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 1995. It is supported by several research units of the Bulgarian Academy of Sciences including:

- Institute of Biodiversity and Ecosystem Research (IBER)
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- Institute of Microbiology
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Contents

1 Foreword

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

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

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

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

Philip K. Maini

2 The Art of Making Mathematical Biology

We cannot debate that the advances made over the past 30 years in molecular biology, biochemistry and cell biology have dramatically changed biology and the biomedical sciences. Academic institutions and funding agencies increasingly recognize the interdisciplinary nature of biology and medicine, including the important role mathematical, statistical and computational modeling play in the analysis and interpretation of data and information. By and large, biologists and biomedical scientists are more attracted to discover new biological principles and mechanisms in collaboration with mathematicians, and therefore have more appreciation for mathematical biology research. As a biomedical scientist active in the field of mathematical biology, I believe that the scope of mathematical biology includes providing novel biological insights that come from the mathematical formulation and analysis of biological problems. I fully recognized, however, that mathematical biology can also stimulate the development of new mathematics.

There are excellent examples in the literature of mathematical biology research that have provided novel and important biological insights. Classical examples may be found in the work of Alan Turing [1] and of Alan Hodgkin and Andrew Huxley [2]. Much has changed since the publication of these papers. A mathematical biology research project is no longer guided by the independent spirit of one or two applied mathematicians working on a biological problem. Modern examples show that mathematical biology research is now a team science effort. How do we presently perform mathematical biology research? An answer can be given by dividing the research process into the three steps of performing applied mathematics research [3].

The first step in performing mathematical biology research requires the formulation of the biological problem in mathematical terms. There is a widespread misunderstanding that this requires a proficiency and encyclopedic knowledge of biology. In reality it requires a good biological intuition and insight into the decision of which biological problems to attack. We need to learn to exercise excellent judgment in the formulation of the problem. This entails deciding what approximations

to adopt in order to achieve the minimal model. The derivation of the minimal model, without losing the essential mechanisms of the problem, is an art form rather than a science. The mathematical biologist cannot master this art by working independently and as an isolated scientist. Biology is so complex that the knowledge, intuitions and insights are now require interdisciplinary team work.

The second step in performing mathematical biology research requires the solution of the mathematical model formulated. In mathematical biology, this now requires an extensive knowledge of mathematical, computational and statistical methods. The selection of the appropriate mathematical or computational technique will depend on the biological and physicochemical scales of the problem under consideration. The solution of most of the mathematical models requires the implementation of complex computational algorithms. Mathematical biologists need to investigate the model dynamics under biologically realistic parameter bounds. At the same time mathematical biologists need to investigate model sensitivity to parameters and initial conditions using statistical approaches and sensitivity analysis. Knowledge of mathematics, scientific computing and statistics is obviously necessary, but there is no person with an encyclopedic understanding of these methods. The isolated mathematician again will have limited chances of succeeding.

The third step in performing mathematical biology research requires the interpretation of the mathematical model solutions and their empirical verification in experimental terms. This step serves as the culmination of the research, but it cannot be accomplished without the interdependence between the mathematical biologists and the experimentalists. Although it would be incorrect to say that all mathematical biology involves this third step (for example, the development of new mathematics and theory may not include this step), mathematical biology research must give priority of the empirical verification and evidence. Novel mathematical biology ideas, methods and techniques will need to show usefulness in the biological and biomedical sciences.

In the context of the International Conference on Mathematical Methods and Models in the Bioscience (BIOMATH 2011), Sofia, Bulgaria 15-18 June 2011, it is a great pleasure to see the steps of mathematical biology research effectively applied to investigate a wide range

of problems in the biological and biomedical sciences. There is no better figure to honor in the Bulgarian sciences for multidisciplinary efforts in the biomedical sciences than Roumen Tsanev (1922-2007), who founded the Central Laboratory of Biochemistry associated to The Bulgarian Academy of Sciences in 1960. The central laboratory, nowadays known as the Institute of Molecular Biology "Acad. Roumen Tsanev", became a center for biologists, chemists, physicists and mathematicians with interests in the field of biochemistry and molecular biology. As Professor Philip K. Maini indicates in the Foreword, these are very exciting times for mathematical biologists. Mathematical biologists are now actively seeking collaboration with experimental biologists and the need for real application is being emphasized in mathematical biology research. There are tremendous opportunities for the new generation of mathematical biologists in interdisciplinary research. BIOMATH 2011 will serve to train and catalyze new research avenues for young scientists. I would very much like to thank the organizers, Roumen Anguelov and Svetoslav Markov (Institute of Mathematics and Informatics) for the kind invitation to be a plenary speaker and member of the program committee. I am much honored and am sincerely sorry that I cannot attend. I hope you have a fruitful conference.

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3 Roumen Tsanev: The father of molecular biology and the pioneer in bio-mathematical research in Bulgaria

Dr. Roumen Tsanev (1922–2007)

Roumen Tsanev — the father of molecular biology research in Bulgaria

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Dr Roumen Tsanev was born in Sofia on the 5th of October 1922. He graduated from the Faculty of Medicine at the University of Sofia in 1946. Together with a group of young scientists, mainly physicians and chemists, Dr Roumen Tsanev founded in 1960 the Central Laboratory of Biochemistry at the Bulgarian Academy of Sciences. This laboratory promptly attracted new young researchers among biologists, chemists, physicists and mathematicians, who showed special interests in studying the molecular basis of life. In 1972 the Central Laboratory of Biochemistry was transformed into the Institute of Biochemistry and in 1977 was changed as the Institute of Molecular Biology (IMB). Dr Roumen Tsanev headed the Institute as its director until 1993. During his 33 years of leadership, IMB established itself as the leading national and well recognized research centre in the field of Molecular Biology, Biochemistry, Biophysics and Biochemical Pharmacology. In 2007 the IMB adopted his name and is now known as the Institute of Molecular Biology "Acad. Roumen Tsanev". Roumen Tsanev dedicated all his energy and talent to uncovering the secrets of life by understanding key mechanisms of cell differentiation and carcinogenesis. He is the pioneer in studying nucleic acids in Bulgaria and is associated worldwide with the separation of RNA by agar gel electrophoresis and discovery the structure of nucleosomes (the smallest structure of the chromatin) and chromatin replication. In the early 1960s Roumen Tsanev decided to take advantage of the spectacular model of Jacob and Monod explaining the mechanisms of gene regulation in bacteria, and develop in eukaryotes. He was particularly interested in a model that could explain gene expression and cell differentiation in multicellular organisms, including mammals and man. His working hypothesis was that about cell differentiation is a one-way street of a permanent state. De-differentiation would be pathological leading to cancer. The discovery of oncogenes and retroviruses lay, of course, much further in the future. In 1971 Tsanev published a seminal paper on cell differentiation which postulated four states of

the gene: repressed or de-repressed (accordingly to repressor-operator interactions) and blocked and unblocked, as defined by a particular differentiated state. Since the DNA sequence is almost identical in all tissues, this model required an epigenetic level of control of block selected regions of the genome and thereby determine a given differentiated state. Thus Roumen Tsanev predicted the existence of a second (epigenetic) code, which was eventually proved during the last 1-2 decades and laid the foundation of the new science epigenomics. The bold conjecture in Tsanev's model was that the two mechanisms of control - repression/de-repression and blocking/de-blocking, are independent. If follows that to propagate a given differentiated state there must be a mechanism to maintain the blocking state. The proposed candidates that could occlude selected regions of DNA were histones, histone modifications, chromosomal RNA, non-histone proteins and stable protein-DNA complexes. Tsanev's model was partly verified by mathematical modelling and computer simulations. In 1970 Roumen Tsanev received (together with Blagovest Sendov) the highest prize for scientific achievements in Bulgaria, for the study of the cellular differentiation and carcinogenesis. Active to the last day Dr Roumen Tsanev passed away suddenly on July 23rd 2007.

Roumen Tsanev — the pioneer in bio-mathematical research in Bulgaria

Blagovest Sendov
Bulgarian Academy of Sciences

The idea of BIOMAT 2011 is to become a forum for biologists and mathematicians, chemists and physicists, computer scientists and others, working together as partners in research connected with living organisms and the applications of the results to medicine, agriculture and elsewhere. It is natural in such collaborations that the leading ideas come from the biologists. However, success depends on the abilities of both sides, especially when complicated mathematical models are involved.

Roumen Tsanev was an excellent biologist, but was also a very competent mathematician. He knew what to ask for from a mathematicians point of view. I was privileged that he chose me as his collaborator in building mathematical models to verify his hypothesis. In [1], Roumen Tsanevs remember:

"At that time I used to spend our summer vacation with my family on the Black Sea coast in the International House of Scientists "Joliot Curie" near Varna. There I met on the beach the Bulgarian mathematician Blagovest Sendov (now member of our Academy and Bulgarian Ambassador to Japan in Tokyo). Burning on the sand under the hot August sun we discussed science and I started to explain a model of cellular activity based on interrelated genes and the equations that may express the control of their activity. Sendov was very much interested in this idea. In these early days of informatics he was involved in work with computers that were already installed in the Institute of Mathematics at the BAS. Finally we decided to use a computer to study a model of cellular activity based on a network of genes interrelated on the basis of equations describing the synthesis of mRNA, controlled by DNA-protein interactions and programming the ribosomes for the synthesis of proteins."

"That time" was in 1965, when Roumen Tsanev already had new hypotheses in mind for the mechanisms for cellular proliferation, differentiation and carcinogenesis. He started by verifying whether such

mechanisms were logically possible to function at all. The results of an active collaboration with long discussions and computer experiments led to several modifications of the models, which were reported in a series of joint papers [7]–[16]. These papers are devoted to modeling of different biological objects such as epidermis and liver, or different processes such as cellular activity, cellular differentiation and carcinogenesis. The main result of these investigations (keeping in mind that the eukaryotic cells have to undergo cytodifferentiation) was that this process has to be controlled by an independent information, which is not necessarily semantically connected to the genetic information. We postulated this independent information as an epigenetic code, see [16. p. 354]. It should be emphasized, that a rather simple mathematical model of living cells in a multi-cellular organism, based on the existence of an epigenetic code, may explain uniformly the processes of embryonic development, cytodifferentiation, vegetative reproduction, somatic embryogenesis, carcinogenesis and even the emergence of new forms of natural selection. All this is carefully explained in [16] with more than 300 references to experimental results showing agreements with the results of our mathematical model.

Roumen Tsanev's main concern was to find the physical carrier of the epigenetic code. He believed the arrangement of different histones to do the job and proposed a possible molecular mechanism, which might play the role of an epigenetic code, see [16. p. 354]. He did not succeed in proving or disproving this hypothesis. Nevertheless, the main conclusion of our mathematical models was that an epigenetic code should exist in one form or another. One of the main purposes of a mathematical model is to predict.

Our first step was to construct a mathematical model of living cells, based on the concept of Jacob and Monod for the existence of conjugate operons, working as a flip-flop. An operon has two states: repressed as inactive and derepressed as active. The mathematical realization of such flip-flop is by formulating a well known set of nonlinear differential equations. The interaction between the different cells in an organism and the role of the nuclear membrane are important for eukaryotic cells. For this we introduce a special variable for the diffusion through the membrane. This variable depends on the functional state of the cell. It is known that when the eukaryotic cell enters in the mitotic cycle, the diffusion through its dissolved membrane stops.

So we add to the system of differential equations, describing the activity of a cell, some additional differential equations with discontinuous right-hand side. The goal of our first model was to find out if it is possible to choose the constants in the mathematical model of a system of synchronized cells, which divides and interacts between themselves by the substances going through the membranes, in such a way that they reach a homeostasis. The result of the computer experiment was that the model is possible. There exists a region R for the vector V of the constants, such that if V is in R, and we start with one cell, this cell begins to divide and after some mitotic cycles, the division stops. If we "kill" some percentage of the cells, the model reacted depending on this percentage. If the percentage is small, there is no reaction, if it is sufficient, then new mitotic cycle starts. This is in good agreement with the reaction of real tissues, as for example the epidermis, which was studied extensively by Roumen Tsanev. The result was reported mainly in [7] and [8].

Encouraged by the adequate reaction of our model for synchronized cells, we constructed a model of non synchronized cells imitating the liver, see [11]. This model demonstrated very good agreement with the experimental data, especially the reaction after "partial hepatectomy". All this was achieved on the basis of repression and derepresion.

