentioned in [2]. We consider two models for cancer growth defined by cross-diffusion equations, which have positive solutions: a model for angiogenesis or classical malignant invasion [1] and a complex model for lymphangiogenesis [2]. In the two models, the underlying point is that the evolution of the tumor cell occurs in a cross-diffusive manner, which makes it difficult for nonstandard finite difference (NSFD) schemes constructed for diffusion equations to be suitable. We then design NSFD schemes that replicate the positivity of solutions by introducing a special numerical treatment of the cross-diffusion terms, combined with Mickens' rules of complex denominator function of discrete derivatives and nonlocal approximation of nonlinear terms. We provide numerical experiments that confirm the reliability of the NSFD schemes.

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# Moment Equations for the Evolution of Quantitative Traits in Space

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*Keywords: population genetics, evolutionary ecology, quantitative traits, partial differential equations, integrodifference equations*

The importance of genetic change, and in particular adaptive evolution, during biological invasions is widely acknowledged, yet has to date received little attention from theoreticians. Here we present analysis of a set of models for the moments of a quantitative trait (i.e. a continuous random variable like body size) in a population that disperses in a continuous spatial habitat with a spatially varying trait optimum, building on work of Kirkpatrick and Barton (1997) and others. We focus on (discrete-time) integrodifference models incorporating "heavy-tailed" dispersal, which is known to strongly influence the speed of traveling wave solutions, representing invasions, in purely ecological models without a genetic component. We obtain both traveling wave speeds and, when maladaptation limits the extend of an invasion, properties of the resulting localized (i.e. range-limited) population. These are contrasted with existing results (Kirkpatrick/Barton 1997, Barton 2001, Garcia-Ramos/Rodriguez 2002) for partial differential equation models representing diffusive movement. The results advance understanding of how dispersal patterns interact with genetics and environmental conditions to determine the extent of a species' range.

Joint work with A. Castorena.

# Zero-Eigenvalue Turing Instability in General Chemical Reaction Networks

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*Keywords: chemical reaction networks, bipartite graphs, Turing instability*

Biochemical reaction networks with diffusion are usually modeled by reaction-diffusion systems of equations and are studied in connection with pattern formation in biology. We say that 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. We describe a necessary condition for zero-eigenvalue Turing instability, i.e., Turing instability arising from a real eigenvalue changing sign from negative to positive, for general chemical reaction networks with any number of species, modeled with mass-action kinetics. The reaction mechanisms are represented by the species-reaction graph (SR graph) which is an undirected bipartite graph. If the SR graph satisfies certain conditions, similar to the conditions for ruling out multiple equilibria in spatially homogeneous differential equations systems, then the corresponding mass-action reaction-diffusion system cannot exhibit zero-eigenvalue Turing instability for any parameter values, rate constants and diffusion coefficients.

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# Estimating the Rate of Aging on Human Mortality Surfaces

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*Keywords: frailty model, Poisson likelihood, rate of aging, mortality surface*

The individual rate of aging is defined as the relative derivative of one's risk of death with respect to one's age. The b-hypothesis, formulated by Vaupel (see [1]), postulates that all humans share the same rate of aging. In order to check this hypothesis given the existing aggregate data on human mortality, we present several statistical approaches, their advantages and shortcomings, as well as some preliminary conclusions.

Lifetable adult mortality data (death counts and exposures in the absence of explanatory variables) are usually fit parametrically by a gamma-frailty model with a Gompertz-Makeham baseline (see [2]). Its straight application to cohort mortality data produces, though, dubious parameter estimates as it does not incorporate improvements in age-specific mortality rates that occur yearly. One possibility of dealing with this is to design an estimation procedure on mortality surfaces for a fixed age range over a fixed period of time:

$$\bar{\mu}(x,y) = \bar{z}(x_0, y-x).\bar{S}^{\gamma}.a(x_0,y)e^{b(x-x_0)},$$

where $\bar{\mu}(x,y)$ demotes marginal hazard; $\bar{z}(x_0, y-x)$ is the average frailty among survivors to age $x_0$ from the cohort born in year $y-x$; $S$ is the $y-x$–cohort survivorship between ages $x_0$ and $x$; $\gamma$ is the squared coefficient of variation of the frailty distribution; $a(x_0,y)$ and $b$ are the Gompertz parameters. This model can be estimated in a number of special cases.

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# Modelling and Parameter Identification of Tuberculosis in Cameroon

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*Keywords: nonlinear dynamical systems, tuberculosis, parameters identification, Gauss-Newton method*

Tuberculosis (TB) is a common lethal infectious disease usually caused by Mycobacterium tuberculosis. TB is a preventable and curable disease which most often affects the lungs. According to the WHO, TB to date, claims the second largest number of victims due to a single infectious agent right after HIV/AIDS. Although a widespread implementation of control measures focus on case finding and short-course chemotherapy, the global burden of TB has increased over the past two decades [1].

A deterministic model of tuberculosis in sub-Saharan Africa in general and Cameroon in particular is designed and analyzed with respect to its transmission dynamics. The model includes both frequency- and density-dependent transmissions. It is shown that the model is mathematically well-posed and epidemiologically reasonable. Solutions are non-negative and bounded whenever the initial values are non-negative. A sensitivity analysis of model parameters is performed and the most sensitive parameters of the model are identified using the Gauss-Newton Method [2]. In particular, parameters representing the proportion of individuals having access to medical facilities have a large impact on the dynamics of the disease. We demonstrate how an increase of these parameter values over time can significantly reduce the disease burden in the population within the next 15 years.

