BIOMATH-95

International Symposium and Young Scientists School on
Mathematical Modelling and Information Systems in
Biology, Ecology and Medicine
Sofia, August 23–27, 1995

Edited by

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This volume contains a collection of abstracts of scientific papers contributed to BIOMATH-95 — an International Symposium and Young Scientists School on Mathematical Modelling and Information Systems in Biology, Ecology and Medicine, held in Sofia, Bulgaria, August 23–27, 1995. Included are also the scientific program and a list of participants with their addresses. A volume containing selected materials for the Young Scientists School (extended abstracts and full versions of some contibuted papers) is also published under the title: Lecture Notes on Biomathematics and Bioinformatics'95, M. Candev (Ed.), DATECS Publishing, Sofia, 1995.

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Foreword

The last twenty years has seen an enormous growth in the subject area of mathematical biology, which incorporates the application of mathematics to problems in ecology, medicine and evolution, as well as biology. This growth has occurred, in part, in response to major technological advances in the life sciences. For example, advances in molecular and cellular biology have resulted in the rapid development of experimental research into the biochemical mechanisms underlying tissue disorders and diseases; large scale studies are being carried out to chart the dynamics of disease spread; data on pollution and environmental hazards is accumulating as more sophisticated measuring techniques are developed.

Mathematical modelling can play a crucial role in the life sciences by providing a theoretical framework within which this mass of experimental information can be analysed. In turn, the life sciences are the source of a great number of very interesting and challenging mathematical modelling problems. As the complexity of the modelling increases, our analytical tools and computational skills are stretched beyond their limits, resulting in exciting new developments. However, for theoretical models to be relevant and useful, it is vital that models are developed in collaboration with experimentalists and that predictions resulting from the analyses of models are experimentally testable. This experimental feedback enhances our understanding of the phenomenon being modelled, which leads to more accurate hypotheses on which models can be built, resulting in more detailed model predictions. Only by this close interaction between theory and experiment can mathematics genuinely help to elucidate the underlying mechanisms that govern the phenomenon being modelled.

Mathematical biology is now a well established subject, as can be seen by the increasing number of centres for mathematical biology that are arising in universities throughout the world. The number of international conferences in the area is increasing, as are the number of young researchers, attracted into the field by the excitement of a new and growing subject.

This conference, the first international conference in biomathematics to be held in Bulgaria, brings together researchers from many different countries working on a diverse number of applications, ranging from medical applications, such as in physiology, immunology, neuroscience and biomedicine,

to population dynamics and ecological and environmental modelling; from neural networks to evolutionary biology and genetics. On the more theoretical side, the advanced methodological and computational tools being developed to analyse models are also presented.

The breadth of interests of the participants at this meeting provides an excellent opportunity for the cross-fertilization of ideas which, it is hoped, will have an impact on the field.

Philip K. Maini
Centre for Mathematical Biology
Oxford

The scientific program is very interesting and very attractive — I wish I could go. Wish you big success for the conference.

Jia Li
Huntsville, USA

I am very impressed by the number and wide of views of contributions of your (Bulgarian) colleagues. Unfortunately, for serious reasons I will be not able to participate at the meeting. I believe that the meeting will be successful.

J. Milota
Charls University
Prague

Acknowledgements

The BIOMATH-95 is the first international biomathematical conference in Bulgaria. The main organizers are the Institute of Biophysics at the Bulgarian Academy of Sciences and the Institute of Informatics of the University of Basel. Many of the members of the Organizing Commitee are present or former members of the Research Group for Mathematical Modelling in Biology (RG for MMB) at the Bulgarian Academy of Sciences (now within the Institute of Biophysics). The conference has been preceeded by eight biomathematical seminars organized at national level by the RG for MMB. BIOMATH-95 is organized in combination with a school for young scientists. The two previous international conferences organized by the RG for MMB were also combined with schools for young scientists: the SCAN-90 Symposium & School in Albena, September 24–28, 1990 and the MMSC-93 Symposium & School in Sozopol, September 14–17, 1993. The combination of an international symposium and a school for young scientists proved to be very useful for the promotion of new interdisciplinary sciences in Bulgaria. Some of the participants have been invited to held lectures that are of interest for a wider audience. Such lectures, called tutorial lectures, do not necessarily involve new scientific results. The organizers encourage young scientists to attend the tutorial lectures, the plenary lectures and the lectures or posters presented by their young colleagues. The set of these three types of lectures constitutes the School for Young Scientists. The available materials for the school are published in: Lecture Notes on Biomathematics and Bioinformatics'95 (Ed. M. Candev), Datecs Publ., Sofia, 1995. Young scientists have been supported to attend the School by contributing a lower registration fee. We are grateful to the Foundations "Evrika" and "Sv. Sv. Kiril i Metodii" and Sofiabank for the provided support, which allowed the reduction of the registration fee for the young scientists and the publishing of the Abstracts, the Lecture Notes and the materials for the Round Table discussion.

We are grateful to all members of the Program, the Advisory and the Organizing Committees and to all participants for their contribution to the success of this Conference. The Scientific Program was compiled with the joint effort of the members of the Program Committee: Blagovest Sendov (Bulgaria), Roumen Tsanev (Bulgaria), Petar Kenderov (Bulgaria), Philip Maini (UK), Pierre Auger (France), Jaroslav Milota (Chech Republic), Vladislav Krivan (Chech Republic), Jean Luc Gouze' (France), Jia Li

(USA), Peter Antonelli (Canada), Yves Cherruault (France), Willard Miranker (USA), John P. Norton (UK), Zahari Zlatev (Denmark). Special thanks are due to P. Maini (UK) and V. Krivan (Chech Republic), who invested much time in the scientific organization of the meeting. We thank all members of the Organizing Committee for their active help. We welcome the participants of BIOMATH-95, who are coming from 19 different countries: Brasil, Bulgaria, Canada, Chech Republic, France, Germany, Greece, Hungary, India, Ireland, Japan, Korea, Poland, Romania, Russia, South Africa, Spain, Switzerland.

For the Organizing Committee:

Evgenija Popova
Institute of Biophysics
Bulgarian Academy of Sciences

Christian Ullrich
Institute of Informatics
University of Basel

Svetoslav Markov
Institute of Biophysics
Bulgarian Academy of Sciences

SCIENTIFIC PROGRAM — BIOMATH-95

Tuesday, August 22

15:00 *Registration starts*

17:00 *Social Program: Walk on the mountain*

19:30 *Meeting of Program Committee Members*

Wednesday, August 23

8:00 *Registration*

8:55 *Opening of BIOMATH-95*

Chairman: V. Krivan

9:10* **P. L. Antonelli** (University of Alberta, Canada)
Starfish Waves and Cycles on the Great Barrier Reef of Australia

9:50* **P. Auger, J.-C. Poggiale**
(Univ. Claude Bernard Lyon-1, Univ. de Bourgogne)
Population Dynamics in a Patchy Environment: Fast Migration and Slow Growth

10:30 *Cofee Break*

Session: Population Dynamics
Chairman: P. L. Antonelli

10:50* **V. Krivan** (Academy of Science of the Czech Republic)
Individual Behaviour and Population Dynamics

11:20* **J. H. Swart** (Univ. of Natal, South Africa)
Some Aspects of Age-dependent Population Dynamics

11:50 **T. V. Kostova** (Bulgarian Academy of Sciences)
On the Eigenvalues of the Linearized Gurtin-MacCamy Operator

12:10 **Hiro-Sato Niwa** (Nat. Res. Inst. of Fisheries Engineering, Japan)
Mathematical Model for the Size Distribution of of Fish Schools

12:30 **V. Mitev, S. Popova** (Bulgarian Academy of Sciences)
Identification of the Parameters of a Model of Yeast Cultivation Process

12:50 **M. G. Blizorukov** (Urals University, Russia)
Comparison of the Qualitative Behavior of Differential and Difference Systems on Plane

13:10 **J. Chattopadhyay** (Embryology Research Unit, India)
Effect of Time Delay and Spatial Dispersion on Phytoplankton Blooms

10:30-13:30 **Poster Session**

N. I. Akberova, A. Yu. Leontyev (Kazan State University, Russia)
The Symmetry Patterns' Analysis as a Tool for Recognition of Functional Sites and Phylogenetic Trees Construction

N. H. Buttimore, D. A. Mac Donaill (University of Dublin, Ireland)
Pre-Processed Amino Acid Sequences for Fast Assembly Language Homology Searches

M. Candev, S. Markov, P. Zlateva (Bulgarian Academy of Science)
A Global Mathematical Model of the Enzyme-catalytic Processes in a Living Organism

T. Christen, W. Gander, I. Vranesic, T. Knoepfel (ETH Zuerich, Switzerland)
Modelling Diffusion in the Synaptic Cleft

D. Radomski, A. Pacut, A. Budzikowski
(Warsaw University of Technology, Poland)
Analysis and Modeling Blood Pressure Wave

R. Radvan, R. Savastru (Institute of Optoelectronics, Bucharest, Romania)
Optical System of Investigation with Variable Geometry

14:00 *Lunch*

15:00 *Social Program*

19:30 *Reception*

Thursday, August 24

Chairman: P. Erdi

8:00* **Y. Cherruault** (Univ. P. & M. Curie - Paris VI, France)
(Lecture presented by K. Abbaoui) Title absent