The next stage was to model the mechanism of cytodifferentiation. It turns out that such a process needs additional information in the model to work. Therefore we introduce blocking and deblocking of the operons. In this situation, every operon has four different states: repressed-blocked, repressed-deblocked, derepressed-blocked and derepressed-deblocked. Only in the state derepressed-deblocked, the operon is active. To test these mechanisms, we constructed a mathematical model of a set of cells, which interacted between themselves. Every cell in the model has 8 operons, one mitotic, responsible for the division of the cell, and seven functional operons. Every operon, when active, produces substances which may repress or deblock another operon. This interconnection between the operons is prescribed in the model by a matrix and represents the meaning of the epigenetic code. In other words, the existence of an epigenetic code means that the operons in a cell form a genetic network. Different types of cells in a organism have the same genetic information and differ by the difference in the set of blocked operons.

To define the interaction between the cells, we had to choose a geometrical arrangement of the cells and prescribed the place of a new cell produced after division. To make it simple, we create an animal called "Cilindros". As in many other mathematical models, to avoid the three dimensional geometry, we consider an infinite cylinder and study a plane intersection of it. So, our Cilindros is a ring of two dimensional cells on the plane with an interior space in the middle. The diffusion of all substances produced in the cells is possible only in the middle space and between the neighbor cells. In this way, the interaction between different cells is fulfilled. After division of a cell, the two new cells stay on the same place on the ring as neighbors.

As reported in [16], by choosing concrete matrix for the genetic net in the Cilindros, we may demonstrate all important behaviors as embryonic development, cytodifferenciation, vegetative reproduction, somatic embryogenesis and carcinogenesis.

From mathematical point of view, the Cilindros is a system of ordinary differential equations of first order with discontinuous right hand sides and the number of the equations in this system depends on the time. A new and interesting problem for this system is to study its stability in respect to the number of the equations [17], [18]. If the system is not stable, which means that the number of the equations go to infinity, this is a model of cancer.

Roumen Tsanev's last interview was published in 2009 [1]. Some of his most substantial scientific contributions are included in the monographs [2]–[6].

I met Roumen two days before he passed away, very energetic and determent to write a paper for the epigenetic code, reviewing our 40 years old mathematical models and the present knowledge for the epigenetic mechanisms. It is a pity, that he is not with us today in BIOMAT 2011, to listen to him.

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4 KEYNOTE PRESENTATIONS

4.1 Selection-Mutation Models with and without Size Structure

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Keywords: Selection-mutation, continuous and discrete trait spaces, long term behavior, Dirac measures, Persistence and Permanence

An attempt is made to find a comprehensive mathematical framework in which to investigate the problems of well-posedness, asymptotic analysis and numerical analysis for fully nonlinear evolutionary game theoretic models. For several such models formulated on the space of integrable functions, it is known that as the variance of the payoff kernel becomes small the solution converges in the long term to a Dirac measure centered at the fittest strategy; thus the limit of the solution is not in the state space of integrable functions. Starting with a classical selection-mutation equation and a generalized logistic equation as bases, in the first part of my talk, a general model is formulated as a dynamical system on the state space of finite signed measures. Well-posedness is established, and then it is shown that by choosing appropriate payoff kernels this model includes classical density (continuous trait space) models, both selection and mutation and discrete trait space models all in a continuous manner. It is then demonstrated that the population is permanent and that for pure replicator dynamics the solution converges to a Dirac measure centered at the fittest strategy; thus this Dirac measure is a globally attractive equilibrium point which is termed a continuously stable strategy (CSS). It is also shown that in the discrete case for pure replicator dynamics and even for small perturbation of pure replicator dynamics there exists a globally asymptotically stable equilibrium.

In the second part of this talk, an extension of the model is introduced where individuals are assumed to be structured by their size (in addition to their trait difference). For this model the trait space

is assumed to be discrete. Uniform persistence and robust uniform persistence are established, when the selection-mutation matrix is irreducible. In the case of pure selection, we prove that the boundary equilibrium that describes competitive exclusion, with the fittest being the winner ecotype, is globally asymptotically stable. We also show that small perturbations of the pure selection matrix lead to the existence of globally asymptotically stable interior equilibria. For the case when the selection-mutation matrix is reducible, we present and discuss the outcome of a series of numerical simulations.

Acknowledgement: This work is joint with John Cleveland, Baoling Ma and Paul Salceanu.

4.2 Modelling of Biogas Production from Glycerol by Anaerobic Process in a Baffled Multi-Stage Digestor

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The anaerobic conversion of glycerol by the bacteria Klebsiella sp. is a well-known process. According to its metabolism glycerol is converted into different products, as 2,3-butanediol, 1,3-propanediol, acetic acid, formic acid, lactic acid and biogas. The latter is produced by two competitive ways: decarboxylation of acetic acid or self-reduction of carbon dioxide by hydrogen, being intermediate products of one of the competitive metabolic routes. It depends on the purpose of the fermentation which of these compounds is desired a final product. In the present work a non-structured mathematical model is developed to describe these competitive processes. The model consists of nine ordinary non-linear differential equations for the kinetics of selected more important reactions from the metabolic pathway. The model takes into account the microbial growth, the pH drop caused by the organic acid formation and the resulting inhibition of the methanogenic microbial activity. The pH-optima of the enzymes are approximated by Gaussian distribution curves. The enzyme sensitivity toward inhibition by pH-variations is presented by the half-width of the Gaussian curve. A large set of experimental data for glycerol anaerobic digestion by Klebsiella sp. in a baffled multistage reactor was used for verification of the model. The comparison of the experimental data with the model results releaved the number of reactor stages, sufficient for complete methanization and to determine the optimum conditions for 2,3-butanediol or methane production.

Acknowledgement. This work was financially supported by Grant DTK-02/36/2009 of the Fund for Scientific research of Republic of Bulgaria.

4.3 An overview on (Mathematical) Plant Growth Modelling and Applications

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Keywords: Plant Growth, Roots Growth, BioMechanics, Mathematical Modeling, Discrete Equation, ODE, PDE, Numerical Simulations

Plants are very complex systems. If agronomic plants, like rice, maize or corn, are essential to provide food or other kind of goods, trees are also essential to preserve the carbon balance, or even to absorb carbon surplus. Despite the great importance of plants, only a small number of modellers, and applied mathematicians are involved in the modelling, the development of mathematical tools, the simulation of plant growth, and, in general, in problems related to Agronomy or Forestry. In fact, the amount of knowledge necessary to understand how a plant is growing is huge and only a multidisciplinary approach can be used to overcome the encountered difficulties. Phenomena are so complex, that even botanist, agronomists and foresters still debate how to handle them efficiently in plant growth models, and, more important, what are the essential ingredients to take into account to obtain a realistic modeling. Indeed, if we know very precisely what is going on in photosynthesis, transpiration processes,..., we didn't yet succeed in the development of macroscopic laws, like in Physics or in Mechanics. Plant growth modelling is not only challenging from the scientific point of view, but is also crucial for real applications, like, for instance, improving crop yields, developing biological tools against Pest attacks, studying the impact of climate change, time evolution of rain forests,.... Thus not only plant growth modeling is challenging but its interactions with the environment too.

Up to now people have used different modeling for plant growth, like empirical models, geometric models, process-based models or functional and structural plant models [7].... AMAP laboratory (Bot**A**ny and co**M**putation**A**l **P**lant architecture) is a place where Botany, Ecophysiology, Plant Architecture, Applied Mathematics, and Computer Science are deeply connected [1]. AMAP has become World leader in

Botany, in Plant Architecture [3], and, based on biological knowledge, has developed several Simulation tools, like AMAPsim [2], see Figure 1 on page 20.

Figure 1: A palm tree and a sunflower powered by AMAPsim

The aim of this lecture is to show the diversity of the problems encountered in the area of plant growth modeling, through an overview on different ongoing studies in AMAP. After a brief recall on some "basic" knowledges' in Botany and in Ecophysiology, I will present different problems related to plant growth, root growth [4], biomechanics [6], ecology, ... using discrete or continuous models. The wide diversity of problems encountered leads to very interesting mathematical problems, that deserve theoretical and numerical investigations.

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

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4.4 Mixed and mixture models for the analysis of clustered and longitudinal data in medicine

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Keywords: joint analysis; repeated measures; random effects; growth mixture models; generalized linear mixed models; competing risks; dropout

Clustered and longitudinal data are very common in biomedical applications, for example when one or more variables are measured on each patient at a number of hospital visits, when several members of the same family are assessed in the same experiment or when a number of questions are asked at a series of interviews. General and generalized linear mixed models (GLM and GLMM respectively) are appropriate for statistical inference in such situations. Herein we consider several extensions of these models to deal with multiple outcome variables of different types, with heterogeneous responses over time and with dropouts in longitudinal studies.

When multiple measures of disease severity are recorded over time, joint analysis of the outcomes variables has advantages over separate analysis such as better control of type I error, improved efficiency of parameter estimates and better understanding of the correlation between the variables. We will define the classical generalized linear mixed models and their extension to combinations of discrete and continuous outcomes in the exponential family. We will also present latent trait models for joint analysis of repeated measurements on ordinal and continuous variables measuring the same underlying disease severity over time. Data from laboratory experiments and depression clinical trials will be used for illustration.

GLMMs allow realistic description of patterns of change over time, use all available data on an individual and allow assessment of the effects of both stationary and time-dependent variables. Traditional modeling assumes that every individual follows the same type of trajectory over time, while growth mixture models (GMM) extensions

allow data-driven identification of distinct classes of developmental trajectories within a population. The latter models also allow characterization of the individuals most likely to belong to each class, assessment of treatment or intervention effects on trajectory membership and simultaneous modeling of trajectories of related behaviors. We will describe GMM-based trajectory approaches, will discuss their advantages and disadvantages, and will use examples from randomized clinical trials in alcohol dependence and depression to illustrate identification of patterns of change over time, selection of number of trajectory classes, assessment of treatment effects and effects of time-dependent covariates, and joint modeling of treatment and compliance trajectories.

Methods for joint estimation of longitudinal data and dropout have received much attention in the statistical literature in recent years. However, all dropout is often treated the same while in reality it can occur for variety of reasons and information on dropout cause is often collected by investigators. Utilizing this information improves inferences and provides better understanding of the association between cause-specific dropout and the outcome process. We will present a model that includes a linear mixed model component for the repeated measures outcome, parametric competing risks models for the cause-specific dropouts and builds in the association between the longitudinal series and the competing risks via shared random effects. Our model easily deals with interval censoring and allows for selection of best-fitting parametric model for each dropout reason. We illustrate the model on data from the large randomized study in schizophrenia and investigate its performance via simulations.

The presentation will conclude with summary of the different types of models, recommendations for their use and discussion of future research directions.

4.5 Mathematical Modeling and Numerical Simulation of Microbial Populations

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In this talk we present several mathematical models of complex biological systems involving microbial populations. We briefly discuss the processes of (1) subsurface biobarrier formation in porous media; (2) bacterial wall attachment in flow reactors; (3) allelopathy in blooms of harmful algae; and (4) immune system response to biomedical implants.

In addition, a new class of one-step compatible finite difference methods is developed to numerically solve the corresponding systems of differential equations. A second-order combination of exact numerical schemes is presented for first-order ordinary differential equations. The numerical technique is based on a nonlocal modeling of the right-hand side function and a nonstandard discretization of the time-derivative. This approach leads to significant qualitative improvements in the behavior of the numerical solution. For multi-dimensional autonomous dynamical systems, positive and elementary-stable nonstandard (PESN) finite difference methods are formulated and analyzed, based on an extension of the nonstandard discretization rules. A series of numerical results are also presented to demonstrate the performance of the proposed new methods.

4.6 Some Mathematical Approaches (Deterministic, Generalized Uncertainty, and Neural Network) in Medical Bio-Mathematical Problems

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An overview is presented of the following problems in medicine for which we obtain solutions using mathematical (including neural network) approaches.

1. The Design of a Radiation Therapy Vault: We use two methods in the design of the enclosure vault containing a linear accelerator for radiation therapy that complies with government standards for maximal radiation exposure to persons outside the vault. The first is a conventional deterministic mathematical programming approach. The second uses new min/max regret on generalized uncertainty entities associated with design information such as cost, material characteristics, availability, and radiation leakage physics. This is a project with the University of Colorado Hospital Department of Radiation Oncology in which the vault was in fact constructed according to the deterministic solution.