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# Modelling of P. Vivax Malaria with Bimodal Incubation Time

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*Keywords: P. vivax malaria, epidemiological model, incubation period*

Malaria parasites are transmitted between mosquitoes and humans. If an infectious mosquito bites a host, symptoms occur after a certain incubation period. The incubation period can vary depending on the species of parasite or the regions. In particular, incubation period of Plasmodium vivax - the malaria inducing parasite species most prevalent in temperate zones in Korea - shows bimodal distribution, with short term and long term incubation periods. In this talk, I compare transmission models for P. vivax malaria having different expression for the incubation period.

# Global Analysis for Spread of Infectious Diseases via Transportation Networks

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*Keywords: epidemic models, transportation networks, global dynamics, delay differential systems*

We formulate an epidemic model for the spread of an infectious disease along with population dispersal over an arbitrary number of distinct regions. Structuring the population by the time elapsed since the start of travel, we describe the infectious disease dynamics during transportation as well as in the regions. As a result, we obtain a system of delay differential equations. We define the basic reproduction number $\mathcal{R}_0$ as the spectral radius of a next generation matrix. For multi-regional systems with strongly connected transportation networks, we prove that if $\mathcal{R}_0 \leq 1$ then the disease will be eradicated from each region, while if $\mathcal{R}_0 > 1$ there is a globally asymptotically stable equilibrium, which is endemic in every regions. If the transportation network is not strongly connected, then the model analysis shows that numerous endemic patterns can exist by admitting a globally asymptotically stable equilibrium, which may be disease free in some regions while endemic in other regions. We provide a procedure to detect the disease free and the endemic regions according to the network topology and local reproduction numbers. For a system consisting of two regions, we find that due to spatial heterogeneity characterized by different local reproduction numbers, $\mathcal{R}_0$ may depend non-monotonically on the dispersal rates, thus travel restrictions are not always beneficial.

# On Nonlinear Waves in the Space-Temporal Dynamics of the ERK Signaling Protein

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*Keywords: ERK and STAT protein interaction, PDEs, Modified method of simplest equation, analytical solution, drop and jump propagation*

In this paper we model the spatial and temporal dynamics of ERK and STAT protein interaction by means of nonlinear partial differential equations. We show that the diffusion together with the corresponding biochemical reactions is likely to play a critical role in governing the dynamical behavior of the ERK and STAT interaction system. We reduce the above mentioned system to analytically tractable PDE with polynomial nonlinearity up to third order. By applying the modified method of simplest equation to the described model we obtain an analytical solution which describes drop and jump propagation of the ERK protein concentration.

# Modelling Endemic Malaria and the Dangers of Partial Immunity

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*Keywords: malaria, modelling, asymptotic, latent asymptomatic, treatment*

In this talk we present human-mosquito interaction model that describes the development of malaria in a human population. The model accounts for the various phases of the disease in humans and mosquitoes, together with treatment of both sick and partially immune humans. The partially immune humans (termed asymptomatic) have recovered from the worst of the symptoms, but can still transmit the disease. We present a mathematical model consisting of a system of ordinary differential equations that describes the evolution of humans and mosquitoes in a range of malarial states.

A new feature, in what turns out to be a key class, is the consideration of reinfected asymptomatic humans. The analysis to be presented includes establishment of the basic reproduction number, $R_0$, and asymptotic analysis to draw out the major timescale of events in the process of malaria becoming non-endemic to endemic in a region following introduction of a few infected mosquitoes. The results suggests that intervention programmes may yield better results if implemented during the time scale when the feedback from infectious humans offsets the linear growth effect of the initial small amount of infected mosquitoes.

The reinfected asymptomatic class is significant to the continuation of malaria in endemic areas and in our analysis of a model describing treatment we show evidence of effective control and possible eradication of the disease, with a "moderate" level of treatment, if partially immune carriers of malaria parasites are treated alongside with sick humans.

# Recalibration of p-values for Multiple Testing Problems in Genomics

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*Keywords: p-values, multiple comparisons, statistical tests, statistical power*

Statistical practice has shown a preference for conservative statistical tests in situations where exact control of the Type I error rate is difficult, likely due to a belief that the consequences of falsely rejecting the null hypothesis are usually greater than the opposing Type II error of failing to reject an incorrect null. Conservative tests, however, prevent us from detecting some of the real differences between two groups and, as a consequence, reduce statistical power. For example, a conservative RNA-seq differential expression test may not allow us to detect some differentially expressed genes, even when the sample size is sufficient for a non-conservative test.

Here, we present techniques for recalibrating the p-values of conservative statistical tests with the aim of increasing the number of true-positive findings at each given p-value threshold. As a secondary benefit, these techniques may allow us to reduce the sample size required to achieve a desired level of power, leading to reduced experimental costs.