8:30* **D. Popivanov** (Bulgarian Academy of Sciences)
Chaotic Dynamics of Short-Term EEG Time Series Related to Cognitive Science

9:00* **A. G. Rigas** (Demokritos University of Thrace, Greece)
The spectral Analysis of Stationary Point Processes and its Applications to Physiological Problems

Session: Modelling in Physiology & Neuroscience

Chairman: A. G. Rigas

9:30* **P. Erdi** (Hungarian Academy of Sciences)
Neural Modelling: Multiple Strategies

10:00* **G. Shkodrov, S. Markov** (Bulgarian Academy of Sciences)
A Dynamical Model of Synaptic Transmission by Acetylcholine

10:30 **T. Christen, W. Gander, I. Vranesic, T. Knoepfel**
(ETH Zuerich, Switzerland)
Modelling Diffusion in the Synaptic Cleft

10:50 **C. Grigorescu, K. Radev, V. Chesaru, T. Necsoiu, I. Pricop**
(Institute of Optoelectronics, Bucharest)
Thermal Fluxes from Human Body

11:10 **Sh. Gizatullin, A. Amirov**
(Burdenko Main Military Hospital, Moscow)
Classification Analysis of Brain Acute States: Patient Desciption in BRAIN-UNICARD System

11:30 *Cofee Break*

Chairman: I. Dimov

12:00* **Z. Zlatev, J. Fenger, L. Mortensen**
(National Environmental Research Institute, Denmark)
Relationship Between Emission Sources and High Ozone Concentrations

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Chairman: Z. Zlatev

12:40 **K. B. Radev** (Bulgarian Academy of Sciences)
Dynamic Models for Coastal Water Ecosystems

13:00 **L. Nikolov, E. Mileva** (Bulgarian Academy of Sciences)
Solids in the Boundary Layer Flow

13:20* **S. Stoyanov, I. Simeonov** (TU Sofia, Bulg. Acad. of Sci.)
Robust Compensator Control of Nonlinear Fermentation Processes

14:00 *Lunch*

15:00 *Social Program*

20:00 **Chairman: J. H. Swart**

P. Maini (Centre for Math. Biology, Oxford)
Mathematical Modelling in Biological Pattern Formation

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Sensitivity Analysis for Mathematical Models

Session: Software & Hardware for Biomedical Applications I

Chairman: Ch. Ullrich

9:00* **D. Lavenier** (IRISA, France)
Dedicated Hardware for Biological Sequence Comparison

9:30 **I. Rouskova, Ch. Urumov** (TU Plovdiv Branch, Bulgaria)
A Program for Human-Eye Iris Data Processing

9:50 **Zdravko Nikolov, Ivan Daskalov, Veselka Baleva**
(Bulgarian Academy of Sciences)
Noise Suppression in Biomedical Signals Processing

10:10 **E. Stancheva** (Bulgarian Academy of Science)
Medical Multiple Distributed Systems

10:30 *Cofee Break*

Session: Software & Hardware for Biomedical Applications II

Chairman: D. Lavenier

10:50* **Gluhchev** (Bulgarian Academy of Science)
Image Processing and Decision Making in Radiotherapy

11:20* **Z. Zlatev, I. Dimov, K. Georgiev**
(Danish & Bulgarian Academy of Sciences)
Experiments with the Danish Eulerian Model

11:40 **Zdravko Nikolov, Ivan Daskalov, Atanas Gotchev**
(Bulgarian Academy of Sciences)
Preliminary Processing of Biomedical Signals Using Wavelet and Wavelet Packet Library

12:00 **P. T. Andreeva** (Bulgarian Academy of Science)
Inexact Information System and its Application to Approximate Reasoning

12:20* **J. Stuller** (Inst. Computer Science, Czech Republic)
Inconsistency Problems in the Information Systems Integration

10:30–13:00 **Poster session**

M. Daskalov, H. Bustince, K. Atanassov, J. Sorsich, P. Georgiev
(Bulgarian Academy of Sciences et al.)
Generalized Net Models in Neurology (NGN7: Spinal Disease and NGN9: Low Back Pain)

Sh. Kch. Gizatullin, A. Kh. Amirov
(Burdenko Main Military Hospital, Moscow, Russia)
Classification Analysis of Brain Acute States: Patient Desciption in BRAIN-UNICARD System

J. L. Gonzalez-Andujar
(INIA-CIFOR. Aptdo., Madrid, Spain)
Knowledge Acquisition for Expert Systems Development in Crop Protection

D. A. Mac Donaill
(University of Dublin, Ireland)
On the Scalability of Molecular Computational Solutions to NP Problems

R. Radvan, R. Savastru
Institute of Optoelectronics, Bucharest, Romania
Zone Plate for Two Wavelengths Used in Biomedical Equipments

G. B. Shkodrov
(Bulgarian Academy of Science)
Computer Program for Performing Whole-Cell Voltage-Clamp Experiments

13:00 *Lunch*

14:00 *Social Program*

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Chairman: S. Ki Kim

8:30* **P. Erdi** (Hungarian Academy of Sciences)
Neurodynamic System Theory: Neurons, Networks, Populations

Session: Modeling in Biotechnology & Bioengineering
Chairman: D. Popivanov

9:00* **P. Angelov, S. Tsonkov** (Bulgarian Academy of Sciences)
Soft Computing in Modelling of Bioprocess Systems

9:30 **P. Koprinkova, M. Petrova** (Bulgarian Academy of Sciences)
Modified Neural Network Model for Biotechnological Processes Modelling

9:50 **J. Tabakov** (Bulgarian Academy of Sciences)
Mathematical Modelling of Anaerobical Digestion Process in CSTR Model

10:10 *Cofee Break*

Session: Modelling in Biomechanics
Chairman: J. Brankov

10:30* **V. Petrov, I. Edissonov** (Bulgarian Academy of Sciences)
The Aggregation Kinetics Role in the Erythrocyte Sedimentation Process

11:00 **M. G. Blizorukov, A. V. Gorshkov, O. V. Baranova, I. A. Kuzmina** (Urals University, Russia)
On Mathematical Modeling for Walking

11:20 **A. Neykov, S. Stoyanov** (TU Sofia, Bulgaria)
An Evaluation of Analytical Amperometric Biosensor Models

11:40 **N. I. Akberova, A. Yu. Leontyev** (Kazan State University, Russia)
The Symmetry Patterns' Analysis as a Tool for Recognition of Functional Sites and Phylogenetic Trees Construction

10:00–12:00 **Poster Session**

B. Bjankova, J. Sorsich, Soon Ki Kim, K. Atanassov
(Bulgarian Academy of Sciences et al.)
Application of the Generalized Net in Medicine (EDEMAS)

M. G. Blizorukov, A. V. Gorshkov, L. I. Myakotina, O. V. Baranova, I. A. Kuzmina, M. A. Kolodina (Urals University, Russia)
On Statistical Processing of Biomechanical Researches for Walking

T. A. Doneva, C. S. Vassilieff (Sofia University, Bulgaria)
Experimental Test of Cross-flow Microfiltration Models

S. Markov, Y. Akyldiz (Bulg. Acad. of Sci., Bosphorous Univ.)
Curve Fitting and Interpolation of Biological Data Under Uncertainties

K. Radev, C. Grigorescu, K. Berovski, B. Logofatu
(Bulgarian & Romanian Academies of Sciences)
Nonlinear Signal Processing in Bioenergetics

R. Radvan, R. Savastru, M. Dumitru
(Inst. of Optoelectronics & Polytechnic University, Romania)
Automatic Iris Diaphragm without Mechanical Elements

12:30 *Lunch*

Session: Math. Tools Involving Uncertainties & Biol. Applications
Chairman: P. Milanov

16:30* **D. M. Claudio** (UFRGS-Inst. Informatica, Brasil)
Solving Equations with Non Sharp Coefficients

17:00* **A. Popov** (Sofia University)
Fuzzy Sets and Convexity Measures

17:30 **N. Dimitrova, P. Zlateva** (Bulgarian Academy of Sciences)
Investigation of the Methane Fermentation Process by Interval Analysis

17:50 **P. Zlateva, A. Kaimaktchiev** (Bulgarian Academy of Sciences)
Growth Modeling of Yeast Citric Acid Producer Using Interval Analysis

18:10 **M. I. Krastanov** (Bulgarian Academy of Sciences)
A Numerical Approach for Positive Reachability

18:30 **M. Candev** (Sofia University)
Verified Mathematical Modeling

Sunday, August 27

Chairman: T. Kostova

9:00* **P. L. Antonelli** (University of Alberta, Canada)
Modelling Colonial Animals Using Methods of Differential Geometry

9:50 **D. A. Mac Donaill, N. H. Buttimore** (University of Dublin, Ireland)
On the Exploitation of Assembly Language Instructions in Nucleotide Text Manipulation

10:10* **R. Tsanev** (Bulgarian Academy of Science)
Genetic Networks and Evolution – the Impact of Nonlinearity

10:40 **Round Table Discussions, Part I:** The Role of Mathematics in Biology. Mathematical Biology or Biomathemastics?
(Moderators: V. Krivan, S. Markov)

Part II: Presentation of Biomathematical Research in Bulgaria and Perspectives for Further Development
(Chairman: R. Tsanev)