2. Radiation Therapy Problems: We show how to use generalized uncertainty approaches that are inherent to the problem of how to kill tumor (cancerous) cells while minimizing damage to surrounding health tissues. This was a project with the University of Colorado University Hospital Department of Radiation Oncology.

3. Lung Disease Detection: We use a particularly excellent approach to input data (called receptive fields but develop a unique receptive field for this problem) to a neural network (a classical probability neural network) which distinguishes between two diseased and

[1] in collaboration with: Francis Newman, Massimo Buscema, Oscar Jenkins, Akbar Esfahani, Linn Wilson

healthy lungs. Preliminary results show excellent promise in classification on the data sets we have.

4. Pediatric Brain: In radiating children who have brain tumors, some children experience loss in IQ. Our novel neural network was able to find structures whose radiation that may arguably be responsible for the loss of IQ. The data set was particularly "noisy" given that the children tend to move quite a bit during their CT scans from which the data was obtained. Thus, the volumetric changes in brain structures were quite "noisy." Nevertheless, the neural network was able to find probable responsible structures. Secondly, we used Support Vector Machines (SVMs) to try and predict which children are likely to lose IQ. This is an ongoing project with the University of Colorado Children's Hospital. Results to date are inconclusive in terms of predictability. However, our approach, we feel, gives some insights into SVMs worth reporting.

5. West Nile Fever and Dengue Fever: Infectious disease dynamics over space and time both forward in time to uncover where it will go next and back in time to uncover the source - the first case, is difficult. We look at novel neural network approaches to look at where the disease originated and where it will go next in space and time by looking at two diseases, West Nile Fever in the area north of Denver, Colorado and the Dengue outbreak in Northwest part of the state So Paulo, Brazil. Both are mosquito borne diseases.

These problems and methods will be discussed in greater detail in the follow-up School for Young Scientis.

4.7 FEM Supercomputing Simulations in Biomedical Applications

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Keywords: finite element method, supercomputing, bone microstructure, hepatic tumor ablation

Computing has become a third branch of research, joining the traditional theorization and laboratory experimentation and verification. The three practices have formed a symbiotic relationship that is now known as computational science. Large-scale scientific computing is one of the most rapidly developing part of computational science, and the advanced finite element methods (FEM) and algorithms are among the most important tools for high-tech simulations. Two biomedical applications will be presented.

μ-FEM analysis of bone microstructures will be discussed first. The geometry of the solid phase is obtained by a computer tomography image at a micron scale. The performed numerical up-scaling is based on a bone specimen modeled as a composite linear elastic material of solid and "fluid" phases. The structure of the trabecular bone tissues is strongly heterogeneous with different levels of osteoporosis. The second problem concerns FEM simulation of thermal and electrical processes, involved in the radio-frequency hepatic tumor ablation. This is a low invasive technique utilizing AC current to destroy the tumor cells by heating. The procedure does not require open surgery. Highly scalable parallel FEM algorithms are developed and implemented in both cases. The presented numerical tests are run on the IBM Blue Gene/P supercomputer at NSCA - Sofia.

Some concluding remarks about recent developments of supercomputer infrastructures and supercomputing applications will be given at the end.

4.8 Cell Proliferation Kinetics: Stochastic Models and Estimation Theory

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Keywords: cell proliferation kinetics, branching stochastic processes, immigration of stem cells, discrete and continuous labels, age and residual life-time distributions, large number of ancestors, asymptotic normality, statistical inference and estimation theory.

The main purpose of this work is to present some new ideas and results obtained in modeling of cell proliferation kinetics (and based on [1-13]). The following topics are considered: some characteristics of cell cycle temporal organization, distributions of discrete and continuous labels, age and residual lifetime distributions, models of leukemia cell kinetics, age-dependent branching populations with randomly chosen paths of evolution as models of progenitor cell populations (*in vitro)* and estimating of offspring distributions, multitype branching populations with a large number of ancestors and asymptotic likelihood estimation of the basic mitotic parameters. A part of the presented results is not published yet.

This is a memorial survey paper on some joint works with Andrei Yu. Yakovlev[†] in cell proliferation kinetics developing some stochastic models in the field of branching processes and their applications. The theory of branching processes has a long history of biological applications. It is worth to point out that the first asymptotic result for branching processes was obtained by Kolmogorov (1938) considering some biological problems. Recall that the terminology "branching processes" was first introduced by Kolmogorov (1947) proposing multitype branching processes, which received much attention in biological applications.

Some basic models and characteristics of cell proliferation kinetics using branching processes are considered in [1], [2] and [5]. An important problem is the distribution of the discrete marks (labels) given in [3-5] and using models with infinite many types of Bellman-Harris branching processes. Generalizations in the case of continuous

labels are presented in [7] and [9]. This work is concerned with an age-dependent branching process with cells bearing a label, the latter being treated as a continuous parameter. The proposed stochastic model is motivated by applications in cell biology. It is assumed that the mitotic division results in a random distribution of the label among daughter cells in accordance with some bivariate probability distribution. In the event of cell death the label borne by that cell disappears. The main focus is on the label distribution as a function of the time elapsed from the moment of label administration. Explicit expressions for this distribution are derived in some particular cases which are of practical interest in the analysis of cell cycle. The Markov branching process with the same evolution of a continuously distributed label is considered as well. Note that processes with continuous labels are first considered by Kolmogorov (1941).

New models of renewing cell populations (*in vivo*) using age-dependent branching processes with non-homogeneous Poisson immigration are proposed in [7] and [10], where is considered an interesting and important problem arising from cell proliferation kinetics: definition and limiting behaviour of age and residual lifetime distributions for branching processes. Leukemia cell kinetics with a stem cell immigration component is studied in [6]. Multitype age-dependent branching processes with randomly chosen paths of evolution are proposed in [11] as models of progenitor cell populations (in vitro) with estimating of the offspring distributions using real data as well as bootstrap methods.

The relative frequencies of distinct types of cells in multitype branching processes with a large number of ancestors are investigated in [12] and [13]. The reported limiting results are of advantage in cell kinetics studies where the relative frequencies but not the absolute cell counts are accessible to measurement. In [12] some relevant statistical applications are discussed in the context of asymptotic maximum likelihood inference for multitype branching processes. In [13] the asymptotic behavior of multitype Markov branching processes with discrete or continuous time is investigated in the positive regular and nonsingular case when both the initial number of ancestors and the time tend to infinity. Some limiting distributions are obtained as well as multivariate asymptotic normality is proved. The results from [12] and [13] have a specific applications in cell proliferation kinetics.

Finally it is worth to point out that the new problems in the theory of branching processes appeared as a result of cell proliferation modeling and the paper is focused on some of these new ideas.

The presented talk does not require any preliminary knowledge in the field of Biology and Mathematics.

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5 Conference Sessions and Presenters

Molecular Modelling

Image Processing in Medicine

Bacterial Growth and Biochemical Processes

Ecosystems and Population Models

Biological Fluids and Membranes

Posters and Computer Demonstrations

6 CONTRIBUTED TALKS

Theoretical Studies of Some Bioreactor Models

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It has been mentioned in literature that Jacob-Monod type models describe adequately bio-processes under certain favorable conditions, when microorganisms actively produce specific enzymes for the degradation and consumption of nutrient substrates and grow at the maximum possible rate. However, conditions in bio-reactors sometimes become unfavorable, microbial growth may be inhibited and bio-technological processes may go out of control. In this work we study under what conditions Jacob-Monod type models do not adequately describe microbial growth, To this end we analyze theoretically several familiar bioreactor models with respect to properties of their solutions under general assumption on the parameters of the models. In particular we study properties of the solutions of some models of a batch mode bioreactor:

$$\begin{aligned} s'_t &= -\alpha\ \mu(s)\ x \\ x'_t &= \mu(s)\ x - k_d x \end{aligned}$$

with initial conditions: $s(0) = s_0 > 0,\ x(0) = x_0 > 0$, where $\alpha > 0$ and $k_d \geq 0$. The function $\mu(s) \geq 0$ is defined for $s \geq 0$ and may take various forms by different authors. We concentrate on the case when $\mu(s)$ is the Monod, Haldane or Andrew's function. It is also shown that in case of approximate values for the different coefficients of these models, stochastic arithmetic is an easy tool to estimate the accuracy of the computed solution.

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Image Reconstruction in Acoustic Reflectivity Tomography

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Keywords: Radon transform, ultrasound, tomography, imaging.

Acoustic reflectivity tomography is a medical imaging modality, which uses an emitter and a receiver of ultrasound waves to collect their reflections from inclusions inside the body. Under certain assumptions, the problem of recovering the reflectivity function in the body from measured echoes corresponds to the problem of inverting a generalized Radon transform [1,2].

In various applications the support of the image function lies outside of the data acquisition set, which is usually a closed curve in 2D or a closed surface in 3D. The problem of image reconstruction in this setup is highly unstable, yet necessary and important (e.g. in intravascular ultrasound). Although one can not expect stable reconstruction of the whole image, microlocal considerations show that certain image singularities can be reconstructed correctly. There are some uniqueness results and exact inversion formulas for a few restricted cases of this exterior problem, however no robust inversion algorithm has been developed so far to recover the "visible" singularities. The talk will discuss the known results and recent advances in this direction.

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Purposeful Model Parameters Genesis in Simple Genetic Algorithms

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Keywords: genetic algorithms, purposeful genesis, model parameters, fermentation process, Saccharomyces cerevisiae

Simple genetic algorithms have been investigated aiming to improve the algorithm convergence time. Because of the stochastic nature of genetic algorithms, several runs have to be performed in order representative results to be achieved. A procedure for purposeful genesis concerning intervals of variations of model parameters is proposed for a standard simple genetic algorithm aiming to improve significantly the algorithm effectiveness. Such stepwise methodology is applied to a parameter identification of a fed-batch cultivation of *S. cerevisiae*. The procedure is further validated to a modified simple genetic algorithm with changed sequence of main genetic algorithm operators, namely mutation, crossover and selection proven as faster than the standard one. Results obtained from both applications show significantly improvement of algorithm convergence time saving the model accuracy.

Sterile Insect Technology for Control of *Anopheles* Mosquito: A Mathematical Feasibility Study

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Keywords: sterile insect technology, compartmental modeling, mosquito control

Anopheles mosquito is a vector responsible for the transmission of diseases like Malaria which affect many people. Hence its control is a major prevention strategy. Sterile Insect Technology (SIT) is a non-polluting method of insect control that relies on the release of sterile males. Mating of the released sterile males with wild females leads to non hatching eggs. Thus, if sterile males are released in sufficient numbers or over a sufficient period of time, it can leads to the local reduction or elimination of the wild population. We study the effectiveness of the application of SIT for control of *Anopheles* mosquito via mathematical modeling. Our main result is that there exists a threshold release rate $\hat{\lambda}$ depending only on the basic offspring number R and the wild mosquito equilibrium for males such that a release rate higher than $\hat{\lambda}$ results in elimination of the mosquito population irrespective of its initial size. A release rate λ which is lower than $\hat{\lambda}$ eliminates the mosquito populations only if it is sufficiently small. If the population is at the wild equilibrium it is reduced by a percentage depending on λ and R only.

Methods in Hemorheology

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A great variety of instruments and methods to study hemorheological parameters under conditions close to physiological are currently used. More of these methods allow determining the average characteristics, measuring erythrocyte deformability and their ability to change their shape under force acting on the cell as a whole. Atomic force microscopy (AFM) permits to investigate living cells and cellular structures per high-resolution visualization and to assess local mechanical properties (elasticity, rigidity index and surface topography of the membrane). Nanoindentors assess deformation and Young modulus of RBCs, measured from nanometers to millimeters. Different biochips and pumps are developed to study cell rolling, adhesion and migration which mimic in vivo vascular flow. A new method, based on dielectric properties of dispersed systems in Couette viscometric blood flow, applied to investigate the kinetics of RBC aggregation and the break-up of the aggregates has been introduced. The experimental relationships between the blood conductivity, apparent blood viscosity, shear rates and time at rectangular changes of shear rates from 94,5 s-1 to 0,945 s-1 at T=37 0C show that the human blood conductivity is time and shear rate dependent under transient flow. It is established that the blood conductivity is dependent on the regime and time of the applied shear rates in the Couette viscometric flow. The results show that valuable information could be received about the mechanical properties of blood, in particular about the kinetics of "rouleaux formation" and that this technique may be used to clarify the mechanism of dynamics of RBC aggregates. Thus a method, based on dielectric properties of dispersed systems in Couette viscometric blood flow could be applied to investigate the kinetics of RBC aggregation and the break-up of the aggregates. The best fit functions of blood conductivity during aggregation - disaggregation process are provided. Their parameters have been determined from the experimental data and can be used to characterise the transient organization of RBCs.