# Modeling the Effect of Climate Change on Rare Genotypes in Nature

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Numerical simulations are employed to model the impact of rare genetic types (or genotypes) experiencing climate change over a long time scale. The physical appearance of many genotypes is impacted by enzymatic functioning. Some enzymes are temperature sensitive and may therefore be impacted by global warming. When enzyme expression changes traits like pigmentation, can be affected dramatically. Genetic polymorphism, where at least two different types of the same species exist, are often maintained by natural selection. There are two color types of mosquitofish (Gambusia holbrooki), melanic (black spotted) and silver. Even though the mosquitofish are one of the most abundant fish species in the southeastern US, the melanic genotype is quite rare. All the progeny of silver mosquitofish are born silver and on average about 20% of the progeny of melanic fish are also silver. However in some populations cold exposure is required for the progeny of melanic fish to develop melanism. Without cold exposure these fish remain silver.

Climate change, resulting in rising water temperatures may affect the expression patterns of the rare genotypes that require cold exposure to turn melanic. To simulate the effect of the rising temperature on the inheritance of melanism parameter we used three different functions as a linear function, a step function, and a random function. In each case simulations reveal that the climate change will have a devastating effect on the melanic genotypes that require cold exposure to express melanism - they will go extinct after a finite number of years. We also report on the effect of a variety of initial conditions on the population growth/decay and the sensitivity of the population to fitness changes.

# TASEP on a Linear Network with a Bypass

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*Keywords: TASEP; traffic flow models; non-equilibrium phase transitions; traffic on networks; biological transport processes*

The asymmetric simple exclusion process (TASEP) is one of the paradigmatic models for understanding the rich world of non-equilibrium phenomena. Interesting realizations of the process on networks with complex geometry have been initiated in [1,2]. Here, we extend our study of TASEP, defined on an open network, consisting of head and tail simple chain segments with a double-chain section inserted in-between [1,3,4]. By considering the case when the two branches of the double-chain section are of different length, we model a bypass on a linear track. This case generalizes also the TASEP with a shortcut [5], where one of the branches has a zero length. Results of numerical simulations for relatively short chains are presented when the current through the system takes its maximum value. The studied system might have interesting implications for the traffic flow control as well as for biological transport processes in living cells. An explanation of this phenomenon is offered in terms of finite-size dependence of the effective injection and ejection rates at the ends of the double-chain section [3,4].

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# Interpolation and Extrapolation of Functions defined by a Cauchy Problem with Applications to Ecological Modeling

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Inherent in the classical approach to function approximation are the limitations placed on the scope of choice for functions of approximation.In this paper a novel method that allows us to approximate functions by means of linear combinations of polynomials, trigonometric and exponential functions, polynomials and periodic functions among others, is presented. This technique uses, on a fixed interval, an initial value linear ordinary differential equation for function approximation and the approximation expressions are obtained in a closed form.

# Analysis on the Cells Growth Dynamics of *Acidithioacillus ferrooxidans* at Adaptation to High Substrate Concentrations

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*Keywords: ferrous ions, cultivation regime, Acidithiobacillus ferrooxidans*

Acidithioacillus ferrooxidans is an autotrophic, acidophilic, mesophile occurring in single or occasionally in pairs or chains, depending on growth conditions. Among the group of Acidithiobacillus, A. ferrooxidans has emerged as an economically significant bacterium in the field of leaching of sulfide ores. The discovery of A. ferrooxidans led to the development of a new branch of metallurgical sciences called "biohydrometallurgy," which deals with all aspects of microbial mediated extraction of metals from minerals or solid wastes and acid mine drainage. This work is a part of studies on the bacterial physiology in regimes of cultivation in media with high substrate concentrations. It aims to evaluate with statistical significance similarity, or differences in biomass experimental curves. Three series of experiments were elaborated for studying the influence of high concentrations of ferrous ions. The bacterial growth was studied by samples, taken from the cultural media troughout the cultivation process, at hours, significant for different stages of periodic cultivation of the strain. The probes were processed using the method of limited dilutions and the cells were grown on solid medium in BIOCENTER 2001 for 25 days, and developed colonies were counted. The experimental data show some statistically significant differences in the studied parameters measured in different cultural media at the beginning and last phases of culture growth.

# Investigation of the Geometry Effect on the Wall Shear Stress on the Aneurysm Wall

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*Keywords: wall shear stress, Computational Fluid Dynamics, geometry paprameters, regression equations*

The variation of wall shear stress (WSS) is hypothesized as a major cause for aneurysm rupture. Objective of many studies is to examine the critical values of WSS, that can lead to aneurysm hemorrhage. Following this aim the authors perform numerical simulations in ANSYS Workbench 14. Ideal aneurysm geometries are constructed in commercial package ANSYS Model Designer. Three main morphological factors are varied: diameter of parent vessel , aneurysm diameter and aneurysm height . Using numerical simulations (in commercial code ANSYS Fluent), contours of both total pressure and velocity magnitude in the symmetry plane , as well as contours of WSS on the parent vessel, and aneurysm walls are obtained. By applying commercial code STATISTIKA a special attention is paid on the WSS on aneurismal wall and its 25th quartile. Regression equations are derived for the WSS on aneurysm wall depending on the above geometric parameters.