12:30 Closing BIOMATH-95

List of Tutorial Lectures

P. Angelov, S. Tsonkov (Bulgaria)
Soft Computing in Modelling of Bioprocess Systems

P. Antonelli (Canada)
Modelling Colonial Animals Using Methods of Differential Geometry

P. Erdi (Hungary)
Neurodynamic System Theory: Neurons, Networks, Populations

G. Gluhchev (Bulgaria)
Image Processing and Decision Making in Radiotherapy

V. Krivan (Czech Republic)
Individual Behaviour and Population Dynamics

D. Popivanov (Bulgaria)
Chaotic Dynamics of Short-term EEG Time Series Related to Cognitive Processes

A. Popov (Bulgaria)
Fuzzy Sets and Fuzzy Convexity Measures

D. Schiriaev (Dresden)
Sensitivity Analysis for Mathematical Models

J. Stuller (Czech Republic)
Inconsistency Problems in the Information Systems Integration

List of Plenary Lectures

P. Antonelli (Canada)
Starfish Waves and Cycles on the Great Barrier Reef of Australia

P. Auger, J.-C. Poggiale (France)
Population Dynamics in a Patchy Environment: Fast Migration and Slow Growth

P. Erdi (Hungary)
Neural Modeling: Multiple Strategies

D. M. Claudio (Brasil)
Equations with Interval Coefficients: Theory and Practice

D. Lavenier (France)
Dedicated Hardware for Biological Sequence Comparison

V. Petrov, I. Edissonov (Bulgaria)
The Aggregation Kinetics Role in the Erythrocyte Sedimentation Process

A. G. Rigas (Greece)
The spectral Analysis of Stationary Point Processes and its Applications to Physiological Problems

S. Stoyanov, I. Simeonov (Bulgaria)
Robust Compensator Control of Nonlinear Fermentation Processes

R. Tsanev (Bulgaria)
Genetic Networks and Evolution – the Impact of Nonlinearity

Z. Zlatev (Denmark), I. Dimov (Bulgaria), K. Georgiev (Bulgaria)
Experiments with the Danish Eulerian Model

Z. Zlatev, J. Fenger, L. Mortensen (Denmark)
Relationship Between Emission Sources and High Ozone Concentrations

The Symmetry Patterns' Analysis as a Tool for Recognition of Functional Sites and Phylogenetic Trees Construction

Akberova N. I. and Leontyev A. Yu.
Kazan State University, Russia

The DNA genetic text is regarded as a unidimensional crystal composed by the atoms of four types — A,C,G,T. On the basis of the so called "colored" symmetry group theory using 4 types of symmetry transformations, 8 types of possible symmetry structures for such DNA model are considered [1]. A pattern of common for a number of DNA fragments symmetry structures – "symmetry consensus" – has been used for recognition of functional sites and phylogenetic analysis of DNA sequences. The algorithm of the recognition process is based on comparison of the sequence under investigation with consensus already found for sequences with known function.

We report results, obtained by this method for a set of bacterial replication origins. Eight types of symmetrical structures in DNA sequences are described and their function is discussed. These 8 symmetry types comprise the common symmetries, such as direct and inverted repeats and potential hairpins, and also purine-pyrimidine and amino-keto patterns, which has been shown to be important for prediction of functional sites' localization in DNA sequences. Phylogenetic analysis was carried out as a process of building a tree, representing a degree of similarity of symmetry patterns. It has been shown that the type and length of specific purine-pyrimidine and amino-keto repeats can be used in studies of evolution of DNA sequences as a distance measure.

References

[1] Leontyev A. Yu., Biofizika, 37, No.5, 1992, 874-878.

Inexact Information System and its Application to Approximate Reasoning

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Acad. G. Bonchev str., bl. 2, 1113 Sofia, Bulgaria

The inexact information system is based on linguistic terms which value is from the interval $[0, 1]$. Imprecision has advantages, because fuzzy sets avoid the rigidity of conventional mathematical reasoning and computer programming. Fuzzy sets simplify the task of translating between human reasoning and operation of digital computers. In fuzzy logic fuzzy quantifiers are made explicit. Many systems for example, complex biological processes are too complicated to be understood fully in terms of exact mathematical relation, and so they cannot be programmed in a precise way. With fuzzy sets the implicit quantifiers that always come up in such situations, as we can seen, can be easy translated into machine usable form.

This paper discuss method for description of fuzzy quantifiers in formal languages. A fuzzy quantifier such as "most" may be represented as a fuzzy number — a fuzzy set that defines the degree to which any given proposition matches the definition of "most". A comparison between approximate reasoning and method of linear interpolation is made. Further we discuss inexact information in biological and medical expert system and reliability of its inferences.

The linguistic approach may well prove to be a step in the direction of lesser preoccupation with exact quantitative analyses and greater acceptance of the pervasiveness of imprecision in much of human thinking and perception.

Soft Computing in Modeling of Bioprocess Systems

P. Angelov, S. Tsonkov
Centre of Biomedical Engineering
Bulgarian Academy of Sciences

An overview of application of soft computing in problems of modeling optimisation and control of bioprocess systems is presented in the paper. The basic directions of their application are outlined and their main shortcomings and advantages are given. Illustrative examples which explain their advantages are used. The so called *soft hybrid systems* are reported as a prospective one in this field of bioprocess engineering. Such a system combine the advantages of neural networks, genetic algorithms and fuzzy sets and is realized as an unified algorithmic and software product.

Starfish Waves and Cycles on the Great Barrier Reef of Australia

P. L. Antonelli
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University of Alberta, Edmonton, CANADA T6G 2G1

Acanthaster planci is a large predatory starfish on the G. B. R. causing major coral devastation over large portions of this ecosystem in 12 to 15 year cycles, producing the so-called Reichelt starfish waves. Mathematical models made in collaboration with Dr. R. Reichelt (Director of Australian Institute of Marine Science) and other scientists will be presented. State and parameter estimation procedures will also be discussed, time permitting.

Population Dynamics in a Patchy Environment: Fast Migration and Slow Growth

Pierre Auger
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43 Boulevard du 11 Novembre 1918,
69622 Villeurbanne cedex, France

Jean-Christophe Poggiale
URA CNRS 755, Universiti de Bourgogne
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We present aggregation methods in population dynamics. Aggregation corresponds to the reduction of the dimension of a dynamical system which is replaced by a smaller model governing a few number of global variables at a slow time scale. Population are sub-divided into sub-populations corresponding to different spatial patches. The dynamical model describes the sub-population dynamics. It is a large scale system of ordinary differential equations involving different time scales. First, we study the case of a single population in a patchy environment. Growth rates are assumed to be linear on each patch. Individuals can migrate from one patch to another at a fast time scale. We choose different density dependent migration processes. In each case, we use aggregation methods to obtain the corresponding growth equation for the total density of the population at a slow time scale. We look for particular density dependent migration processes leading to an aggregated logistic-like equation and to various types of growth models. Secondly, we study the case of two interacting populations in a heterogeneous environment. A particular choice of density dependent migrations leads to an aggregated competition like model. prey-predator models are also investigated. Aggregation allows one to obtain different types of functional responses with respect to different density dependent migration models.

Application of the Generalized Net in Medicine (EDEMAS)

B. Bjankova[1], J. Sorsich[2], Soon Ki Kim[3], K. Atanassov[4]

[1] Mathematical Faculty of Sofia University, Sofia, Bulgaria
[2] 2-nd City Hospital, Ch. Botev Boul. 120, Sofia-1202, Bulgaria
[3] Dept of Statistics, Chon Buk National University, Chonju, Chonbuk 560-756, Korea
e-mail: soonki@chonbuknms.chonbuk.ac.kr
[4] Central Lab. of Biomedical Engineering, Bulg. Acad. of Sci.
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The Generalized nets (GNs) [1] are abstract mathematical objects for modelling, simulation, optimization and control of real processes. These nets include as particular cases the ordinary Petri Nets (PNs) and the other their extensions and modifications. All models, described by the means of another type of nets can be described by GNs, too.

In a series of papers the authors describe the processes of di- agnostics of different medical diseases (see, e.g., [2]) by GNs. The present study is based on the book [3], where the process of diagnostic of different cases of edema are described.

References

[1] Atanassov K., Generalized Nets, World Scientific, Singapore, New Jersey, London, 1991.

[2] Sorsich J., Atanassov K., Application of generalized nets in nephrology, in Applications of generalized nets, (K. Atanassov, Ed.), World Scientific, Singapore, New Jersey, London, 1992, 220-290.

[3] Taylor R., Difficult diagnosis, W. Saunders Company, Philadelphia, 1985.

Comparison of the Qualitative Behavior of Differential and Difference Systems on Plane

M. G. Blizorukov
Department of Mathematics, Urals University, Ekaterinburg, Russia

On the starting step in creation of mathematical model for population dynamic all investigators collide with the choice of the type of equation (differential or difference) for description of the process. If we prefer differential equations, we again have the problem what discrete model to use for the numerical solution of initial equations. This problem is multicriterial and difficult at least because the class of difference equations is much wider than the class of differential equations. Underestimation of these facts may reduce us to essential transformation of dynamic in transition from differential equations to difference equations, and as a result it reduces to erroneous numerical model. All these make the problem of comparison for the dynamic of ordinary differential equations and difference equations actual. In particular, it is interesting to compare these two types of equations on the plane. Even on the level of phase portraits (behavior of solutions in state spaces) of linear equations we can detect a surprise. In the class of linear difference equations we can find all types of singular points which are known for linear differential equations, but this set of points does not exhaust the set of singular points of difference equations. Moreover, this distinction between these two types of equations increases in the passage from linear to nonlinear systems. All these problems are under consideration in the communication.