A Mathematical Model for Wound Healing and Dorsal Closure

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Keywords: Forces in embryogenesis; Biomechanics; PDE models.

In many species adult wound healing generates a mass of fibrotic tissue which is not only aesthetically undesirable but has also serious clinical consequences. A good understanding of regenerative healing mechanisms is an important public health issue. Dorsal Closure in Drosophila embryos (the common fruit fly) consists of the migration of cells to recover a hole in the dorsal epidermis. It has been extensively studied since numerous physical mechanisms and signaling pathways are conserved in other morphogenetic events and species. We present a simple mathematical model for dorsal closure and wound healing [1] that involves a reduced number of parameters directly linked to the intensity of the forces involved. The variations of the parameters will give phenotypical indications as to what contributions are being affected in the different genetically perturbed settings. Our approach is a natural generalization of the one proposed in [2] that allows us to go beyond strong symmetry assumptions. We validated our model in native and mutant setting. After this first model, based on tissue mechanics of elastic nature, we are now evolving towards more realistic viscoelastic models.

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Bayesian networks for breast cancer prognosis and prediction of metastasis risk

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Keywords: Bayesian network, Implicit estimation, Modeling, breast cancer.

In this work we use Bayesian networks to develop a decision support system that is based on the modeling of relationships between key signalling proteins and clinical and pathological characteristics of breast tumors and patients. Motivated by the lack of prior information on the parameters of the problem, we use the Implicit inference for the structure and parameter learning ([1], [2]). A database of 84 Tunisian breast cancer patients was used and new prognosis factors were identified. The system predicts a metastasis risk for different patients by computing a score that is the joint probability of the Bayesian Network using parameters estimated on the learning database.

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Computer Modelling of Haematopoietic Stem Cells Migration

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Keywords: Haematopoietic stem cells, chemotaxis, finite volume method

The high migratory activity and the ability of haematopoietic stem cells (HSCs) to home to their niche in the bone marrow play a key role in the therapy of various pathological blood diseases. It has been shown that one of the factors that influence *in vitro* and *in vivo* the human HSCs migration is the so called SDF-1, produced by stroma cells in the bone marrow stem cell niches. Taking this into account, the chemotactic movement of HSCs is modelled by a nonlinear system of chemotaxis equations coupled with an ordinary differential equation on the boundary of the domain in the presence of nonhomogeneous boundary conditions. Various classical numerical methods applied directly to a general chemotaxis system and in particular to HSCs migration model may lead to numerical instabilities and loss of the positivity property of the solution. A finite-volume method, based on a second-order positivity preserving central-upwind scheme is proposed by A. Chertock and A. Kurganov in 2008 for a class of chemotaxis and haptotaxis models with homogeneous Neumann conditions. Their approach with appropriate modifications is applied in the current work for space discretization of the HSCs migration model. A strong stability preserving method (e.g. Runge-Kutta or a multistep one) for ODEs is applied for time integration of the resulting semi-discrete problem. The stability, consistency, convergence and positivity properties of the modified scheme are theoretically and experimentally analyzed with the help of numerical tests with C/C++ implementation of the solvers for the obtained nonsymmetric algebraic systems.

Modelling a tunable magnetic bead trap for capturing circulating tumor cells in the lattice–Boltzmann blood flow

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Keywords: Fluid dynamics, lattice–Boltzmann method, blood flow.

We propose to use tunable structures of magnetic beads (MB) to isolate circulating tumor cells (CTC) in a microchip. Blood flows past the structures functionalized with antibodies that capture CTC. We aim at creating a simulation tool to design and optimization of the microchips. Blood is composed of a viscous fluid (plasma), elastic red blood cells (RBC) and rigid MB. The fluid is modelled by the lattice-Boltzmann method on a fixed Eulerian grid. This method is explicit and guarantees fast computations. Its local character ensures an efficient parallel implementation. The model of RBC includes volume and surface conservation, and stretching and bending of the surface [1]. Movement of magnetic beads is described by rigid body motion including the magnetic interactions between the beads driven by the external fields. RBC and MB are described by discretization of their boundaries. Discretization points lie on a flexible Lagrangian grid that is free to move. The coupling between Eulerian and Lagrangian grid is done using immersed boundary method. Forces and velocities are transferred from the fluid to boundary points, and vice versa, by suitable delta approximation. We use ESPResSo [2] as a basis for the development of our simulation tool.

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Stability Analysis of a Bioreactor Model for Biodegradation of Xenobiotics

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Keywords: nonlinear model, equilibrium points, bifurcation analysis

We consider the following model describing 1,2-dichloroethane biodegradation by *Klebsiella oxytoca VA 8391* strain immobilized on granulated activated carbon [2]

$$\begin{aligned}
\dot{x}_1 &= (\mu_1(s) - D)x_1 + k_{im}x_{im} \\
\dot{x}_{im} &= (\mu_{im}(s) - k_{im})\, x_{im} \\
\dot{s} &= -\left(\frac{1}{\gamma}\mu_1(s) + \beta_1\right) x_1 - \left(\frac{1}{\gamma}\mu_{im}(s) + \beta_{im}\right) x_{im} \\
&\quad + D(s^{in} - s) - k_L a(1 - \mu_2(s))s \\
\dot{p} &= \left(\frac{1}{\gamma}\mu_1(s) + \beta_1\right) x_1 + \left(\frac{1}{\gamma}\mu_{im}(s) + \beta_{im}\right) x_{im} - Dp,
\end{aligned}$$

where the growth rate functions $\mu_1(s)$ and $\mu_{im}(s)$ are presented by the Andrews (Haldane) law. We compute the equilibrium points of the model and investigate their stability and bifurcations with respect to the parameters D and k_{im}. Thereby we use an extension of the *Maple* package BifTools [1].

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Deformation of Injected Cells Adhered to Flat Substrates

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Keywords: Cell, Vesicle, Adhesion, Microinjection

Here we address the problem of determination of the shape of a cell adhered to a flat substrate during the process of microinjection. For that purpose it is assumed that the cell is a closed lipid bilayer (vesicle) which can be treated within Helfrich spontaneous curvature model. Additionally, it is assumed that the part of the vesicle adhered to the substrate is a circle and that the injection pipette is normal to the substrate and directed to the center of the contact circle. In this setting the differential equations and the boundary conditions providing the extremum of the vesicle bending energy are derived and solved numerically. The effect of the spontaneous curvature and the size of the vesicle on its equilibrium shape is analyzed.

On the number of births and deaths during an extinction cycle, and the survival of a certain individual in a two-species competition process

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Keywords: bivariate birth and death process; Markov chain

Competition processes, as discussed in [1,2], have been frequently used in biology to describe the dynamics of population models involving some kind of interaction among various species. Our interest is in the stochastic model of a two-species competition process analyzed by Ridler-Rowe [3]. In this talk, we focus on the number of births and deaths during an extinction cycle. Specifically, we discuss an approximation method inspired from the use of the maximum size distribution, which is equally applicable to the survival of a certain individual. In order to study the survival probability, we propose three models depending on the way individuals are selected to die. Our results are illustrated with reference to simulated data.

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A Multi-Layered Hidden Markov Model with Entropy Gradient

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

An extension of the classical hidden Markov model (HMM) for sequential data probabilistic modeling is presented. A multi-layer structure is derived from the double-chain Markov model in [1]. The proposed recursive procedure assumes the hidden state chain of a given (outer) layer as the observation sequence of the next (inner) layer. The three canonical problems of HMM are formulated according to the extension and their solutions are proposed. Special attention is paid to the third problem - model parameters estimation or learning. The idea to gradually increase/decrease the Markov chain entropy across consecutive layers is introduced and embedded into parameters estimation. Analysis of entropy gradient reveals deeply hidden properties of the sequential data source - either completely i.i.d. stochastic or entirely deterministic nature of the most inner layers. Further investigation is directed towards maneuvering with model order. The multi-layered HMM is experimentally tested on synthetic sequential data, various types of coding DNA and finally - on various types of non-coding DNA.

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PRACE Project and High Performance Computing for Bioscience Applications

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PRACE, the Partnership for Advanced Computing in Europe, is creating a persistent pan-European High Performance Computing (HPC) Research Infrastructure (RI) and related services. Four nations (France, Germany, Italy and Spain) have agreed to provide 400 million Euro to implement supercomputers with a combined computing power in the multi Petaflop/s range over the next five years. This funding is complemented by up to 70 million Euros from the European Commission which is supporting the preparation and implementation of this infrastructure. These leadership class systems will help European scientists and engineers to remain internationally competitive.

PRACE will maintain a pan-European HPC service consisting of up to six top of the line leadership systems (Tier-0) well integrated into the European HPC ecosystem. Each system will provide computing power of several Petaflop/s (one quadrillion operations per second) in midterm. On the longer term (2019) Exaflop/s (one quintillion) computing power will be targeted by PRACE. Users will be supported by experts in porting, scaling, and optimizing applications to novel, highly parallel computer architectures. An in-depth training program accompanies the PRACE offering teaching scientists and students how to best exploit the unprecedented capabilities of the systems. A scientific steering committee will provide advice to PRACE and operate alongside a bespoke peer review process through which access to the Tier-0 resources will be granted based on scientific excellence.

At present, PRACE members are: Austria (JKU), Bulgaria (NCSA), Cyprus (CaSToRC), Czech Republic (VB), Finland (CSC), France (GENCI), Germany (GCS), Greece (GRNET), Ireland (ICHEC), Italy (CINECA), The Netherlands (NCF), Norway (SIGMA - UNINETT Sigma AS), Poland (PSNC), Portugal (FCTUC), Serbia (IPB), Spain (BSC), Sweden (SNIC), Switzerland (ETH Zurich, CSCS), Turkey (UYBHM), UK (EPSRC).

Maximum number of individuals alive during an extinction cycle in a two-species competition process

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Keywords: Competition process; extinction time; quasi-stationary regime

Our interest is in a two-species competition process, which is closed in the sense that no immigration or emigration is supposed to take place, and transitions in the process are only allowed to neighboring states. Based on percentiles of the maximum number of individuals in the ecosystem, we present an approximating model for which the extinction time can be thought of as a phase-type random variable. We determine formulae for the probabilities of extinction and the moments of the extinction time. Numerical results are presented to illustrate the effects of the birth and death rates on the expected extinction times and the extinction probabilities, depending on various quasi-stationary distributions for initial population sizes. We carry out numerical experiments to compare the asymptotic results of Ridler-Rowe [2], results obtained by simulation, and our approach [1].

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Iterative operator splitting method for capillary formation model in tumor angiogenesis problem: Analysis and Application

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Keywords: Iterative operator splitting method, capillary formation, tumor angiogenesis, stability and consistency analysis.

Iterative operator splitting method is used to solve numerically the mathematical model for capillary formation in tumor angiogenesis problem. The method is based on first splitting the complex problem into simpler sub-problems. Then each sub-equation is combined with iterative schemes. The algorithms are obtained by applying the proposed method to the given model problem. The explicit local error bounds are derived to show consistency. Also, we explained the stability by constructing the stability functions. The obtained numerical results show that iterative splitting method provides high accuracy and efficiency with respect to other classical methods in literature.

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Optimization of a Whey Bioprocess using Neuro-dynamic Programming Strategy

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Keywords: Neuro-dynamic Programming, Whey Bioprocess, Optimization, gain-to-go function

In this paper a method for finding the optimal feeding profile for a whey fermentation by strain *Kluyveromyces lactic MC 5* in a fed-batch bioreactor has been developed. The optimal profile maximizes the process effectiveness and minimizes the bioprocess duration. The method is based on Neuro Dynamic Programming (NDP), wherein the optimal control decision is parameterised in the form of a cost-to-go or gain-to-go functions. The suggested method employs simulations from a heuristic feeding strategy as an initial point to generate the gain-to-go to experimental data. A neural network is applied to obtain gain-to-go as a function of system state. Iterations of Bellman equation are included to improve the gain function. Thus, the obtained approach guarantees optimal control of the bioreactor when disturbances are present. The developed approach is compared with other methods - the Pontryagin's Maximum Principle and with Fuzzy Sets Theory. The NDP method provides better results than the other methods.