# Skew Box Enclosure for the Parametric AE Solution Set

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*Keywords: linear systems, dependent interval data, AE solution set*

Consider linear algebraic systems $A(p)x = b(p)$ where the elements of the matrix $A(p)$ and the vector $b(p)$ are linear functions of uncertain parameters varying within given intervals, $p_i \in [p_i]$, $i = 1, \ldots, k$. For two disjoint sets $\mathcal{E}$ and $\mathcal{A}$, such that $\mathcal{E} \cup \mathcal{A} = \{1, \ldots, k\}$, the parametric AE solution set of the above system is defined by

$$\begin{aligned}\Sigma^p_{AE} &= \Sigma(A(p), b(p), [p]) \\ &:= \{x \in \mathbf{R}^n \mid (\forall p_{\mathcal{A}} \in [p_{\mathcal{A}}])(\exists p_{\mathcal{E}} \in [p_{\mathcal{E}}])(A(p)x = b(p))\}.\end{aligned}$$

A single step parametric method, called Bauer-Skeel method, based on the left-preconditioned system, is proposed in [1] for the outer estimation of a parametric AE solution set.

In this talk we present a outer estimate of the parametric AE solution set by right-preconditioning of the parametric matrix. The obtained outer estimate is in the form of a parallepiped, called skew box. A right-preconditioning version of the parametric Bauer-Skeel method for outer estimation of the parametric AE solution set will be presented. In the special case of parametric united solution set a right-preconditioning version of the parametric fixed-point iteration will be outlined. The properties and the usefulness of the new outer estimation will be discussed on a number of numerical examples.

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# On the Mathematical Modelling of EPS Production by a Thermophilic Bacterium

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*Keywords: EPS production, thermophilic bacterium, numerical simulations*

An increasing interest towards microbial exopolysaccharides (EPSs) is determined by the wide variety of their properties as a result of diversity in their composition. Thermophilic microorganisms suggest non pathogenic products, appropriated for application in food industry, pharmacy and cosmetics. They offer also short fermentation processes, better mass transfer, decreased viscosity of synthesized polymer and of the corresponding culture liquid. Only a few EPS-secreting thermophilic bacteria were isolated [2]. In the current work we report on the mathematical modeling of the fermentation processes based on experimental results for EPS production by a thermophilic bacterium, *Aeribacillus pallidus* 418, isolated from Rupi basin, South-West Bulgaria. An investigation on the influence of agitation and aeration on the bacterial growth and EPS synthesis revealed high mass transfer dependence of the polymer production. The polymer production is associated to growth. Microbial and substrate dynamics are described by means of systems of ODEs. Two possible dynamical models based on ideas from [1] are proposed and numerical simulations are presented.

**Acknowledgements**. The authors are grateful to the National Fund for Scientific Research, Bulgaria for financial support of this work (Contract DTK 02/46).

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# Variance Estimators in Branching Processes with Non-Homogeneous Immigration

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*Keywords: branching processes, non-homogeneous immigration, conditional least-squares estimators.*

Branching processes with immigration were proposed to study the temporal development of populations of differentiated cells in [3] and more recently in [1]. More specifically, terminally differentiated oligodendrocytes of the central nervous system and leukemia cells were analyzed. In both cases the cell population expanded through both division of existing (progenitor) cells and differentiation of stem cells. The population's viability was preserved by allowing the immigration distribution to vary in time. We construct conditional least-squares estimators for the offspring variance assuming that the immigration mean increases to infinity over time. The asymptotic normality of the proposed estimators is established. Part of the results was published in [2].

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# Modelling Protein Oscillations in *Myxococcus xanthus*

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*Keywords: dynamical systems, reaction-diffusion equation, cell polarity.*

Spatio-temporal oscillations of proteins in bacterial cells play an important role in fundamental biological processes. Motility of the rod-shaped bacterium *Myxococcus xanthus* is due to two motility systems: an A-motility system and a type-4 pili system [1]. Both motility systems depend on the correct localisation of regulatory proteins at the cell poles which set up a polarity (front-to-back) axis. The oscillatory motion of the individual cell results from dynamic inversion of the polarity axis due to a spatiotemporal oscillation of the regulatory proteins between the cell poles. A mathematical framework for a minimal macroscopic model is presented which produces self-sustained oscillations of the protein concentrations. The mathematical model is based on a reaction-diffusion system and is independent of external triggers. Necessary conditions on the reaction terms leading to oscillating solutions are derived theoretically. Several possible cases are studied based on different rates of interaction between the regulatory proteins. The interaction laws are then chosen according to mathematical analysis to produce different spatio-temporal oscillation patterns [2]. The different scenarios are numerically tested for robustness against parameter variation. Finally, possible extensions of the model will be addressed.

This is joint work with B. A. Schmitt, S. Dahlke, P. Lenz, L. Søgaard-Andersen. This work has been supported by the Centre for Synthetic Microbiology in Marburg, promoted by the LOEWE Excellence Program of the state of Hessen, Germany.