On Mathematical Modeling for Walking

M. G. Blizorukov, A. V. Gorshkov, O. V. Baranova, I. A. Kuzmina
Department of Mathematics, Urals University, Ekaterinburg, Russia

This message is devoted to some aspects of mathematical modeling for walking. In particular, such the model can be helpful to analyze and to improve surgeon correction methods for locomotor apparatus pathologies, which are results of damages or diseases. The system approach for solving this multidimensional problem was developed by mathematicians in cooperation with orthopedists. In the framework of the approach and according to the known results (refer to [1]) the plane model for walking and standing was realized in both the frontal and the saggittal planes. At the moment, one of the problems is the creation of three-dimensional dynamical model.

To construct the model we divided human locomotor apparatus into several segments. The following assumptions were made:

– the main part – vertebrarium is a solid or it consists of several solids;

– a head connected with a vertebrarium rigidly or with a spherical hinge;

– hands and legs may be considered as pivotal systems consisted of one or a few elements.

References

[1] V. V. Beletskii. Dvunogaya hodba: Modelirovanie zadachi dinamiki i upravlenia. M., Nauka, 1984.

On Statistical Processing of Biomechanical Researches for Walking

M. G. Blizorukov, A. V. Gorshkov, L. I. Myakotina, O. V. Baranova,
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This message describes software for statistical processing of biomechanical researches for walking pathologies. The software package is result of long-time fruitful team-work of orthopedists and mathematicians, who specialize in mathematical modeling. The package enables to perform statistical processing in such areas as: biomechanical researches of locomotor apparatus, reovasography, stimulating electromyography. It makes possible to input, edit and to analyze information about patient as well as about group of patients. By using the package you can generate histograms of relative and cumulative frequency of selected parameters for a group of patients. It also allows you to determine certainly criterium of distinction between two groups of patients; to generate plots, illustrating range of research parameters in periods etc. The following methods were realized by creators: the position analysis, podography, goniography, foot support reactions, registration of body segments angular deviations, walking velocity evaluation. The package produces both the screen account and standard hard copy. The software is successfully user at the Institute of Traumatology and Orthopedy in Ekaterinburg.

Pre-Processed Amino Acid Sequences for Fast Assembly Language Homology Searches

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Amino acid residues that form proteins may be partitioned into sets with functionalities that are broadly comparable. Useful for rapid preliminary searches, for example, a three bit coding results from a divisi on into the following eight sets of similar amino acids

$$\{P\},\ \{A, G\},\ \{Q, N, E, D\},\ \{T, S\},\ \{C\},\ \{V, I, M, L\}, \{F, Y, W, H\}, \{H, K, R\}$$

while a further two bits serve to identify the amino acid uniquely. A number of partitions of this nature facilitate the rapid initial comparison of protein sequences. Amino acid sequence data are pre-processed to form strings of highest bits, strings of the next highest bits, etc. The search string is similarly pre-processed. A fast assembly language *exclusive or* operation on the echelons of bit-strings followed by rapid *or* operations would lead to a string consisting of *zeros* for homologies and *ones* indicating mis-matches. Various pre-processing strategies would be adopted to suit the particular search criteria selected.

TABLE: Coding that reflects the functionalities of amino acid residues.

Hydrophilic, Small, Simple				Unique, Large, Hydrophobic			
Small & Aliphatic		Amide or Acidic		Reactive Branched		Large, generally	
Smallest	Smallest	Carbonyl	Hydroxyl	Sulfhyd	Aliphatic	Aromatic	Basic
P P P P	A A G G	Q N E D	T T S S	C C C C	V I M L	F Y W H	H K R R
0 0 0 0	0 0 0 0	0 0 0 0	0 0 0 0	1 1 1 1	1 1 1 1	1 1 1 1	1 1 1 1
0 0 0 0	0 0 0 0	1 1 1 1	1 1 1 1	0 0 0 0	0 0 0 0	1 1 1 1	1 1 1 1
0 0 0 0	1 1 1 1	0 0 0 0	1 1 1 1	0 0 0 0	1 1 1 1	0 0 0 0	1 1 1 1
0 0 1 1	0 0 1 1	0 0 1 1	0 0 1 1	0 0 1 1	0 0 1 1	0 0 1 1	0 0 1 1
0 1 0 1	0 1 0 1	0 1 0 1	0 1 0 1	0 1 0 1	0 1 0 1	0 1 0 1	0 1 0 1

The sixth and seventh bits could identify the third nucleotide base. The eighth bit could provide a determination of amino acids L, S and R.

Verified Mathematical Modeling [1]

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A method for parameter estimation, based on the interval analysis, is presented. It can serve for a rigorous assessment of the imperfections of the mathematical models. It is compared with the least-squares criterion by a numerical example.

Keywords: interval analysis, mathematical modeling, parameter estimation, self-validating numerical methods, set inversion.

[1] For the full version of this lecture see Lecture Notes on Biomathematics and Bioinformatics'95, M. Candev (Ed.), DATECS Publishing, Sofia, 1995.

A Global Mathematical Model of the Enzyme-catalytic Processes in a Living Organism[2]

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We propose a global mathematical model of the enzyme-catalytic processes in a living organism under the following assumptions [1]:

1. A living organism is considered as a biochemical reactor (or a system of bioreactors). All substances entering the organism are considered as substrates, involved in subsequent enzyme-catalyzed processing by means of the enzymes present in the organism. No distinction is made between catabolic and anabolic processes and between digestic and metabolic processes. The system of all enzyme-catalyzed reactions in the living organism is shortly denoted as bioconversion. All substrates, entering the organism which are subject to any kind of bioconversion, are further named nutrition substrates or N-substrates (water and oxygen are N-substrates, too).

2. Theoretically all enzyme-catalytic reactions in a living organism can be described mathematically using enzyme-kinetic equations. In order to keep the mathematical model as simple as possible, we unify the biochemical reactions in groups under certain characteristic properties. Such unification gives excellent practical results in many cases. As a typical example in the Monod-Jacob models all biochemical reactions of a microorganism are unified in one (several) group, i. e. it is assumed that the whole organism (or population of organisms) acts as one single (or several) biochemical reaction(s). This idea encourages us to summarize all bioconversion reactions in the organism into a small number of subgroups. Here we start with just two groups and leave the model open for further sophistications.

3. Our model stresses on the basic fact that the role of the enzymes in the bioconversion processes is twofold. From one side, they are catalysts needed for the bioconversion, and on the other side, they are themselves final products of the metabolism. This twofold appearance of the enzymes leads to a basic feedback in the proposed bioconversion model, where the reproduction of enzymes presents a major issue.

4. The effectiveness of the above mentioned feedback is checked in the proposed model by numerical simulations of the intake of various types of N-substrates and various regimes of nutrition (or malnutrition, fasting, starving). It is well-known that certain symptomatic phenomena can be observed under such regimes, e. g. a slow restoration of the bioconversion activity of the organism after a prolonged lack of food, a dangerous poisoning whenever consuming certain types of foods, etc.

5. The N-substrates are subdivided into two categories: (i) such which are easily bioconverted (e. g. need shorter metabolic cycles and simpler enzymes for their bioconversion) and therefore substantially contribute to the reproduction of the enzymes needed for the normal

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metabolic state of the organism and (ii) such which have a longer way (time) of bioconversion and require a large quantity and big variety of enzymes for their bioconversion.

6. It has been assumed that the bioconversion processes can be summarized into two large groups. In the first one we classify the enzyme-catalytic reactions responsible for the reproduction of the enzymes needed for the bioconversion processes. The rest of enzyme-catalytic reactions constitute the second group; typically here belong the reactions, partaking in digestion and in the "lower" metabolic circles. Clearly, such a classification is rather abstract, since in reality there is no rigorous distinction between these two groups of reactions.

7. The inability of the organism to bioconvert certain N-substrates due to the lack of sufficient amount of certain suitable enzymes leads to poisoning of the organism.

In the proposed model we mathematically describe the bioconversion of the two types of the N-substrates by means of ordinary nonlinear differential equations and study numerically the system under various extreme values of input data. The simulations are performed using a computer algebra system Mathematica.

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Effect of Time Delay and Spatial Dispersion on Phytoplankton Blooms

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In this paper we have proposed a simple model modifying the model of Beltrami and Carroll [1] for the dynamics of susceptible phytoplankton, infected cells and their grazer. The modification has been made by (i) considering the mixing rate by simple law of mass action in contrast to proportional mixing rates, (ii) incorporating the spatial effects on the system via simple diffusions and (iii) taking into account the time dealy (T) in the interaction of the infected cells with the phytoplankton and the grazer. When $T = 0$, we have observed that the system is locally and globally stable. It has been also observed that diffusions have some stabilizing effect on the system in local and global sense. When T is not equal zero, we have estimated the length of time delay for which the system is locally stable and beyond which the system bifurcates into a small amplitude periodic oscillation around the interior equilibrium point. These observations are considerably different from the observation of Beltrami and Carroll [1].