Stability of some stochastic model of gene expression involving a stochastic delay differential equation driven by a Lévy process

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We study (see [2]) some stochastic delay differential equation of the form

$$dX(t) = \left(\int_{[-\tau,0]} X(t+s)\mu(ds) \right) dt + F(X)(t-)dL(t), \qquad (1)$$

where the driving process L is a certain Lévy process and μ is a signed measure. We prove that some natural conditions are sufficient to establish the existence and uniquness of the solution of (1) for every appropriately chosen initial condition. Next we show that the segment process corresponding to the solution of (1) constitutes a semigroup with an eventually Feller property. We prove that the semigroup has a unique probability measure, which is attractive. We also discuss the rate of convergence to an invariant measure.

Our results seems to be significant for the development of understanding of stochastic behaviour of some biological systems that are too compex to be modelled determinictically. For example, we shall show the application of our results to a model of gene expression inspired by a model considered in [1].

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Data Extraction Module - A Supplementary Tool for *AMMOS_ProtLig* Software Package

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Keywords: virtual ligand screening, post-docking optimization, AMMOS_ProtLig, data extraction

Data Extraction Module is developed as a supplementary tool to help in using the results of the software package *AMMOS_ProtLig* (Automated Molecular Mechanics Optimization tool for *in silico* Screening of protein-ligand interactions). The tool is an open-source graphical application that automatically processes the output files after post-docking optimization with *AMMOS_ProtLig*. *Data Extraction Module* extracts the ligand and the protein data files for a specific protein-ligand complex depending on the user preferences thus facilitating the further analysis of the results after
AMMOS_ProtLig application. The tool has been tested for several protein-ligand complexes of different physicochemical properties and topology. *Data Extraction Module* speeds up the process of data extraction from the *AMMOS_ProtLig* output files and considerably reduces the user involvement in this process.

A biomathematical model for Phoma tracheiphila Citrus resistance screening

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Keywords: Fungi, Citrus, Biomathematics, Modelling.

The causal agent of Mal Secco, P.tracheiphila, is responsible of many important losses in the Citrus crop worldwide [1]. The resistance enhancement of Citrus susceptibles to the pathogen infection depend on the availability of a valid test for the disease assessment. However, the resistance analysis tests used give controversial results [1,2]. In this paper, we propose a new mathematical model to conduct a rapid and efficient resistance screening test. This model have the advantage to give a strict evaluation of the resistance and not a relative estimation as its in the usually tests. The Results obtained by this model are in concordance with those observed in the orchards.

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A criterion for selection of hernia meshes according to their viscoelastic properties

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Keywords: hernia meshes,viscoelastic properties,mechanical compatibility.

Synthetic hernia meshes are widely used in the abdominal hernia surgery. The success of the surgical operation depends in a great extent on mechanical behavior of used hernia meshes. A method for proper choice of hernia meshes based on their elastic mechanical behavior has already been published [1]. The aim of this study was to suggest the criterion for selection of hernia mesh within physiological range of deformation, according to viscoelastic properties of used biomaterial (Surgimesh (SM), Tecnomesh (TM)) and substituted soft tissue- human abdominal fascia. The proposed criterion for selection of a hernia mesh was based on the values of an objective function defined as the sum of mean square distance of stress reduction or ratio of elastic and equilibrium moduli obtained for abdominal fascia and hernia meshes after relaxation experiments. It was accepted that optimal synthetic hernia mesh is one, which mechanical parameters minimize the objective function. When the criterion was applied a good similarity between the stress reduction of the fascia and the meshes was obtained. The mean square error was between $2.5\ \% - 10.5\ \%$ .In case of ratio matching the discrepancy between results was higher, with the mean square error up to 22.58 %. The proposed method can be used to specify the type of the hernia mesh which viscoelastic properties are close to those of the human abdominal fascia.

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A Common Approach to Finding the Optimal Scenarios of a Markov Stochastic Process over a Phylogenetic Tree

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Keywords: phylogenetic tree, maximum parsimony, maximum likelihood, Markov stochastic process

Inferring phylogenetic trees is a general approach in the reconstruction of the evolutionary histories of organisms. In order to estimate the events over a phylogenetic tree, several criterions and algorithms are used. In the present work, a common approach, together with an effective algorithm is proposed. The approach aims to unify the applying of the Maximum Parsimony and Maximum Likelihood criteria over a phylogenetic tree with various branch lengths. The events over a branch of the phylogenetic tree are described by a Markov stochastic process. Explicit formulae for the simplest case are given. Maximum Likelihood is reformulated from the point of view of Information Theory as Minimum Surprisal.

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Model-Based Biological Control of the Chemostat

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Keywords: population dynamics, chemostat model, competitive exclusion principle, biological control

The competitive exclusion principle (CEP) is a well known concept in microbial ecology. CEP means that when two or more microbial species grow on a single resource in a chemostat, at most one species eventually survives – this is the species that possesses the best affinity to the substrate [2]. We consider the following model with two populations x_1 and x_2 competing on a single substrate s with growth rate functions $\mu_1(s)$ and $\mu_2(s)$:

$$\begin{aligned} \dot{s} &= (s^0 - s)D - \mu_1(s)x_1 - \mu_2(s)x_2 \\ \dot{x}_1 &= (\mu_1(s) - D_1)x_1 \\ \dot{x}_2 &= (\mu_2(s) - D_2)x_2 \\ & s(0) \geq 0, \;\; x_i(0) > 0, \; i = 1, 2. \end{aligned}$$

The main objective is to present sufficient conditions for global stability of the equilibrium points of the model. The results obtained are generalizations of the recently developed concept of biological control of the chemostat [1].

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Metadynamics study of mutated human interferon gamma forms

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Keywords: Human Interferon Gamma, Molecular Dynamics Simulations, Metadynamics Simulations

Human interferon gamma (hIFN-γ) is an important antiviral and immunomodulating signaling molecule. In search for a mechanism for suppressing its biological activity, the possibility of finding a mutated form of the protein was investigated, which is able to bind to hIFN-γ cellular receptors but does not trigger biological response in the cell. The mutations should not induce significant conformational changes in the local structure of the mutated amino acids. Therefore we performed molecular dynamics simulations to study the effects of 100 different random mutations with substituted amino acids $Lys^{86}LysLys^{88}$ on the secondary structure of hIFN-γ. The stability of the local structure of all hIFN-γ forms was investigated by means of metadynamics. It was found that some of the mutated forms preserve the local secondary structure and show similar or higher stability of the mutated helix, compared to the native form. Among them, 12 were suggested for experimental investigation.

Nonstandard Finite Difference Schemes for Michaelis-Menten Differential Models

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The Michaelis-Menten (M-M) enzyme kinetics ordinary differential equation arises in many areas of biosciences such as biochemistry, pharmacology, etc. The corresponding nonlinear term is often used as a functional response in ecological and epidemiological models. The M-M differential equation is simple. However, its solutions cannot be found explicitly. Thus, there has been a surge in the construction of numerical methods that can provide reliable information on the essential features of this differential model. In particular, several researchers have designed Nonstandard Finite Difference (NSFD) schemes, which are dynamically consistent with the positivity of the solutions and their monotonic convergence to the zero equilibrium point. In this work, we show that the exact solutions of the equation can be expressed in a compact form in terms of the so-called Lambert W function or Omega function. This representation enables us to design exact schemes for the model. We compare and investigate the performance of the exact schemes with NSFD schemes obtained by using Mickens' classical rules. We study the impact of the exact schemes on the design of NSFD schemes for the SIR and SIS models in epidemiology as well as for the advection reaction equation. Numerical simultations that support the theory, including the stability properties of the two epidemiological models, and demonstrate computationally the power of NSFD schemes, are presented.

To the memory of Dr. R. Tsanev

On the mathematical modelling of microbial growth[2]

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Keywords: microbial growth, bioreactors, enzyme kinetics

It has been recognized [1], [2], that classical models describe adequately bio-processes under certain favorable conditions, when microorganisms actively produce specific enzymes for the degradation and consumption of nutrient substrates and grow at the maximum possible rate. However, conditions in bio-reactors sometimes become unfavorable, microbial growth may be inhibited and bio-technological processes may go out of control.

A new approach to the mathematical modelling of microbial growth is proposed. Our approach differs from familiar models by considering two phases in the physiological states of the microorganisms and makes use of basic relations from enzyme kinetic. Such an approach may be useful in the modelling and control of biotechnological processes, where microorganisms are used for various biodegradation purposes and are often under extreme inhibitory conditions.

We formulate two particular models involving microbial phases. Computational experiments are performed in support to our modelling approach.

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Defect detection in the wall of complaint blood vessel

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Keywords: blood flow model, inverse problem, detection

We aim to employ a well-known one dimensional model of the blood flow in an compliant vessel [1] to detect pathological changes in the vessel wall. The model describes the blood flow using certain average quantities along the axial direction of the vessel. Consequently we detect the defects as the corresponding averages as well.

The defects such as stenosis and calcification are considered, which should be detected solely on the basis of Doppler ultrasound measurements. This would allow for an inexpensive diagnosis of the vessel wall degradation.

We analyze the identifiability and the sensitivity of the detection in different cases.

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Membrane growth induces neuronal bipolarity

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Keywords: Neuronal polarity, reaction-diffusion systems, Turing instability.

The generation and maintenance of asymmetric changes in cellular organization, (polarity), are very important for many complex biological activities. Neurons are among the cell types with the most prominent asymmetry. Neuronal polarization starts with the selection of the site from which the first neurite will grow before morphological changes are evident. It happens shortly after cell division and it is followed by the growth of a second neurite at the opposite pole. The site from which the first neurite emerges is defined by the localized accumulation or activation of molecules with the capacity to directly or indirectly induce a local deformation in the plasma membrane. However, it is not known if a direct relationship exists between the formation of the second, opposite, neurite and the mechanisms involved in the formation of the first. We tackled this issue through mathematical modeling, based on membrane traffic (exocytosis-endocytosis), and lateral diffusion. Our model assumes an activator-inhibitor dynamics and diffusion-driven instabilities. We study spontaneous symmetry breaking and how polarity domains are affected by membrane growth. With this approach, we demonstrated that a single pole of molecular asymmetry is sufficient to induce a second one at the opposite side, upon induction of growth from the first pole.

Preferences and Determination of the Nominal Growth Rate of Fed-Batch Process: Control Design of Complex Processes

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Keywords: Preferences, Expected utility, stochastic approximation, complex process, optimal control, Monod kinetic, Monod-Wang model

The complexity of the biotechnological cultivation processes makes difficult the determination of the optimal process parameters. The incomplete information usually is compensated with the participation of imprecise human estimations. The specific growth rate of the fed-batch processes determines the nominal technological conditions. Here is proposed a mathematical approach for elimination of the uncertainty in the DM preferences and for precise evaluation of the optimal specific growth rate of a fed-batch process. The dialogue between the technologist and the computer is a stochastic machine learning procedures. Expected utility theory is one of the approaches for assessment and utilization of qualitative conceptual information. An example of evaluation of utility and complex control preferences based design is demonstrated. The control design includes the stochastic control conditions.

Modeling water-gas flows in artificial soils with plants by invasion percolation model

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Keywords: porous media, soils with plants, invasion percolation model.

Cultivation of plants in artificial soils in space greenhouses is a complex biological and physical problem. Due to the reduced gravity in space, the water together with the dissolved in it mineral salts is supplied to the plants roots mainly under the action of the capillary pressure. The artificial soils used for the space greenhouses are granular materials which when packed represent porous media. The random character of water invasion in porous media has encouraged the idea to use Monte Carlo methods to describe this process. Regular lattices are often used to represent porous media in the percolation theory approach. In this theory the invasion percolation (IP) model [1] is the one that introduces dynamics describing the displacement of water by gas in porous medium. Following the same approach we have modified [2] the IP model by introducing special extraction sites on the lattice with given concentration which model effectively the presence of plants roots in artificial soils. These sites, when invaded by the water, can block with certain probability, called extraction probability, the further spreading of the water in the network. Through Monte Carlo simulations we study how the presence of the extraction sites modifies the amount of the residual air (or, respectively, the amount of the water) on the lattice and its distribution.