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# Quorum Sensing and Nonlocal Hydrodynamics of Swimming Bacteria

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*Keywords: quorum sensing, nonlocal hydrodynamics, Burger equation, kinematic viscosity.*

Water fluidity is modified, in a non trivial manner, by the presence of bacteria, above a threshold number density. At such threshold conditions suspensions of swimming bacteria impose a coordinated water movement on a length scale of the order of $(10-100)$m with bacterial size of the order of 3 m. This observation leads to fundamental questions relating to the mechanism of cell-cell communication among bacteria, presently known as quorum sensing. Hydrodynamic model of "swimming" bacteria or bacterial colonies seems to be one of the most comprehensive alternate model in defining possible quorum sensing mechanism. Here the densely packed bacteria may be viewed as a"bacterial fluid" or "living fluid" similar to that of dense granular systems. Lega and Passot initially assumed a two-phase hydrodynamic equations taken the bacteria and water as two interpenetrating and interacting continuum. However, by considering the relatively high bacterial density, given the fact that no water motion is observed (under isothermal conditions and in the sense of displacement sheer viscosity, while rotational bulk viscosity may be present) in absence of the bacteria, we assume the dynamics of the suspended bacteria is governed by bacterial dynamics. Under these conditions bacteria and water appear to move as a single fluid at hydrodynamic scale. We propose that "bacterial fluid" is consistently described by weakly non-local hydrodynamics where kinematic viscosity is generated due to self- induced noise. This viscosity leads to form a metastable state of the actively moving bacteria. This meta-stable state is necessary for the simultaneous activation of the bacteria to support quorum, given the existence of non-local nature of stresses mediated by autoinducers. The stability of noisy Burger equation for this metastable situation will be also studied in this approach.

# A Hypothesised Mechanism for Viral Budding, Supported by Integration of New Protein Associated Curvature Data into a Mathematical Model of the Cell Membrane

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*Keywords: virus budding, cell membrane model.*

Following replication within cells, new virus particles may be released either upon cell death or gradually, by budding out of the surface of still living cells. To develop treatments that can inhibit or interrupt this process requires a better understanding of how it occurs. Here the hypothesis that for certain viruses budding may driven by viral-protein associated curvature of the cell membrane is supported by the application of a mechanistic mathematical model of the membrane. We show that localised increases in curvature alone are sufficient to generate viral buds, while locally induced increases in stiffness accelerate the process and results in tighter buds. Numerical results show good qualitative and quantitative agreement in bud shape and size with experimental observations for arenavirus, for which recent experimental results have confirmed that viral protein is associated with increased membrane curvature.

# Spatial Autocorrelation in Mumps Data

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*Keywords: spatial autocorrelation, mumps, Moran's test, Geary's test*

This paper aims to ascertain the presence or absence of spatial autocorrelation in the dissemination of the disease parotitis. For the solution of similar problems the Moran's $I$ and Geary's $c$ tests (see for example [1] and [3]) are applied over the real data set from Bulgaria.

In order to apply the Moran's $I$ and Geary's $c$ tests we need to find a geographic center in accordance with which to orientate the rest of the counties. In our case it is convenient to put in this center the beginning of the coordinate system whose axes coincide with geographical directions east, west (axis $x$) and north, south (axis $y$). The center of the coordinate system is selected as the county center with the highest dissemination of mumps. This way every county center is uniquely determined with its coordinates $x$ and $y$.

Although, with the reduction of the distances the p-value diminishes, we can not reject the null hypothesis that there is zero spatial autocorrelation in the variable morbidity.

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# Pólya–Aeppli–Lindley Process

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*Keywords: Pólya–Aeppli distribution, Lindley distribution, mixed distribution.*

In this study we introduce the Pólya–Aeppli–Lindley distribution as a mixed Pólya–Aeppli distribution with Lindley mixing distribution. Some properties, probability mass function and recursion formulas are given. Then we define a stochastic counting process with Pólya–Aeppli–Lindley distribution. An equivalent definition as a pure birth process and some additional properties are given. As application, we introduce a Pólya–Aeppli–Lindley risk model, and analyze some properties, ruin probability and deficit at the time of ruin.

**Acknowledgements:** This work was supported by the European Social Fund through the Human Resource Development Operational Programme under contract BG051PO001-3.3.06-0052 (2012/2014).

# Modern Numerical Methods for Continuous Time Markov Chains of High-Dimensions

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*Keywords: Continuous Time Markov Chains, stochastic processes, chemical master equation, hybrid approximations*

The aim of the talk is to present modern methods for computing large Continuous Time Markov Chains (CTMC) which arise in Biology. These modern methods have theoretically and experimentally overcome key obstacles of dimension and computation inherent in high dimensional CTMC [1,2,3]. Continuous Time Markov Chains (CTMC) are a key tool in describing discretely interacting biological systems. Biological processes such as RNA transcription, signalling cascades and catalysis are key examples where the system is being driven by independent inhomogeneous Poisson processes. Researchers have used realisation based simulation methods, such as the Stochastic Simulation Algorithm (SSA), for in-silico observations of these systems. Even though simulations are cheap and quick to implement, it has been shown that they do not always guarantee the capture of critical features such as bi-modality, without multiple realisations. In this talk, we will be presenting the Optimal Finite State Projection method, proposed by Sunkara and Hegland [1] and the Hybrid method proposed by Jahnke and Schütte independently [2,3]. For the two methods, we will discuss their respective error bounds and computation times for particular examples.

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# Boundary Integral Method in the Theory of Bone Porothermoelasticity

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*Keywords: bone porothermoelasticity, double porosity, boundary integral method, 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. A porothermoelastic approach for double porosity materials combines the theory of heat conduction with poroelastic constitutive equations, coupling the temperature field with the stresses and the pore and fissure fluid pressures.