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Modelling Diffusion in the Synaptic Cleft

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During synaptic transmission a chemical substance (neurotransmitter) is released from a presynaptic neuron into the synaptic cleft, diffuses through the cleft to finally bind to and activate receptors at the postsynaptic side of the cleft (see Figure 1 left). Many neurons in the central nervous system use glutamate as their neurotransmitter. It has been proposed that, following the release of a quantum of glutamate into the synaptic cleft, the glutamate concentration at the postsynaptic receptors rises transiently from about 1 μM to 1 mM and decays with a time constant in the order of 1 ms. It is thought that these concentration dynamics are mainly diffusion-limited. To test the plausibility of this hypothesis, we performed computer simulations of glutamate diffusion in the synaptic cleft.

Figure 1: left: schematic view of release process, right: concentration distribution in the cleft

The partial differential equations describing diffusion were integrated on a cartesian three-dimensional mesh with boundary conditions imposed by the pre- and postsynaptic membranes (diffusion barriers) and flux conservation at open ends. The glutamate release process was modeled as a time-triggered concentration at open ends. The glutamate release process was modeled as a time-triggered concentration change at a mesh point in the presynaptic membrane. The right side of Figure 1 illustrates the concentration gradient in a 2D submodel after the release.

Equations with Interval Coefficients: Theory and Practice[3]

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This paper brings several approaches which aims to find the solution of some equation types with not exact coefficients, which commonly arise in mathematical modelling in biology. Its main goal is to supply the space of interval mathematics with an algebraic structure that allows direct and iterative solutions of equations with interval coefficients. To do this, we use Moore's basic arithmetic, and through an approximation concept we modify the original definition of equality and obtain an algebraic structure like a field, where is possible to deal with interval directly. For example, it is not possible to find, by using the Moore equality, an interval X that contains all solution of $a + e^x = b$ when $a \in [3, 5]$, $b \in [6, 10]$. With our approach we obtain the interval $[0, ln7]$, i e, the exact solution.

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Generalized Net Models in Neurology (NGN7: Spinal Disease and NGN9: Low Back Pain)

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In a series of papers the authors plan to show the way for Generalized Net (GN) modelling of the Decision Making (DM) schemes in neurology (for the GNs see, e.g., [1,2]). They use the DM schemes from [3]. These schemes are described by separate GNs. The basic difference between these approaches (the binary graph approach from [3] and the GN-approach) is the following. The first approach reflects the statical structure of the process of the DM, i.e. the sequential activities which the specialist (doctor) has to perform during the diagnostic process for a given patient.

In the paper we shall construct two relatively short GN-models.

The present study is based on the book [3] and our research [4]. It uses the schemes on pages 14 and 18 from [3]. We shall construct the GNs NGN7 and NGN9 (see [4]).

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Study of the Steady-state of Methan Fermentation under Uncertain Data[4]

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The static model of the continuous methane fermentation process is

$$\frac{k_1 s}{k_2 + s} - u = 0 \tag{1}$$

$$-\frac{1}{k_3}\frac{k_1 s}{k_2 + s}x + u(s_0 - s) = 0, \tag{2}$$

$$y(u) = k_4 \frac{k_1 s}{k_2 + s}x. \tag{3}$$

wherein s and x are state variables, the substrate and biomass concentrations resp., k_1, k_2, k_3 are kinetic coefficients, k_4 is a proportional coefficient, s_0 is influent substrate concentration and u is the dilution rate. The function $y(u)$ presents the static characteristic of the process.

In general, the kinetic coefficients k_1, k_2, k_3 are unknown. From biological considerations bounds for k_1, k_2, k_3 can be given. Our goal is to investigate the static characteristic function $y(u)$ with respect to uncertainties in the kinetic coefficients. We assume there are enclosing intervals K_i for k_i, $i = 1, 2, 3$. The mathematical problem is to describe the family of all curves obtained when the kinetic coefficients k_i vary independently in the prescribed intervals K_i, $i = 1, 2, 3$.

The function $y = y(u; k_1, k_2, k_3)$ from (3) depends explicitly on k_1 and k_2 and implicitly on the same k_1 and k_2 and also on k_3 by means of the variables s and x in (1)–(2). The problem then reduces firstly to finding the solution set $\{(s, x)\}$ of the nonlinear system (1)–(2) for $k_i \in K_i$, $i = 1, 2, 3$. In general this solution set can have a very complex structure, which can make it practically useless. Using techniques from interval analysis we can find enclosing intervals $S = S(u)$, $X = X(u)$, for s, resp. x, at a given point u such that the interval vector (S, X) presents an enclosure for the solution set, that is $\{(s, x)\} \subseteq (S, X)$. By means of S and X, intervals $Y(u)$ for the static characteristic function $y(u)$ at the same point u can be derived by computing the range $Y(u) = \{k_4 \frac{k_1 s}{k_2+s}x : k_1 \in K_1, k_2 \in K_2, s \in S, x \in X\}$.

From the literature, values for the coefficients and the parameters in the static model are known, $k_1 = 0.4$, $k_2 = 0.4$, $k_3 = \frac{1}{27.4}$, $k_4 = 75$, $s_0 = 3$. We consider k_i as midpoints of the intervals K_i; the radia of K_i are taken to be of the form pk_i, $0 < p < 1$, that is $K_i = [k_i(1 - p), k_i(1 + p)]$, $i = 1, 2, 3$.

A program in Pascal-SC is written for numerical computation of S and X at points $\{u_j\}$ from a regular mesh and of the intervals $Y(u_j)$. The numerical results are interpolated and displayed using the computer algebra system *Mathematica*.

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Experimental Test of Cross-flow Microfiltration Models

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In the last decades continuous cross-flow microfiltration is widely used in the fields of biomedicine (continuous filtration of plasma from whole blood), biotechnology, wastewater treatment etc. The colloidal particles, cells, microorganisms and large macromolecules in the suspension can be removed effectively by this process.

Steady-state cross-flow filtration requires a "sink" for the rejected particulate (cellular) component. Different hydrodynamic models are based on different mechanisms of cellular removal:

– "lift-force" acting on a single particle

– "shear-enhanced" diffusion

– "convective" model – the dense cake flows tangentially

– force-balance on an individual particle at the boundary feed suspension/dense cake, and

– pore plugging in the filter – no steady state is possible.

In order to test different theoretical predictions cross-flow filtration experiments were performed with a model inorganic suspension (bentonite-in-water). In a small laboratory set up, using an acquisition system, the time traces of five parameters were recorded: pressures at tangential inlet, tangential and filtration outlets and tangential and filtration flow-rates. The observed behaviour is consistent with the predictions of the convective model. Steady state conditions are ensured by a tangential outflow of the dense cake.

Neurodynamic System Theory: Neurons, Networks, Populations

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It will be shown why and how dynamical system theory provides the mathematical tool for describing the (spatiotemporal) operation of the nervous system

1. Neurodynamic System Theory
   - 1.1. Neurodynamical Phenomena: General Concepts
   - 1.2. Single Neuron Dynamics
   - 1.3. Multi-level Models
2. Temporal Pattern Formation
   - 2.1. The Conncetivity - Stability Dilemma
   - 2.2. Oscillation:
     - Single Cell Oscillations
     - Central Pattren Generator
     - Synchronized Activity in Cortical Structures
   - 2.3. Chaos
     - Neural Membranes
     - Global Cortical Dynamics
     - Dynamical Disease and Controlling Chaos
3. Self-organization in the Nervous System
   - 3.1. Learning Rules
   - 3.2. Normal Development and Plasticity

Neural Modeling: Multiple Strategies

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Both single-cell and network level modeling has neurobiological relevance The combination of different modelling strategies will be demonstrated. The dynamics of the olfactory bulb (the first relay center of the olfactory system) is the subject of the studies.

The rhythmic and arrythmic behavior of the olfactory bulb occurs due to the excitatory and inhibitory interactions between mitral and granules cells. Systematic numerical bifurcation analysis showed that chaos occur in case of excitatory lateral connections between mitral cells.

Simulation of detailed models of single mitral and granule cells have been done using morphological and physiological data. The morphological data used to characterize the basic structure of each cell type are: soma size, length of interbranch segments, diameter of branches, branching probabilities., and density of dendritic spines. Physiological data on the kinetics of voltage- and calcium-dependent ion channels are incorporated into the model. The rhythmic and bursting firing patterns, the propagation of stimuli through the different compartments of the cells is simulated. Computer simulations have been done by the NEURON simulation program.

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Classification Analysis of Brain Acute States: Patient Description in BRAIN-UNICARD System

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Classification analysis of the brain acute states of various nosologies is actual problem of neurology and neurosurgery. In such analysis the patient is considered as a complex system that functions in some time interval. The state of the system could be characterized by some set of parameters. For selective ensemble of parameters which descipt the system it is supposed that the system status could be completely enough determined by the parameters values. In the framework of such approach the patient status could be considered as a vector in the multidimensional space of the parameters.

The attempt to evaluate complex many-sided processes in the acute pathological situation of brain is one of the main tasks for developed unified informational systems "BRAIN-INICARD". "BRAIN-INICARD" informational system is the medical record system for neurology and neurosurgery. It includes a system of 29 data bases and special programs for their processing.