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Assessment of the influence of Ca^{2+} and pH on bacterial growth of *Acidithiobacillus ferrooxidans*

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Keywords: suspended cells, cultivation regime

Studying the biofilm system for last decade is with high importance for ecologically friendly biotechnologies. The capability of *Acidithiobacillus ferrooxidans* to oxidize ferrous ions is successfully used for treatment of gas and water pollution and in biometallurgy. That bacteria forms solid bofilms, which are included in waste water and tail gas treatment and bioleaching technologies. As the experiments show it forms jarosite - extracellular solid substance which helps for biofilm formation and forms sediments in cultures from suspended biomass. In previous work the oxidation capacity of the bacteria has been assessed only on the base of the average velocity of ferric ion production without investigation of biomass growth process. Basing on some mathematical models which describe the initial processes of biofilm formation and functioning, the significance of the specific cells growth was shown. It is important to know more about the cultivation regimes of the suspended cells of the strain for later biofilm cultivation. This work is a part from studies on influence of different regimes of cultivation on bacterial physiology. Three series of experiments are elaborated for studying the influence of different pH and Ca concentrations on cells growth of the strain. The results were statistically assessed. The experimental data show some significant differences in studied parameters, measured in different cultural media in the beginning and last phases of cultural growth.

Rough Sets in Biometrics and Biomedical Informatics

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Keywords: granular computing,computer graphics

The intent of this paper is to face the essentials of granular computing and in its major component – the rough sets theory, intoduced by Pawlak, since any rough set represents an information granule.As a part of modern soft computing paradigm, rough sets have been introduced as an interval-like extension of the usual sets with main applications in the intelligent systems. The proposed rough approach provides efficient algorithms for finding hidden patterns in data, finds minimal sets of data (data reduction), evaluates significance of data. Most algorithms based on the rough set theory are particularly suited for parallel processing. Rough set theory expresses vagueness, not by means of membership, but employing a boundary region of a set. If the boundary region of a set is empty it means that the set is crisp, otherwise the set is rough (inexact). In general, in rough sets theory the data can be considered as collected in a decision table. Rows of the table correspond to objects, and columns correspond to features. For example, a set of samples with a class label to indicate the biometric tasks as face detection in images and video is one of the most popular object detection problems. The proposed approach can be applied also for finding skin cancer regions and phylogenetic granules. By the connections with mathematical morphology it can be used in approximate shape modeling such as in augmented reality in computer aided surgery. Also, this theory can answer the problem to what extent a DNA sequence encodes a protein and eventually what is the 3d shape of this protein molecule.

Parameter Optimization of a Bioprocess Model using Tabu Search Algorithm

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Keywords: Methaeuristics, Tabu Search, Parameter Optimization, Cultivation process, E. coli

Real parameter optimization of bioprocess models has become a research field of great interests. Such problems have widespread application. The model building leads to an information deficiency and to non unique parameter identification. This problem is known to be frequently ill-conditioned and multimodal. Thus, gradient-based local optimization methods fail to arrive at satisfactory solutions. While searching for new, more adequate modeling concepts, metaheuristic methods have received the early attention. Popular metaheuristics include SA, GAs, ACO, and Tabu Search (TS). In this paper the problem of parameter optimization is examined using TS algorithm. A case study considering the parameters optimization of a nonlinear dynamic model of an E. coli fed-batch cultivation process is taken as a test problem. A system of five ordinary differential equations is proposed to model biomass growth, glucose utilization, acetate formation, oxygen consumption and volume variation of the regarded cultivation process. Parameter optimization is carried out based on real experimental data set using Tabu Search algorithm. Simulation results reveal that the model predicts accurate the variation of the considered state variables. The obtained results are comparable to the results obtained with other metaheuristics, as GAs and SA. A general comment on this study is that the application of TS algorithm leads to a successful parameter optimization with a main advantage - less computational time, in comparison with other metaheuristics.

Protein-Protein Interaction Prediction by Topological Assignment of Biological Networks

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Keywords: Biological Networks, Functional Modules, Evolutionary Conservation,Network Topolology

Cellular networks can be decomposed into simple and recurrent patterns, which accomplish discrete biological functions in isolation from other modules in the networks [1]. The accessibility to vast amount of biological data of more than 200 organisms has exposed the prevalent modular nature of cellular systems as protein-protein interaction [2]. The conservation of functional modules during the evolution enables to shed new light on the way to understand protein-protein interaction.Here mathematical approach has been used to find topological similarity between these functional modules during evolution for capturing functional conservation. Proposed method may help to predict the conserved functional modules which are responsible for the biological behavior of protein interaction network within different organisms.

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A formula for the oxygen uptake of thin tissue slice in terms of its surface oxygen tension

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Keywords: thin tissue slice, oxygen uptake, diffusion-consumption equation, zero- to first-order kinetics, tissue respiration parameters

An analytical solution to the oxygen diffusion equation with a sink term representing the oxygen consumption rate is obtained for thin tissue slice. The model of the oxygen consumption rate used depends on the oxygen tension and is known as zero- to first-order kinetics model (Michaelis-Menten-like kinetics model). The solution reflecting the conditions in Warburg-type experiments yields a formula for the oxygen uptake of a tissue slice as a function of the oxygen tension at its boundary. This formula is used to estimate the tissue respiration parameters in two cases: slices of skeletal muscle tissue [1] and six albino-rat tissues (kidney, heart, liver, brain, diaphragm, lung) [2].

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Modelling of receptor-toxin-antibody interaction

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Keywords: Receptor, toxin, antibody, receptor-toxin interaction

A model of receptor-toxin-antibody interaction near a cell surface is studied numerically. The diffusion fluxes of species are explicitly taken into account. The protective properties of an antibody against a given toxin are evaluated for a spherical cell placed into a toxin-antibody solution. The selection of parameters for numerical simulation corresponds to the case of ricin competitive binding to cell receptors and the mono-clonal antibody 2B11.

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Age-dependent branching processes for surveillance of vaccine-preventable diseases with incubation period

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Keywords: Age-dependent branching process, time to extinction, vaccination policies, Monte-Carlo method

The purpose of this paper is to review the recent results in the area of infectious disease modelling by means of branching stochastic processes. This is a new approach involving age-dependent branching models, which turned out to be more appropriate and flexible for describing the spread of an infection in a given population, than discrete time ones.

Concretely, Bellman-Harris and Sevastyanovs branching processes are investigated. It is justified that the proposed models are proper candidates as models of infectious diseases with incubation period like measles, mumps, avian flu, etc. It is worth to notice that in general the developed methodology is applicable to the diseases that follow the so-called SIR (susceptible-infected-removed) scheme in terms of epidemiological models. Two policies of extra-vaccination level are proposed and compared on the ground of simulation examples.

Efficient, accurate and flexible Finite Element solvers for Chemotaxis

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Keywords: Chemotaxis, Keller Segel, Finite Element Method, FCT/TVD, fast solver, Multi-Species

Up to the present, many scientists encouraged themselves in modelling complex chemotaxis systems of PDEs by introducing kinetic terms, incorporating certain quorum-sensing or volume-filling mechanisms or even extend the system to multiple species/chemical agents. However most of this research lacks of a very important issue, the implementation of a numerically well elaborated solver. From numerical point of view this is far from being trivial. Even for the minimal model it is numerically challenging to tackle the chemotaxis term. Almost comparable with convection-dominated flows in the CFD world, the main task is to guarantee positivity and mass conservation, which necessitates special stabilization techniques.
We developed a Finite Element based solver for chemotaxis PDEs incorporating various finite elements in 2D and 3D, a variety of boundary conditions, a large selection of iterative sub-solvers, a FCT/TVD stabilization technique and arbitrary user-prescribed model parameters. Its applicability on serveral models, like blowing up solutions and pattern formation, has already verified the reliability of this solver. Moreover integrating already developed paradigms, like parallelization, fast multigrid solvers and r- and h-adaptivity, will extend the application to a level which enables to tackle even fully coupled multi-species systems of chemotaxis.

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A new integer programming model for HP problem

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Keywords: protein folding lattice models, linear programming. HP model

Protein is a biological macromolecule compounded of a sequence of amino acids. The functional properties of a protein is based on its three-dimensional (3D) structure. One of the most popular protein structure prediction method, called hydrophobic-hydrophilic (HP) model is based on the observation,that in a polar environment, peptides hydrophobic amino-acids are in a kernel of the molecule - in contact between them and more polar amino-acids in contact with the polar environment. The fold spaces are integer lattices of various kind.

For this problem, we propose a new integer programming model, whose LP relaxation provides sharp upper bound for the maximum number of contacts and allowing for solving the problem by the usage of conventional tools such as CPLEX solver. The proposed model is easily adaptable to arbitrary search space: square or cubic lattices, face centered cubic lattice, etc. Comparative results for two concrete peptides: orexin and Hypotensive hormone will be presented as well.

Evaluation of the van der Waals and Casimir forces between biological objects

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Keywords: SIA approximation, red blood cells, toroidal proteins.

Within a new approach, presented in [1], which can be considered as a generalization of the Derjaguin approximation and provides exact means to determine the interaction force between a three-dimensional body of any shape and a plane mutually interacting via pairwise potentials, we derive exact expressions for the non-retarded and retarded (Casimir) van der Waals interactions between an object of toroidal shape (*E. coli* protein ybgI, RecR, ring chromosomes, nanorings from amphiphilic molecular dumbbells) and a plane (cellular membrane), as well as between a red blood cell and a plane (artery or vein wall). The results are obtained for the case when the objects are separated from the plane via a non-polar fluid. The red blood cell is modeled on the base of a Cassini oval, and the relations between the parameters of the Cassini oval and those of the cell (minimal and maximal thickness and diameter) are obtained. The corresponding force between the biological object and the plane is also calculated in the case when they interact via a Lennard-Jones potential.

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Generalized Net model of an intuitionistic fuzzy clustering technique

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Keywords: distributed clustering, fuzzy C-Means, generalized net

Due to explosion in the number of autonomous data sources, there is an emergent need for effective approaches to distributed clustering. Intuitionistic Fuzzy Set is a suitable tool to cope with imperfectly defined facts and data, as well as with imprecise knowledge. One of the authors introduced a novel intuitionistic fuzzy based distributed clustering algorithm, to cluster distributed datasets, without necessarily downloading all the data into a single site in two different levels: local level and global level. In this paper, a generalized net model of the algorithm has been presented.

Comparison of two fungal strains biodegradation capacity toward mixture of phenol and cresol by mathematical modeling

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The examined strains of *Aspergillus awamori* NRRL 3112 and *Ttametes versicolor* 1 were cultured in media containing as components phenol, p-cresol and their mixture as single carbon substrates. The concentrations applied were corresponding to their concentrations in the mixture (0.3 g/l phenol and 0.2 g/l p-cresol). The results showed that a strain of *Trametes versicolor* 1 degraded p-cresol much faster than the strain *Aspergillus awamori* NRRL 3112.

The experiments on the degradation of a mixture of phenol and cresol by mycelia mass of *A. awamori* NRRL 3112 showed a complete degradation of both components, the 0.2 g/l p-cresol was degraded for 192 h, and 0.3 g/l phenol for 120-144 h. The positive influence of phenol on the degradation of cresol in *A. awamori* NRRL 3112 was observed. In experiments on degradation of a mixture of phenol and p-cresol in *T. versicolor* 1 was also observed a complete utilization of both compounds, but in a significantly shorter time: 0.2 g/l p-cresol - 48 h, and 0.3 g/l phenol - 96 h.

The influence of mixed substrate on the growth of microbial cultures was followed. SKIP- models (Sum kinetics with interaction parameters) expressing the total kinetics of the degradation of a mixture of phenol / p-cresol in *A. awamori* NRRL 3112 and *T. versicolor* 1 were created. The SKIP models were built based on the Haldane equation, supplemented with two additional terms. Furthermore, the mathematical description of the target process in *A. awamori* is improved by including two additional correction coefficients.

7 Posters

On Reconstruction in Thermoacoustic Tomography

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Keywords: Radon transform, ultrasound, tomography, imaging.