This paper concerns with the quasi-static coupled linear theory of bone porothermoelasticity for materials with double porosity and some basic results of the classical theory of thermoelasticity are generalized. The system of equations of this theory is based on the equilibrium equations, conservation of fluid mass, the effective stress concept, Darcy's law for material with double porosity and Fourier law of heat conduction. The fundamental solution of the system of governing equations is constructed by means of elementary functions and its basic properties are established. The Green's formulas in the considered theory are obtained. The formulas of Somigliana type integral representations of regular vector and regular (classical) solutions are presented. The uniqueness theorems for classical solutions of the internal and external boundary value problems are proved. The single-layer, double-layer and volume potentials are constructed and their basic properties are established. Finally, the existence theorems for classical solutions of the boundary value problems are proved by means of the boundary integral method and the theory of singular integral equations.

# Homogenization Results for Ionic Transport in Periodic Charged Media

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*Keywords: homogenization, ion transport, the periodic unfolding method.*

A macroscopic model for a nonlinear system of coupled partial differential equations arising in the modeling of ionic transport phenomena in periodic charged porous media is rigorously derived.

Our model can serve as a tool for biophysicists to analyze the ion transport through protein channels. Ion channels are very important in biology, because they control many vital biological functions, such as information transfer and processing in the nervous system, the muscle contraction and coordination, the regulation of hormone secretion, etc.

Also, this setting proves to be relevant in the modeling of the flow of electrons and holes in a semiconductor device.

The main tool for obtaining our macroscopic model is the use of the periodic unfolding method, which allows us to deal with general media.

# The Impact of Allee Effect on Infectious Disease Dynamics

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*Keywords: Allee effect, mathematical epidemiology, multistability, disease induced extinction*

It is well known that the Allee effect contributes to developing complicated infectious disease dynamics like multistability, oscillations and disease induced extinction of the host population. Here we characterize and quantify its epidemiological impact within a relatively simple SI model excluding vertical transmission. In such setting, the vital dynamics (births and deaths), which are responsible for the Allee effect, affect significantly the course of the disease. In the presented model the birth rate and the death rate are both modeled as quadratic polynomials. This approach provides ample opportunity for taking into account the major contributors to the Allee effect (mating opportunities, cooperative feeding, joint defence, reduced exposure to predators, cooperation in raising the young) and is an extension of the model presented in [1]. We determine two essential threshold values $\lambda_0$ and $\lambda_1$ of the infectiousness/transmissibility $\lambda$ of the disease. For $\lambda \leq \lambda_0$ the disease free state is stable and attractive and the model exhibits the same bistability as the one of the the disease free state. Under certain conditions the Allee effect causes epidemic like behavior as the disease runs its course to extinction. When $\lambda > \lambda_1$ the disease free state is also stable and attractive but the origin is the only stable equilibrium. Hence introducing the disease at any population size leads to extinction. For $\lambda$ between the two thresholds the eventual outcome of introducing the disease, namely an endemic state or a population extinction, depends on the population size. Some conditions distinguishing between the two outcomes have been derived.

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# Stability and Limit Cycles for a Predator-Prey Model with Predator Population Saturation

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*Keywords: predator-prey, prey carrying capacity, predator population saturation, extinction boundary, limit cycles.*

A multitude of predator-prey models is discussed in literature. The models originated with Lotka (1925) and Volterra (1931). Since then there have been many refinements, but unfortunately not many of the resulting models have been tested against actual data. Thus there is no consensus even on a basic model which can be tweaked for specific prey and predators. In this paper an original predator-prey model, referred to as the Fay Greeff Hoff (FGH) model, that might just provide such a basic model, is proposed. This model subsumes many over the models found in literature and has the advantage that each term in the model has a firm ecological basis for its inclusion and form. The model is, in essence, a classical Rosenzweig-MacArthur model, but with an added function $h(y)$ that includes a constant $L$, called the population saturation of the predator. The FGH model therefore has bounded solutions $x(t)$ and $y(t)$ at the onset. The relevance of having bounded solutions is reflected in the Poincaré-Bendixson Theorem. Thus, the FGH model, with specific parameter values to ensure the existence of a unique equilibrium in the population quadrant, yields equilibrium values which lead to either limit cycles or attracting spiral points. From mathematical analysis a model may yield trajectories indicating the co-existence of species, when, in fact, ecologically extinction might occur. With this in mind an added constraint in the form of an extinction boundary is set. Thus the distinction is made between mathematical stability and ecological stability. In the absence of real data, the FGH model is used in an exploratory way, to gain insight in the dynamics of mathematical modelling and to explore the potential of this model as a tool in studying biological systems.

# Linear and Quasi-linear Spaces of Interval Maps

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*Keywords: Interval functions, linear space, quasi-linear space.*

Interval-valued functions, or briefly interval functions, are traditionally associated with numerical analysis and validated computing, see for instance [4, 5]. Such maps also occur naturally as mathematical tools for modeling phenomena where uncertainty is present, such as in biological dynamical systems [3]. Recently interval functions have also been applied to problems in pure mathematics, such as the Dedekind order completion of spaces of continuous functions [1]. In [2] the structure of a linear space was introduced on the set of finite Hausdorff continuous interval functions with domain an open subset of Euclidean space $\mathbb{R}^n$. In this paper we generalize this result to the case of functions defined on an arbitrary topological space. It should be noted that problem of defining algebraic operations on spaces of interval functions is nontrivial, due to the fact that the set of compact intervals in $\mathbb{R}$ is not a group with respect to the Minkowski sum.