The problem of classification of brain acute states is very complex both for formulation of the study and for it solution. Nowadays enormous number of data at the cell, subcell, tissue and system levels on the diseases and traumas of the brain were gross accumulated. Processing, classification and analysis of the available data are impossible without use of the modern computer systems and special software for data handling. Thus at the first stage it is necessary to limit up a set of observed indicators to the optimal volume. On the other hand a set of indicators have to provide exact, complete and non-contradictory description of a patient state and health care process.

Modern approaches to the estimation of the patient state severity both for various acute cerebral situations and for urgent medical states were used. The set of the patient state evaluation systems were used in the "BRAIN-INICARD" system with the aim of results comparison. They includes Clinical Classification System (CCS), Therapeutic Intervention Scoring System (TISS), Multiple Organ System Failure (MOSF), Acute Physiology And Chronical Health Evaluation (APACHEII), elaborations of A. N. Khlunovskiy M.D. (1985), some positions of structured patient record for cranium-brain traumas of A. N. Konovalov, L. B. Lichtenman, A. A. Potapov (Eds.) (1986-1990).

For all indicators (parameters) included to the system the structuring procedure — graduation separation — was carried out. According to influence on the system status indicators could be separated into guided and functional indicators. Indicators that register outer effect on system are related to the former class. For example, they could be health care procedures, drug dosage, surgical operation, diet, etc. Indicators that register a state of functional systems are related to the second class. For example, they are variation of the blood leucocyte concentration, blood acid-alkali state, arterial pressure, etc.

For example, dynamic data base on neurological examination was created to involve various neurous system pathology at the maximum completeness. To fill in an indicator value the system proposes to user a questionnaire with a set of structured variants of the answers (up

to 17). Quantitative scales (Glasgow scale and Konovalov et al. scale (1982)) were used for examination of the conscience disturbance level. The patient status, coma duration, serious state duration are estimated. List of indicators that have a structured set of answers includes headache, vomit, eyes opening, motor and verbal response, orientation, ten syndroms, amnesia, aphasia, cornea reflex, enunciation breach and 27 other indicators.

Image Processing and Decision Making in Radiotherapy[5]

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The radiotherapy is a widely used and effective method for cancer treatment where a high-energy beam is targeted at the tumor volume. To prevent vital tissue from destruction, the beam has to be confined by a prescribed geometric shape, called treatment field. The treatment accuracy depends on how accurate the field parameters are set up before every session. This requires their measurement and comparison to the prescribed values. For this an image obtained during the radiation delivery, called portal image, is registered to a reference image, that may be a simulator film or another portal image. If a significant offset in field parameters is present, a correction must be applied.

Portal image processing and analysis aimed at the improvement of the accuracy of radiation treatment of tumors is a complicated problem that requires new algorithms to be developed. It has two major aspects: a) image enhancement, and b) decision making and evaluation of the correction action. An approach is described for the comprehensive image enhancement based on the properties of different types of contextual regions. Also, a new approach is proposed for the correction of systematic displacement. The experimental results have shown that these techniques lead to better quality of images and more effective correction of the displacement error.

[5]For the full version of this paper see Lecture Notes on Biomathematics and Bioinformatics'95, M. Candev (Ed.), DATECS Publishing, Sofia, 1995.

Knowledge Acquisition for Expert Systems Development in Crop Protection

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The first step in the development of an expert system is the extraction and characterization of the knowledge of an expert. This step is widely regarded as the major bottleneck in the system development process and is the most critical process since the operative of expert system will depend on the expertise that can be obtained from the expert.

A short review of the methodology and the experience about knowledge acquisition in the development of two expert systems: SIEXMAL (identification of weed seedlings) and CAES (information delivery, control and identification of aphids) are presented.

Thermal Fluxes from Human Body[6]

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The thermoregulation, an exceptionally complex physiologic process, involves the functioning of all other systems in mammals — neural, cardiovascular, pulmonar, muscles, skin, etc. The classical approach to study this process is based on measurements of both hypothalamic ("central") and skin ("outside") temperatures and looking for the correlations between them [1, 2]. Unfortunately, the data obtained from wide range of experiments *in vivo* contradict one another and, as we have shown, are not enough reliable in achieving correct models.

There are attempts to develop mathematical models of the heat balance based on either the irreversible thermodynamics [3], or on the automatic control theory [4]. The first of them *à priori* involves the principle for local equilibrium applicable only to closed systems near their equilibrium state. The second one avoids the influence of the distributed parameters and operates only with characteristic parameters attached to given points or organs.

Our aim is to review critically the literature and to work out an approach based on the imagination about the body as an open thermodynamic system. We are searching for new physical tools and mathematical models for studying the thermoregulation by employing the thermal fluxes between the body and the environment and the thermal and the information exchange in the body itself. The emphasis is made on the possible relationships between the thermal and the information fluxes.

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Modified Neural Network Model for Biotechnological Processes Modelling

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Neural networks are a promising tool for modelling of such complex nonlinear plants as biotechnological processes. Since neural networks are created for pattern recognition purposes, their inputs and outputs usually take values in the range from 0 to 1 or from –1 to +1. Because of this it is necessary to scale the training data set in this range. Moreover it is well known that for the proper training of a neural network it is necessary training data set to be distributed around midpoint of the allowed interval.

The experimental data of biotechnological processes can vary in a wide interval. Hence after scalling the smallest data values approach to zero and the biggest ones — to 1. Moreover in the usually used square error a big error for the smallest data can be very small in comparison with a small error for the biggest one.

To overcome this problems in the present paper we have proposed a modified neural network which can be trained with data set containing the values in the extended interval and accounts equally for the bigger and the smaller data in this data set.

The usually used output function of neurons is sigmoidal function which takes values in the range [0,1]. In the present paper the following modified sigmoidal function is proposed:

$$x_i = k_i/(1 + exp(-net_i/m_i).$$

As can be seen the adjustable parameters k_i and m_i determine the range and the slope of the curve depending on the used training data The training procedure learns not only the weight connections values, but also the values of k_i and m_i.

In the process of learning the following error is minimized:

$$E = \sum_{t=1}^{T}\sum_{i=1}^{n}(yh_i(t) - y_i(t))^2/y_i(t)^2,$$

where T is the number of input/output pairs in the training data set; n is the network outputs number; y_i is the desired output value; yh_i is the actual output value. The training algorithm is the error backpropagation.

The proposed modification of neural network is tested by two data sets for a continuous and a batch biotechnological processes. Comparison with the classical neural network models is made. Simulation results are given as well as the values of the introduced new parameters k_i and m_i. Investigations are made by authors software for PC.

On the Eigenvalues of the Linearized Gurtin-MacCamy Operator

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Population dynamics is a very fast developing field of biomathematical modelling having applications in mathematical epidemiology and mathematical ecology as well. An important contemporary branch of it is structured population dynamics modelling and age-dependent population dynamics in particular. The continuous age-dependent models are partial differential – integral equations with nonlocal boundary conditions. One of the most renowned is the nonlinear model of Gurtin and MacCamy. An important issue in characterizing the properties of its solutions is the nature (real or complex, with positive or negative real part, etc.) of the roots of its characteristic equation. Knowledge about this issue will let us state theorems about the existence of oscillatory solutions or about the stability properties of the equilibrium solutions of Gurtin-MacCamy's model. This is the kind of investigations we are going to report in this talk.

A Numerical Approach for Positive Reachability

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Let us consider the following linear time-invariant discrete control system:

$$x_{t+1} = A\ x_t\ +\ B\ u_t,\ t = 0, 1, 2, ... \tag{4}$$

where $x_t \in R^n$, $u_t \in R^m_+$ (the set of elements of R^m with non-negative coordinates), and A and B are matrices of suitable dimensions. Such control systems are abundant in ecology, biology and medicine. Take, for instance, hunting and fishing without the renewal of stock, irrigation without the removal of surplus, injection of a drug in a living body and so on.

Let us fix some $x \in R^n$. The reachability problem is to find a function $u_t \in R^m_+$, $t = 1, 2, ..t_0$, such that

$$x_0 = 0 \ \text{ and } \ x_{t_0} = x. \tag{5}$$

This means that

$$x = \sum_{t=1}^{t_0} A^{t_0 - t}\ B\ u_t, \quad u_t \in R^m_+, \text{ for } t = 0, 1, ..., t_0.$$

Henceforth we assume that equation (5) is solvable for some t_0. Let us denote by U_s the set of solutions of (5) such that $u_t = 0$ for $t \geq s$. Let $t^* = \min\{t|\ U_t \neq \emptyset\}$. Then t^* is called settling time of the time optimal control.

The straightforward use of traditional numerical techniques for solution of the positive reachability problem is impracticable. The main difference between sign-restricted and sign-free problems lies in determining of the settling space. For instance, for a controllable discrete system with unrestricted inputs the settling time is less or equal to the dimension of the state space. However, there exist positive controllable systems with sign-restricted inputs for which the settling time is greater then the dimension of the state space (we present a such kind of example).

The numerical approach for finding the settling time is based on the properties of cones, generated by finite number of points, and their conjugate cones. The second step of the approach is to provide the optimal control law.