Thermoacoustic Tomography (TAT or TCT) is one of the promising new methods of medical imaging (e.g., [1]–[4]). TAT procedure: a short microwave (MW) or radiofrequency (RF) electromagnetic pulse is sent through a soft tissue. At each internal location x certain energy $H(x)$ is absorbed. The cancerous cells absorb several times more MW (or RF) energy than the normal ones. The resulting heating causes thermoelastic expansion of cancerous masses, which in turn creates a pressure wave. The acoustic wave is detected by ultrasound transducers outside the object. Assuming the sound speed c constant (a reasonable assumption for mammography), the acoustic signal detected at a moment t comes from the locations at the distance $r = ct$ from the transducer. Thus, one effectively measures the integrals of $H(x)$ over all spheres centered at the transducers' locations. To recover $H(x)$ and hence detect the tumors, one needs to invert the generalized Radon transform of H that integrates a function over all such spheres.

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Start-codon usage in mitochondrial genomes

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Mitochondria are small, oval shaped organelles surrounded by two specialized membranes. Mitochondria are important for the aerobic respiration, and are the major energy producers in eukaryotes. Metazoan mitochondrial genomes are circular DNA molecules of about 16 kB in length, and typically encode 13 proteins, 22 tRNAs and 2 ribosomal RNAs. It is known that the mitochondrial genetic code is highly degenerated and differs drastically from the standard (that of the nucleus) genetic code. Unlike the latter, mitochondrial code and therefore the mitochondrial codon usage has been sporadically investigated so far.

Taking advantage of the fact that more than 2200 mitochondrial genomes have been completely sequenced during the last decade, we determined in this study the start-codons usage in 1300 animal mitochondria. The obtained results showed that unlike in bacteria, where the protein biosynthesis is initiated mainly by three start-codons (ATG - 79.98%, GTG - 11.04% and TTG - 8.6%), in mitochondria many more sense codons serve as initiators. Here, as in the standard genetic code, ATG is also the most preferred start-codon (76.40%). Other codons playing the role of initiators in mitochondria and their frequency of usage are: ATA - 7.74%; GTG - 6.66%; ATT - 5.77%; ATC - 1.27% and TTG - 1.13%. All they can be regarded as variations of the basic start-codon ATG and their function can be explained by the Francis Crick's "Wobble" hypothesis.

A Cellular Automata Model of Infection Control on Medical Implants

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S. epidermidis infections on medically implanted devices are a common problem in modern medicine due to the abundance of the bacteria. Once inside the body, S. epidermidis gather in communities called biofilms and can become extremely hard to eradicate, causing the patient serious complications. We simulate the complex S. epidermidis-Neutrophils interactions on medical implants under a variety of protein-coating mixtures in order to determine the optimum conditions for the immune system to be able to contain the infection and avoid implant rejection. Our cellular automata model can also be used as a tool for determining the optimal amount of antibiotics for combating biofilm formation on medical implants.

Stability Analysis and Dynamics Preserving Non-Standard Finite Difference Schemes for a Malaria Model

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Keywords: Malaria, global asymptotic stability, bifurcation analysis, non-standard finite difference, dynamic consistency

The model presented here is based on a few malaria models, with both the human and mosquito populations not being constant, which were proposed and studied a couple of years ago. It was shown that forward bifurcation occurs when the basic reproduction number, R0, is less than one in the absence of disease-induced death. In contrary, when the disease-induced death rate is large enough, it was shown only numerically that R0 = 1 is a subcritical (backward) bifurcation point. The aim of the study carried out here is threefold. Firstly, the study of the dynamics of the system is reduced to a compact biologically feasible region, in which the system is shown to admit a specific algebraic decomposition into infective and non-infected humans and mosquitoes. Secondly, the previous stability results are extended by computing an additional threshold number ξ, establishing the global asymptotic stability of the disease free equilibrium when $R_0 \leq \xi \leq 1$ and thus making more precise the interval $\xi < R_0$. 1 of possible backward bifurcation phenomenon. Thirdly, a nonstandard finite difference (shortly NSFD) scheme which is dynamically consistent with the continuous model is designed. Numerical simulations are presented which, apart from confirming the theory, help to further empirically investigate the properties of the continuous model.

Segregation of bacterial plasmids expressing 3'-end truncated human interferon-gamma genes in *E. coli* cells

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Plasmid segregation is a well known phenomenon in recombinant DNA biotechnology and a major factor reducing the yield of recombinant proteins. It is due to the irregular distribution of plasmid molecules between the daughter cells during cell division and results (under nonselective growth conditions) in generation of heterogeneous cell population, where the nonproductive plasmid-free cells overgrow the plasmid-harbouring cells. This study aims to investigate the effect of the hIFNγ gene 3'-end truncation on the segregation of the corresponding expression plasmids in *E. coli* cells. To this end a series of expression plasmids was constructed containing 3'-truncated hIFNγ genes and their segregational stability was investigated under batch fermentation conditions in non-selective Luria Bertani medium, where the cell cultures were maintained at exponential growth phase. The fraction of plasmid-harbouring cells in the total cell population versus the cultivation time for all investigated plasmids was determined. To describe the population dynamics a mathematical model proposed by Stewart & Levin was applied. Using nonlinear fitting technique both the difference in specific growth rate between plasmid-free and plasmid-harbouring cells and the specific generation rate of plasmid-free cells (as well as the relative plasmid loss rate) were calculated. The obtained results demonstrated that variations in the 3'-terminus of the hIFNγ gene strongly affected plasmid segregation. To explain this influence the model parameters were juxtaposed with experimental data characterizing hIFNγ gene expression such as yield of recombinant protein and mRNA and plasmid copy-number value. A clear cut correlation was found between the relative plasmid loss rate and mRNA content, which however was not associated with the plasmid copy-number value. This observation suggested that the strong transcription affects plasmid segregation not only by plasmid replication (trough the copy-number control) but also via other obscure molecular mechanisms.

Simulated force developed by a realistic muscle model composed by 30 motor units applying impulsations with different patterns

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Introduction. Motor Units (MUs) are the smallest functional unit independently controlled by the nervous system and consist of motor neuron and muscle fibers. Muscle fibers develop force when innervated by the axon of the MU's motor neuron. Each skeletal muscle consists of numerous MUs and its force is determined by the forces developed by its individual MUs. Nervous system regulates the force produced by a muscle by recruitment/decruitment of new MUs or by changing the number or the inter pulse intervals (IPI) of the innervation. Since in vivo experiments for studying these processes are currently limited, models remain the main plausible way for their deeper understanding.

Model. The new muscle model consists of 30 MUs, which are described by 6-parameters analytical function (Raikova et al., 2008) approximating the in-vivo measured force in Dep. of Neurology, University School of Physical Education, Poznan (Celichowski, 2000), developed by the MU as result of single impulse, during experiments on a rat muscle medial gastrocnemius (Raikova et al., 2007).

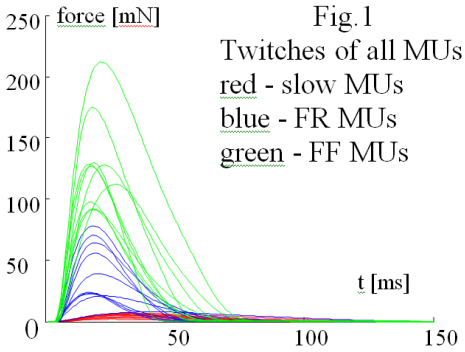
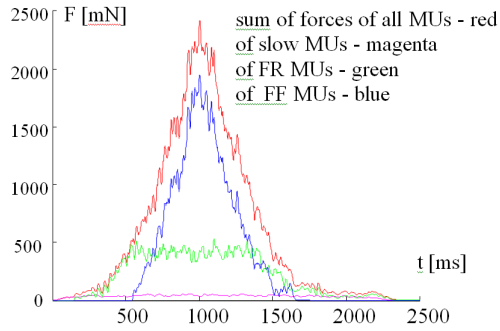


Fig.1
Twitches of all MUs
red - slow MUs
blue - FR MUs
green - FF MUs

Ten of those MUs are slow (S), ten are fast-fatigue resistant (FR) and ten fast fatigable (FF) - Fig.1. When multiple impulses are applied, the tetanic force developed by MU is calculated as a sum of single twitches shifted in time. The total muscle force is obtained as sum of all MUs forces - Fig.2. Different patterns of impulsation were simulated: regular firing identical for all MUs with IPIs $10, 20, 30, \ldots, 100$ ms; irregular impulsation with mean frequency $15 - 25$ Hz for S MUs, $40 - 70$ Hz for FR MUs and 40-80 Hz for

FF MUs. The irregular IPIs are randomly generated. The size principle of MUs activation (Henneman et al., 1965) is also simulated with irregular IPIs. MUs are recruited with type dependent delay in the order of their maximal force (from weakest to strongest) and then stimulated with irregular impulses with constant mean frequency until decruited in reverse order.

Results and discussion. Results of the simulations confirm that: slow MUs develop less but smoother force which has better fused tetanus. The resynchronization of MUs activity also produces smoother output. The steepness of the total force (red Fig. 2) curve depends on the chosen recruitment/decruitment delay.



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A bioinformatic prototype model for Phoma tracheiphila virulence screening

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Keywords: Fungi, Citrus, Biomathematics, Bioinformatic, Modelling.

The response of the infected Citrus plants either in laboratory or in field natural infections depends on many factors influencing the results of the plant resistance tests. Among these factors, the virulence of the pathogen plays an important role in the host-parasite interactions. In order to reduce the effects of this biotic factor a biosoftware is developed as a standardized tool of virulence Assessment. The biosoftware prototype uses the object-oriented programming coding and its interface is built with Microsoft Visual Studio 2008 [1].The program is executable in OS Windows environment NET Framework 3.5 [2].The software prototype is described as VE version 1.0.

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8 School for Young Scientists

Some Mathematical Approaches (Deterministic and Generalized Uncertainty) in Two Radiation Bio–Medical Problems

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We develop mathematical models and solve two radiation related medical problems.

1. **The Design of a Radiation Therapy Vault:** We will develop two methods in the design of the enclosure vaults containing a linear accelerator for radiation therapy that complies with government standards for maximal radiation exposure to persons outside the vault. The first is a conventional deterministic mathematical programming approach. The second uses new min/max regret on generalized uncertainty entities associated with design information such as cost, material characteristics, availability, and radiation leakage physics. This is a project with the University of Colorado Hospital Department of Radiation Oncology in which the vault was in fact constructed according to the deterministic solution.

2. **Radiation Therapy Problems:** We show how to use generalized uncertainty approaches that are inherent to the problem of how to kill tumor (cancerous) cells while minimizing damage to surrounding health tissues. This was a project with the University of Colorado University Hospital Department of Radiation Oncology.

Generalized uncertainties are mathematical entities that not only capture the traditional ideas of variability and frequency but also of lack of (complete) information and non–] specificity. For example, intervals are

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entities that can be (and are) used to model lack of complete information, non-specificity. Intervals may also be used to model the case where all that is known about a parameter is that the parameter belongs to a set of probabilities whose support is a given closed compact set (an interval). The entities of generalized uncertainties of interest to this talk are, (1) intervals, (2) belief and plausibility pairs over nested focal elements (that is, possibility and necessity pairs), and (3) interval–]valued probabilities. We show how both radiation–]related problems exhibit, in a natural way, underlying generalized uncertainties and how to compute optimal (the sense will be specified) solutions when information is incomplete. Actual large (half a million or more constraints) models for radiation therapy problems will be shown.

Robot Motion Planning in Biomedicine

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Keywords: motion planning, probabilistic roadmap, protein folding, radiation therapy

For robots with many degrees of freedom, including multi-robot systems, solving the task and motion planning problem is usually hard because of the great amount of data which have to be stored and proceeded. One of the methods giving good results in the case of robots with many degrees of freedom is the so-called Randomized Path Planning based on Probabilistic Roadmaps (PRM's). The intent of this paper is to face the essentials of this method and its application for biomedical objects considered as abstract robots. Nowadays, the dynamic nature of biological macromolecules, opposed to the static picture provided by X-ray crystallography, is generally accepted. It has been shown that flexibility plays key roles in molecular interactions such as protein-ligand and protein-protein docking. *In silico* methods provide great advances achieved in the last years. One of the simplest, but very important problems in this field is to fold a one-dimensional amino acid chain into a three-dimensional protein structure, showing that such folding (i.e. motion in the configuration space) is realizable. It is known from physics and biology that reaching the stable configurations needs little energy. Thus, high energy configurations above 500 kJ/mol are marked as forbidden. The potential energy of configuration is calculated using Van der Waals law. Then it is not difficult to built PRM and to query it to find different configurations of molecules. Another useful application of PRM is treatment planning of brain radiosurgery. The aim is to plan such a motion of the effector which will not destroy the health tissue with high amount of radiation in opposite to the tumor.