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# Mathematical Model for Temperature Regulation of Self-Sustained Glycolytic Oscillations in a Closed Reactor

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*Keywords: glycolytic reaction, temperature control, nonlinear oscillations*

We base on the Selkov system [1] to construct the model for temperature control of glycolytic reaction in a closed spatial reactor. To establish a correspondence with the experiment [2] we add the slow catalytic term $\alpha x$ which describes the small value of additional substrate influx and product outflow and introduce a temperature-dependent coefficient $\beta$ satisfying the Arrhenius law. We obtain the following temperature model of glycolysis:

$$\begin{aligned} \dot{x} &= \nu - \alpha x - \beta(T) x y^2, \\ \dot{y} &= -wy + \alpha x + \beta(T) x y^2, \\ \dot{\nu} &= -\varepsilon v, \end{aligned} \tag{6}$$

where the last equation corresponds to a consumption of the substrate.

The considered model explains the key experimentally observed phenomena [2]: 1) decaying of the average concentrations of reagents during the reaction, 2) Arrhenius-type temperature dependence for frequency of oscillations, 3) change of the form of oscillations with the temperature growth, 4) modulations of oscillations induced by a periodic temperature variation.

The addition of the diffusion terms to the system (1) allows to reproduce the emerging of glycolytic travelling waves observed in a closed reactor in the presence of a temperature gradient [2]. Comparison of the dynamics of travelling waves in the numerical solution with the experimental data [2] permits to propose a new method to estimate the diffusion coefficients of reagents in the case of a chemical reaction occurring in a dense media.

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# Diffusion Influence on Phase Synchronization in the Glycolytic Reaction in a Distributed Medium

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*Keywords: glycolytic reaction, phase clusters, synchronization, diffusion*

We study the synchronization process during the glycolytic reaction in a distributed medium. We base on Selkov model [1] extended with diffusion:

$$\begin{aligned} \dot{x} &= \nu - xy^2 + D_1\nabla^2 x, \\ \dot{y} &= xy^2 - wy + D_2\nabla^2 y. \end{aligned} \tag{7}$$

The distributed Selkov system is considered in a one-dimensional case, i.e. we assume that reaction occurs in a homogeneous medium inside a long tube impermeable at end faces. The linear analysis shows that the simplest solution with divergent oscillations is both synchronous oscillations along the tube and a cosine wave.For the numerical analysis of synchronization processes we use the following values of parameters corresponding to relaxation regime: $\nu = 2.55$, $w = 2$. The space of a tube was shared on 1024 nodes ("generators") in such a way that each small volume in the space represents a point oscillator. The initial values for the nodes correspond to the values taken from the limit cycle of the local Selkov system presented in the modified Rayleigh form [2] with linear growth of a phase angle. Using the continuous wavelet transform it was shown that there exist various patterns for different diffusion coefficients: from the birth of a hierarchy of phase clusters to their complete phase synchronization. The emergence of spatial phase clusters occurs at equal diffusion coefficients and is connected with various local rotation velocities in phase space, so these structures are not the Turing ones. Large diffusion coefficients stabilize process while small diffusion provides an asynchronous regime only.

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# Population Dynamics in Presence of State-Dependend External Perturbations

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*Keywords: population dynamics, state dependent external perturbations, multiplicative noise*

We study the influence of a class of state-dependent small external perturbations on the population dynamics of a system of competing populations. The class of the external perturbations is modelled by multiplicative Gaussian white noise. We discuss the stationary probability density functions for the studied cases of population dynamics. In addition we discuss the possibilities for perturbation-induced transitions between different probability density functions.

# Subcritical Bifurcation and Global Dynamics in an Imperfect Pulse Vaccination Model

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*Keywords: impulsive differential equation, backward bifurcation*

In this talk we investigate an SIVS epidemic model with imperfect vaccine, thus vaccinated individuals can also contract the infection. We consider pulse vaccination, that means we vaccinate fraction $\varphi$ of population at times $t = nT$. The model reads as

$$\begin{cases} S'(t) &= \mu - \beta S(t)I(t) - \mu S(t) + \gamma I(t) + \theta V(t) \\ I'(t) &= \beta S(t)I(t) - (\mu+\gamma)I(t) + \sigma\beta V(t)I(t) \qquad \text{if } t \neq nT, \\ V'(t) &= -\sigma\beta V(t)I(t) - (\mu+\theta)V(t) \end{cases}$$

$$\begin{cases} S\left(nT^+\right) &= (1-\varphi)S\left(nT^-\right) \\ I\left(nT^+\right) &= I\left(nT^-\right) \qquad\qquad\qquad \text{if } t = nT, \\ V\left(nT^+\right) &= V\left(nT^-\right) + \varphi S\left(nT^-\right) \end{cases}$$

where $T > 0$ is fixed and $n \in \mathbb{Z}^+$.