Individual Behavior and Population Dynamics [7]

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Differential equations have been used in population biology to describe dynamics of interacting populations since the pioneering work of Lotka and Volterra. However, most of the work on population dynamics does not take into consideration individual decisions of animals. In behavioral ecology it was shown that animals often behave in such a way which maximizes certain criterion like energy or nutrient intake. Typically, this criterion is related to reproduction of animals, thus to fitness. We show how the theory of optimal foraging may be included into models of population dynamics. Typically, this leads to discontinuous differential equations, or more generally, to differential inclusions. We will discuss a few biologically relevant examples together with the underlying mathematics.

[7] For the full version of this paper see Lecture Notes on Biomathematics and Bioinformatics'95, M. Candev (Ed.), DATECS Publishing, Sofia, 1995.

On Mathematical Models for Embryonic Pattern Formation

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Many models have been proposed to account for spatial pattern formation in embryogenesis. These models fall into two main classes: reaction diffusion prepattern models and cell movement models. Both classes of models consist of coupled systems of nonlinear partial differential equations. We shall present and motivate these models and illustrate their use by application to a number of phemonena in embryogenesis, including, spatial patterning in the limb bud, propagating patterns in skin organs, and spatio-temporal patterns in tooth morphogenesis.

Dedicated Hardware for Biological Sequence Comparison

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The scan of biological databases is a fundamental task in molecular biology. This task consists of identifying those sequences in the database which contain at least one segment sufficiently similar to some segments of a query sequence to be of interest.

The computational complexity of this operation is proportional to the product of the length of the query sequence and the total number of nucleic acids in the database. In general, segment pairs (one from a database sequence and one from the query sequence) may be considered similar if many nucleotides within the segment match identically.

Presently, software such as BLAST or FASTA are extensively used to perform the scan of databases. They have been designed to run on standard computers (i.e. von Neuman machine) and include software techniques for speeding up the scans. These techniques are based on heuristics which can be tuned by setting external parameters.

The search sensitivity depends mainly on these parameters. In general, a low sensitivity implies a short computation time (a few minutes), while a high sensitivity involves very long computation time (a few hours).

One might expect that the increasing power of micro-processors would, in the future, decrease the computation time. Unfortunately, the banks of DNA sequences grow in size by approximately 50 % per year and there is no reason to expect this progression to change in the next few years.

The biological databases and the micro-processor performance grow approximately at the same currently rate. Thus, biologists will continue to have the dilemma of getting incomplete results in a short time or waiting a long time for satisfying solutions when standard computers are used.

This paper presents different hardware solutions which have been developed to speed up the sequence comparison process, and more precisely, the scan of large biological databases. It explains how time-consuming algorithms, such as the Smith and Waterman algorithm, can be parallelized and then implemented on a processor array, decreasing the computation time by several orders of magnitude.

On the Scalability of Molecular Computational Solutions to NP Problems

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Adleman recently proposed a molecular computational procedure in which the enormous parallelism of chemical systems was harnessed to solve a classical problem in NP – the directed Hamiltonian path problem [1,2]. The specific chemical system employed consisted of oligonucleotides with highly specific binding properties such that each oligonucleotide could be unambiguously mapped to a vertex or edge on the corresponding graph of interest. The polymers resulting from ligation reactions correspond to paths on the graph. A variety of suitably primed PCRs (polymerase chain reactions) were employed as an output device to selectively search for and amplify any polynucleotides corresponding to a Hamiltonian path. More recently, Lipton has adapted the method for the solution of another classical problem in NP – the SAT problem [3].

Adleman's system is in effect a massively parallel chemical analog computer. Using picomole concentrations of oligonucleotides the molecular system yielded ~ 1 computation per oligonucleotide, giving a total of $O(10^{14})$ computations. Concentrations could easily be scaled to yield $O(10^{20})$ computations (1), corresponding to $\sim O(10^5)$ CPU years on a typical 10 MFLOP workstation. Given the phenomenal computational capacity of such systems and the ease with which chemical systems can be scaled, it would be easy for the non-specialist to conclude that the potential for molecular computation is practically unlimited.

In this paper limitations on the potential scalability of molecular computation are considered. A simple analysis of the time complexity function shows that, notwithstanding the enormous computational capacity Adleman's approach, the potential of molecular systems to *increase* the size of generally solvable problems in NP is *fundamentally* limited to $O(10^2)$. More relevantly, over the chemically measurable picomolar to molar concentration range the greatest practical increase in problem size is limited to $\sim O(10^1)$. This conclusion is in accord with the conventional view that NP problems cannot be solved in polynomial time, even using a "non-deterministic" computer with the ability to pursue an unlimited number of computational sequences in parallel [4].

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On the Exploitation of Assembly Language Instructions in Nucleotide Text Manipulation

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Biological texts as expressed in DNA can be interpreted as numeric strings of radix-4 [1]. Thus processes corresponding to the manipulation or comparison of biological texts can also be interpreted as manipulations and comparisons of binary strings (Fig. 1a).

Fig. 1 (a) Mapping the nucleotide alphabet (N={A,T,C,G}) to the quaternary (Q={0,1,2,3}) and binary (B={0,1}) number systems respectively. (b) $P_N = \{p_N\}$ is the set of all operators which manipulate strings in N^*; P_Q and P_B are the corresponding operators in Q^* and B^*. $ALI \subset P_B$ is the set of Assembly Language Instructions available for the manipulation of binary strings [2].

In this paper we explore the relationship between nucleotide, numerical and assembly text manipulation processes. Nucleotide text manipulation processes (corresponding to p_N) which map onto an assembly language instruction, i.e. $p_N \in P_N \rightarrow p_B \in ALI \subset P_B$, may be particularly efficiently modelled since an entire text string can be manipulated in a single instruction cycle. It is shown that whether a particular nucleotide manipulator p_N maps to $p_B \in ALI$ or to the less efficient $p_B \in P_B \subset ALI$ dependscriticalli on the particular mapping chosen for the quaternary interpretation of the nucleotide text $f_{NQ} : N \rightarrow Q$. The paper is illustrated by considering the special case where p_N is the polymerase operator.

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Curve Fitting and Interpolation of Biological Data Under Uncertainties

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A characteristic feature of the present rapid involvement of mathematics with biological applications is the consideration of uncertainties present in the input data. This stimulates the development of new specific mathematical tools. For biological applications involving both short and uncertain records it seems that such interrelated mathematical tools like differential inclusions, set-valued analysis, viability analysis and interval analysis, will play a major role in the near future [1-5]. In this work we make use of interval analysis to interpolation/fitting problems involving uncertain data. A technique for nonlinear interval data related to enzyme-katalyzed reactions has been demonstrated.

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Identification of the Parameters of a Model of Yeast Cultivation Process

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A structural mathematical model of the process of yeast cultivation, based on the approach of Shicher [1], is presented.

The concentration of the cells during the process of yeasts cultivation is considered as a sum of the concentrations of the cells divided in four groups: active, budding, weakened and dead, marked as C_a, C_b, C_w and C_d respectively.

$$C = C_a + C_b + C_w + C_d. \tag{6}$$

The differentiation of the cells in these groups is accomplished by automated morphometric analysis. Analytic relations of the parameters of the model and the specific growth rate μ are deduced [2].

The specific rate of transformation of the active cells into weakened is designate as r_1, the rate of transformation of the weakened cells into active as r_3 and the rate of transformation of the weakened cells in dead as r_2. The rate by which the buds of the budding cells grow and transfer into active cells after their separation we define as r_4 and the rate of transformation of the active cells into budding as r_5.

A method for identification of the morhophisiological parameters is discussed. The parameter evaluation of the differential equations of the model was performed by means of the least squares method considering m discrete values of the process. These values are presented as functions of the unknown parameters $r_1, \ldots, r_5$. If at the same time the values C_ae, C_be, C_we and C_de are measured experimentally, it is necessary to minimize the function of the sum squares of differences between the calculated from the model values and the ones — experimentally measured.

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An Evaluation of Analytical Amperometric Biosensor Models[8]

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Engineering design of biosensors is an attractive scientific direction with many problems. In previous works we proposed mathematical analytical models of amperometric biosensors with different enzyme kinetics and made comparative metrological analysis. This allows us to make prognosis about biosensor technical properties and to design optimal measuring devices. The basis of this research is the approximation of substrate concentration profile in membrane set for biosensors with Michaelis-Menten and ping-pong enzyme kinetics [1].

This work is devoted to the following questions: how precise is this approximation in different biosensor variants and which are the limitations for practical use. For this purpose we take 7 terms of Taylor infinite series to form an expression for output current error and to make some enaluation of the accuracy and the adequacy of the model. We have analysed two general cases — one with Michaelis-Menten kinetics and another with ping-pong kinetics. The limitation values for the model parameters were established by evaluating the maximal nonlinear biosensor's error for each nominal measuring range. This analysis gives some regions in the three-dimensional space, which define the limitations for the model applicability.

Digital simulations of the model have been performed using MATLAB. The results have been summarized in grafical and table form. Some of these results are very interesting and are discussed in the paper.

The analysis of the approximation errors allows to prove the adequacy of the analytical amperometric biosensor in the real measuring range.