System for computer-aided merging of anatomical ontologies

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Anatomical ontologies of various species typically contain several thousand terms and relations (normally around 10,000 of each) but often the semantics employed in them is enormous in scale. The major problem with such ontologies is that they do not have the necessary means to aid researchers when doing various cross-species text (literature) searches or to help them design new experiments with other species (different than those referred to in the particular species-specific ontology). This is where the process of merging anatomical ontologies comes into use. To merge two or more anatomical (source) ontologies basically means: 1. to draw cross-species edges between the DAGs representing their ontologies (DAG - directed acyclic graph); 2. to merge nodes and edges from the two source ontologies and to promote them to a more general model (again an ontology) thus generating as a result a new ontology (super-ontology or target ontology). The only requirement for the super-ontology is that it makes sense from the points of view of both source (input) species-specific ontologies. The requirement to make sense and the models employed (ontologies, graphs, DAGs) makes that task a typical Artificial Intelligence (AI) with certain Information Retrieval (IR) features. For solving that task an intelligent software system for merging two (or more) source anatomical ontologies into a generic super-ontology has to be designed and implemented. The working title of our software system is AnatOntoMerger (abbreviation from Anatomical Ontologies Merger) and its main module is based on two novel models designed to bridge the gap between the two source ontologies and an original automation procedure proposed by the authors for merging the source anatomical ontologies into a more general super-ontology. Additional modules of the software system include but may not be limited to: o Communications module interrogating (querying) external structured anatomical knowledge sources like UMLS, FMA, WordNet, GO. The data obtained by data module will be used to extend and enrich the knowledge

incorporated into two source ontologies and to aid the automated process of merging them. o Visualization module allowing the user to easily navigate through the super-ontology as well as visualize its links to the two (or more) source ontologies. o Searching (mining) module providing capabilities for performing intelligent text searches or text mining into various external unstructured (natural language based) knowledge resources (scientific literature, the web) using the richness of the generated super-ontology model. The results of those searches is the main practical value brought by AnatOntoMerger and aims to help researchers in finding scientific results already published by others which may help them extrapolating the results obtained by their own experiments or help them design new experiments to perform on their own.

Extracting homoeologous genomic sequences from Next Generation Sequencing reads - the challenge of the wheat genome

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We can now generate a huge amount of data and provide high coverage of genes of interest using Next Generation Sequencing platforms. The alleles present in a genome can be determined along with their respective SNPs (single nucleotide polymorphisms) by selective amplification (PCR) and sequencing of the PCR products. However, when more than one allele is present, only one of them will emerge in the consensus sequence. When there is more than one genome in the respective organism the loss of information is even greater. Such is the case with the hexaploid common wheat (Triticum aestivum L.), where three separate genomes exist. When sequenced reads are assembled the most commonly occurring bases at the SNP positions mask the rarer variants, even if there are some reads that show the respective nucleotide. Thus the most often occurring base is assumed to be the true one, but in different positions different homoeologous sequences may include this base. This leads to the case in which none of the actual sequences present in the organism match the consensus one. This may not be an issue for simple genome sequencing projects, but in plant breeding the productivity of the plant depends on the combination of particular alleles in the genome. Thus the actual sequence of each allele must be known so that a relation between phenotype and genotype can be built. Furthermore, for specific amplification of one of the three genome copies researchers use specific primers that have to cover one or more genome specific SNPs. Without the correct combination of SNPs this will not be possible, or will require a combinatorial approach, which is never an option for with expensive studies and processes like PCR and sequencing technologies. The script we build in this work solves this problem by selecting the variable positions from the sequencing reads and grouping them into continuous groups. This allows us to follow the variation in each of the genome copies present in the respective sequencing run and provide a modification of the consensus sequence that will contain the proper SNP bases. This provides valuable information for sequencing studies that aim to use SNP specific primers to differentiate the three genome copies. The script also replaces the manual look-up of the SNP variants, which is a long and difficult process, and impossible for a large number of genes.

Estimation of sequencing error rates present in genome databases

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The quality of next-generation sequencing data is a major problem in today's bioinformatics. The validation of sequences, either by resequencing or pure statistical error evaluation, is the tool needed to ensure the correct results of all following research done with the data. In this work we evaluate the quality and inherent errors present in the database sequences of the Oryza Sativa (japonica cultivar group) genome by aligning them with the respective sequences of the genes of the organism. The chromosome sequences are retrieved from the NCBI Genome database and the annotation from the entries is used to provide links to the mapped coding sequences on each chromosome. Data are retrieved also from Plant Genome Database analogously, as the locus of intron-exon boundaries were estimated applying BLAST on both genomes - one versus the other. After alignment of the CDS with the respective chromosome we use the highly invariable donor and acceptor dinucleotides (GT and AG) that take part in splicing to measure the amount of error present in the genomic sequence. The results are expected to explain to some extent the nature of errors in sequenced data. These results show us some inside information about the genome. We could analyze errors' differences in genomes and predict what error we could expect from de novo sequencing other organism, classified in certain group (plants, animal groups, etc.). The same manner could be used for examining (verifying) results from NGS. It is important to take in account such type of errors because they symbolizing the mean error rate about the whole genome. Moreover, these errors affect onto annotation and mapping the genes, i.e. such errors are cumulative, or with inheritance.

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10 Conference Program

Wednesday 15 June 2011 BAS, Big Salon, Central Building, "15th November" place		
		Chair-person
09:00 – 09:10	*Opening*	Stefan Dodunekov
09:10 – 09:20	*Welcome addresses*	
09:20 – 09:30	Blagovest Sendov	
09:30 – 10:10	Ralitza Gueorguieva	
10:10 – 10:40	*Tea/coffee 30 min*	
10:40 – 11:20	Weldon Lodwick	Blagovest Sendov
11:20 – 12:00	Yves Dumont	
12:00 – 12:20	Eugene Nickolov	
12:20 – 12:40	Elena Lilkova	
12:40 – 14:00	*Lunch*	
14:00 – 14:40	Venko Beschkov	Ivan Simeonov
14:40 – 15:00	Neli Dimitrova	
15:00 – 15:20	Rene Alt	
15:20 – 15:40	Patrizia Bagnerini	
15:40 – 16:10	*Tea/coffee 30 min*	
16:10 – 16:30	A. Gomez-Corral	Vladas Skakauskas
16:30 – 16:50	M. Lopez Garcia	
16:50 – 17:10	Silvia A Menchon	
17:10 – 17:30	Roumen Anguelov	
17:30 – 18:30	*Poster session and a glass of wine*	

Thursday 16 June 2011 BAS, Big Salon, Central Building, "15th November" place		
09:00 – 09:40	Svetozar Margenov	Krassimir Georgiev
09:40 – 10:20	Azmy S. Ackleh	
10:20 – 11:00	Madhvi Shakya	
10:40 – 11:10	*Tea/Coffee*	
11:10 – 11:30	Gergana Bencheva	Svetozar Margenov
11:30 – 11:50	Robert Strehl	
11:50 – 12:10	Dessislava Jereva	
12:10 – 12:30	Vladas Skakauskas	
12:30 – 12:50	Jean Lubuma	
12:50 – 13:50	*Lunch*	
13:50 – 19:00	*National Museum of History/Excursion*	
19:00 – 23:30	*Conference Dinner*	

Friday 17 June 2011 IMI – Multimedia room, BAS		
09:00 – 09:40	Hristo Kojouharov	Jean Lubuma
09:40 – 10:00	Joanna Zofia Jaroszewska	
10:00 – 10:30	*Tea/coffee*	
10:30 – 10:50	Gaik Ambartsoumian	Yves Dumont
10:50 – 11:10	Ivan Cimrak	
11:10 – 11:30	Valdemar Melicher	
11:30 – 11:50	Nurcan Gucuyenen	
11:50 – 12:10	Antony Popov	
12:10 – 12:30	Mikhail Krastanov	
12:30 – 14:00	*Lunch*	
14:00 – 14:20	Nadia Antonova	Hristo Kojouharov
14:20 – 14:40	Georgi Simeonov	
14:40 – 15:10	Nina Pesheva	
15:10 – 15:20	Ivan Trenchev	
15:20 – 15:40	Khaled Khanchouch (demo: E Ustimovich)	
15:40 – 16:10	*Tea/coffee*	
16:10 – 16:30	Hannen Ben Hassen	Nickolay Yanev
16:30 – 16:50	M. Slavtchova-Bojkova	
16:50 – 17:10	Jordan Genoff	
18:00 – 19:00	*Symphony concert*	

Saturday 18 June 2011 IMI – Multimedia room, BAS		
09:00 – 09:40	Nickolay Yanev	Rene Alt
09:40 – 10:00	Krassimir Georgiev	
10:00 – 10:30	*Tea/coffee*	
10:30 – 10:50	Olympia Roeva	Nina Pesheva
10:50 – 11:10	Tatiana Ilkova	
11:10 – 11:30	Yuri Pavlov	
11:30 – 11:50	Plamena Zlateva	
11:50 – 12:10	Maria Angelova	
12:10 – 12:30	Petar Konovski	
12:30 – 14:00	*Lunch*	
14:00 – 14:20	Peter Vassilev	G Ambartsoumian
14:20 – 14:40	Miglena Kirilova	
14:40 – 15:10	Elica Petrova	
15:10 – 15:20	Galin Valchev	
15:20 – 15:40	Peter Djondjorov	
15:40 – 16:10	Svetoslav Markov	
16:10 – 16:30	*Closing*	

Social Program

16 June 2011, Thursday, 14:00-23:00.

14:30-16:00. Visit to the National Museum of History in Sofia. Founded in 1973, the National Museum of History in Sofia contains more than 650,000 exhibits and is one of the largest history museums on the Balkans. The aim of the museum is to provide a comprehensive view on Bulgarian history from the prehistory to present, in as broad an European context as possible.
http://www.historymuseum.org/?lang_id=1

16:00-17:00. Visit to the Boyana Church is a medieval Bulgarian Orthodox church situated on the outskirts of Sofia, the capital of Bulgaria, in the Boyana quarter. The east wing of the two-storey church was originally constructed in the late 10th or early 11th century, then the central wing was added in the 13th century under the Second Bulgarian Empire, the whole building being finished with a further expansion to the west in the middle of the 19th century. The church owes its world fame mainly to its frescoes from 1259. http://en.wikipedia.org/wiki/Boyana_Church

17:00-18:30. Excursion to Vitosha. Vitosha is a mountain massif, on the outskirts of Sofia, the capital of Bulgaria. Vitosha is one of the tourists symbols of Sofia and the closest site for hiking, alpinism and skiing. Convenient bus lines and rope ways render the mountain easily accessible. Vitosha has the outlines of an enormous dome. The territory of the mountain includes Vitosha national park that encompasses the best known and most frequently visited parts. The foothills of Vitosha shelter resort quarters of Sofia; Knyazhevo quarter has mineral springs. Vitosha is the oldest national park in the Balkans. http://en.wikipedia.org/wiki/Vitosha

19:30-23:00. Official dinner, Student City, Sofia, Restaurant Biliana
http://en.wikipedia.org/wiki/Studentski_grad_(Sofia)

17 June 2011, Friday.

18:00. "Pancho Vladigerov" National Academy of Music (NMA), "Evlogi Georgiev" str, 94.
http://nma.bg/en/
Concert of the Academic symphony orchestra of the NMA directed by Tsvetan Krumov. In the program: Eduard Elgar: Concert for violin and orchestra; Joaqun Rodrigo: Concert for guitar and orchestra. Solists: Gabriela Tsvetkova (violin); Boian Doichev (classic guitar)

Visit to other museums, galleries or churches in Sofia (by choice)
http://www.geology.bas.bg/museums.html
http://www.foreignartmuseum.bg/en/index.html
http://www.nga.gov/