It is known that in some vaccination models, backward bifurcation occurs and multiple subthreshold endemic equilibria exist, thus the behaviour of solution depends on the initial value [1]. We know that pulse vaccination can be more effective than constant vaccination, thus it is an interesting question to study whether backward bifurcation can arise in a pulse vaccination model. We prove that backward bifurcation can occur in pulse vaccination model. First, we find a disease-free periodic solution, which is locally asymptotically stable in the whole phase space if $R_c < 1$. If $R_c > 1$, then the infection is strongly uniformly persistent in the population. We perform the complete bifurcation analysis of a fixed point equation, where the most important tool was the Lyapunov-Schmidt method and we obtain a sufficient and necessary condition for the existence of subcritical bifurcation.

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# Cell Proliferation Kinetics and Branching Stochastic Processes

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*Keywords: cell proliferation kinetics, immigration of stem cells, branching stochastic processes, limiting distributions, asymptotic normality.*

The main purpose of this work is to present some new ideas and results obtained in modeling of cell proliferation kinetics. Recent advances in experimental techniques of flow cytometry have made it possible to collect a wealth of information about the status of individual cells isolated from dissociated tissues. When one is interested in modeling tissue development starting from the earliest embryonic stages it is reasonable to begin with 0 cells because these cells appear only in the course of embryogenesis. New type cells (immigrants) of age zero arrive in the population of cells in accordance with a non-homogeneous Poisson process with arrival rate $r(t)$. Upon arrival, these immigrants are assumed to be of age zero. Upon completion of its lifespan, every cell either divides into two new cells, or it goes out of the process of proliferation (differentiation or death). These two events occur with probability $p$ and $q = 1 - p$, respectively. The time to division or differentiation of any cell is described by a non-negative random variable $\tau$ with c.d.f. $G(x) = \mathbf{P}\{\eta \leq x\}$. Cells are assumed to evolve independently of each other. Motivated by the above example, we investigate properties of a class of Markov branching processes with non-homogeneous Poisson immigration. We consider a more general process than the one presented above so that the scope of our work does not remain limited to the study of oligodendrocyte generation. Limiting distributions are obtained in the supercritical case and among them an analogue of the LLN and of the CLT.

# Numerical Analysis of the Coupled Modified Van der Pol Equations in a Model of Heart Action

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*Keywords: van der Pol equation, heart action, coupling, synchronization,SA node, relaxation oscillator. 00A69 (General applied mathematics); 92B05 (General biology and biomathematics)*

In this paper, modified van der Pol equations are considered as description of the heart action. Wide ranges of the model parameters yield interesting qualitative results, e.g. Hopf bifurcation, Bogdanov-Takens bifurcation, transcritical and pitchfork bifurcations, but also stable solutions can be found. The physiological model works in nearest range of parameters and allows to obtain stable behaviour which is important for solving the biological problem. When some kinds of pathologies appear in the heart, it is possible to obtain a chaotic behaviour. My aim is to compare the influence of two types of coupling (unidirectional and bidirectional) on the behaviour of the van der Pol system. The coupling takes place in the healthy conductivity system between two nodes, SA and AV, but in some circumstances the pathological coupling can occur in the heart. The Van der Pol oscillator is a type of a relaxation oscillator, which can be synchronized. Synchronization properties of such a system is studied in the following work. For numerical analysis of the discussed system a numerical model was created.

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# 4 Special Sessions

## 4.1 Microbial growth dynamics
## Friday, 21st June 2013
## Session organiser: Neli Dimitrova

Aims and scope

The session is devoted to dynamical models of bioprocesses (bacterial growth in chemostats and bioreactors) related to substrate consumption and product excretion. Scientists are interested in various aspects of the microbial growth dynamics, such as kinetics of secondary metabolite production, microbial population stability and optimization strategies. Theoretical modeling of a bioprocess results in better understanding of the real process providing the basis for developing new hypotheses and helping to design strategies for optimization and control of the bioreactor. The model-based approach in the study of bioprocesses is also justified by the fact that even small performance improvements in the bioreactor may result in substantial economic benefits. There is a big variety of mathematical models due to the enormous variety of bacteria species and environmental situations. Studying the models poses a challenge to the development of suitable mathematical techniques from dynamical systems and control theory, statistical, software and simulation tools.

## 4.2 Modeling under Uncertainty
## Friday, 21st June 2013
## Session organisers: Neli Dimitrova and Evgenija Popova

Aims and scope

Advanced mathematical and computational tools for "Modeling under Uncertainty" are much useful under conditions of extreme sensitivity that is often a characteristic for some biological processes where, in addition, the experimental input data for the parameters may have large uncertainty. The study of dynamical biological processes usually requires sophisticated mathematical tools for testing the process stability and for obtaining guaranteed bounds for the solution which are needed for the verification of the model. The presentations in this session emphasize on various suitable mathematical and computational tools for handling problems in biomathematics. Such tools are: interval analysis, parameter identification, verification tools, set-valued analysis, differential inclusions, impulsive and delay DE, convex analysis, stochastic and fuzzy-set arithmetic (analysis), etc.

# 5 Research Articles in Peer-Reviewed Journals from Past BIOMATH conferences

## 5.1 Journal of Universal Computer Science (J. UCS), Volume 2, Issue 2, Pages 59–95

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## 5.2 Computers & Mathematics with Applications, Volume 32, Issue 11, Pages 1–123 (December 1996)

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