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Solids in the Boundary Layer Flow

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Fine solids are the most usual contaminants that are found in natural and industrial waters. If the particles are hydrophilic and chemically inactive towards the usual purifiers their removal poses a practically unsolvable problem. In the case of boundary layer flows however, the hydrophilicity and the chemical inertness of such species are an advantage. A group of experiments gives a notion for the possible solution of this problem using only a hydrodynamic approach.

A model for the interaction of a solid sphere with the boundary layer on a wall is proposed. The full Navier-Stokes equations are analyzed. It is established that the finite dimension of the solid results in the appearance of an additional flow field that may be regarded as a disturbance of the background flow. The problem for the interaction is then brought to the solution of comparatively simple partial differential equations that are easily solved via familiar methods. The study confirms the experimental observation that boundary layer flows at solid walls retain fine solids. This effect is most prominent for smaller particles ($R_p < L/Re_i^{5/4}$, R_p is the solid's radius, L is the length of the wall, Re_i is the Reynolds number of the background flow). The interaction in this case has a clear viscous character, the major changes in the disturbance flow being in the transverse direction. Larger particles ($L/Re_i^{5/4} < R_p < L/Re_i^{1/2}$) exhibit a definite inertial character of the perturbation field, the basic effect being the longitudinal changes. The entrapment here is not so remarkable. The individual trajectory studies for the above cases are also presented. They point out that if other solids are also to be found in the already perturbed boundary layer flow the tendency of their capture is further increased.

Noise Suppression in Biomedical Signals Processing

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The biomedical signals come as a result of different physiological processes. Unfortunately, the registered signal values are usually influenced by the inevitable negative action of a number of factors. The extraction of the source signal from its mixture with the noise is quite a serious and complicated problem. The classical spectral analysis is not very efficient because of the spectral overlapping of most of the sources.

In the present investigation we have reviewed the different methods for signal extraction and noise suppression that have been practically applied. We have also pointed out their positive characteristics and their utmost capabilities. We have inve vestigated the adaptive methods for signal extraction with or without a model source. We have proposed a method for the desired signal enhancement which applies an adaptive filter of lattice type. Such an approach offers the important advantage (as far as research work is concerned) assuring the simultaneous results for different length filters. We have presented experimental results received from ECG signals and respiratory acoustic signals processing.

Preliminary Processing of Biomedical Signals Using Wavelet and Wavelet Packet Library

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The biomedical signals are usually non-stationary to a large extent and the substantial information is concentrated in their singularities. The preliminary processing of biomedical signals includes two tasks that can often be controversial. The first one is noise reduction (or denoising) while the second one is signal feature extraction. The main problem is what is noise and what is a feature. The solution of both tasks can be obtained using wavelet bases approach which applies the specific property of wavelets to compress signal energy in a few coefficients. The prerequisites for implementation of such an approach are the following: (a) There is one or several bases efficiently representing the informative signal; (b) No basis can represent the noise component of the signal efficiently. We have searched for the most appropriate basis (the best basis) in wavelet and wavelet packet bases library consisting of compactly supported wavelets (Daubeshies wavelets) and cubic spline wavelets (Battle-Lemarie wavelets). The chosen basis assures minimum entropy decomposition. On obtaining the best signal representation we have selected the coefficients which are bigger than an experimentally determined threshold. The received reduced "truncated" coefficients vector can be considered the vector representing the denoised signal features. This vector can be subsequently recognized or transmitted.

We have carried out experiments including natural (respiratory-acoustic and voice) and synthesized signals decomposition. On getting the reduced feature vectors we have done inverse transform. The restored signals have shown a good coincidence with the original ones at lowered noise level.

Mathematical Model for the Size Distribution of Fish Schools

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Acoustical observations for many pelagic fish species revealed that the size distribution of schools shows a well-defined peak frequency. A mechanistic approach to the size distribution of fish schools is presented based on the optimal foraging theory. The survival and reproduction of fish depend on their success at locating food resources, e.g., plankton patches distributed randomly in a feeding sea-area. This success is determined by the individual foraging behavior. The individual behavior also determines the population properties such as the size distribution of schools. This study deals with the connection between individual-level performance and patterns at the population level. A school moves and cuts a swath through the water within which patchily distributed food resources are detected. A model for schooling behavior developed by Niwa (*J. Theor. Biol.*, **171**, 123–136, 1994) tells that the movement path of a school searching for food in absence of any landmark is regarded as the correlated random walk whose persistent length, i.e., correlation length, depends linearly on school size (number of individuals in a school), and intersects itself with frequency dependent inversely on school size. Because there is supposed to be no food in the intersections, i.e., the sites which a school revisits, an increase in these overlapping forage sites is reflected in a decrease in searching efficiency for prey patches. Schooling fish find food faster in patchy environments, i.e., reduced overlapping area and increased swath, but the energy expenditure for a unit revenue in a prey patch (specific energy cost) increases with school size as well because of taking the trouble to break up and regenerate a school for exploiting patches, or because of intraspecific competition. Efficient predators, therefore, swim together forming a school of an optimal size where the net benefit is at a maximum. Because many schools nomadize in a limited area, interaction between schools occurs so that two of them meet and join, or so that a school splits into smaller ones. These processes controlling the school size are decomposed into the systematic processes of joining and splitting schools which depend on the sizes through the long-term average rates of per capita net energy intake, and the stochastic processes which fluctuate the sizes. It is asked what the probability that a fish engages in schools of size N is. The stationary distribution of school size which is realized with an overwhelming probability is elucidated by the use of the principle of maximum entropy of the probability distribution subject to two constraints, i.e., the probability distribution is normalized and the population mean logarithm of the long-term average rate of per capita net energy intake is kept fixed at a maximum. The predicted size distribution function is peaked at the optimal size, i.e., most individuals engage in schools of optimal size. The optimal size is unlikely to be set by food supply but by the features of overlap and swath of forage path, and the specific energy cost of prey capture. The most frequently observed size also depends on overlap, swath and specific cost, and is expected to be regulated by the fish population density in a feeding area.

The Aggregation Kinetics Role in the Erythrocyte Sedimentation Process[9]

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The wellknown S-shaped settling curves are obtained as solutions of an autonomic dynamical system deduced mathematically from the generalized Stokes formula, the blood volume conservation law and the Smolouchowski theory of particles coagulation. Numerical computations and parametric analysis of the deduced two nonlinear differential equations for the plasma zone thickness and aggregates size are accomplished. It is shown the presented model give a possibility on the base of experimentally recorded sedimentation curve and aggregate size grouth to identify quantitatively the values of the essential physical parameters of the coupled process of erythrocyte aggregation and sedimentation. This method of identification could be used as an indicative test in the haematological laboratories.

[9]For the full version of this paper see Lecture Notes on Biomathematics and Bioinformatics'95, M. Candev (Ed.), DATECS Publishing, Sofia, 1995.

Chaotic Dynamics of Short-term EEG Time Series Related to Cognitive Processes[10]

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An approach to discover the static and dynamic behavior of EEG activity accompanying cognitive processes related to the preparation of the voluntary movements is described using two different methods of nonlinear dynamics, appropriate for short and noisy time series. It is demonstrated that short chaotic transients exist in EEG activity around the onset of the trend component considered to reflect the intention for and preparation of the motor action. They were located using Reconstructed Components based on Singular Spectrum Analysis and by highest absolute error between real and short-term predicted observation using Nonlinear Prediction. The both methods based on different philosophy gave similar results.

[10]For the full version of this paper see Lecture Notes on Biomathematics and Bioinformatics'95, M. Candev (Ed.), DATECS Publishing, Sofia, 1995.

Fuzzy Sets and Convexity Measures[11]

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Fuzzy sets are generalization of conventional set theory that were introduced by L. Zadeh in 1965 as a mathematical way to represent vagueness in everyday life and natural phenomena. In modelling natural phenomena in climatology, ecology or in social sciences precision may be quite useless. Everyday language is one example of ways vagueness is used and propagated (for instance people say "This man is thin and this is tall") - we assimilate fuzzy data (like 'tall' and 'thin') and imprecise information just as we are able to make decisions about situations which seem to be governed by an element of chance. In this sequel, it is useful to work with fuzzy or imprecise geometrical objects in the study of natural images, for instance created by microscopical, X-ray or ultrasound scanning.

Shape analysis is of great importance for different tasks in computational biology, for instance in the recognition of pathological objects on X-ray or microscopic images. Convex sets play an essential role in shape analysis. However, in practical image processing (including electronic microscopy and tomography) real convexity is rarely encountered. Yet in real vision systems, whether machine or human, imprecisions are inherent in the spatial and intensity characterization of the image. At the low levels of image representation, there are effects of noise in sensory transduction and of limits of sampling frequency.

Unlike computer systems, human beings are more flexible. In general, they can easily say whether a pattern looks convex or not. The notion of concavity tree, defined by Foster gives a simple hierarchical description of a shape, but it cannot produce a simple quantitative measure of approximate convexity. The approach of Held and Abe is based on geometrical probability. It derives a measure for approximate convexity for objects in binary images.

The techniques presented gives a novel approach based on fuzzy set theory. Grey-tone images can be regarded as fuzzy sets with membership function defined by the grey level of every pixel. In this paper we derive a new measure for approximate convexity of halftone objects, employing concepts from fuzzy set theory. This measure is based on the notion of an inclusion indicator, introduced by Sinha and Dougherty.

[11] For the full text see the Lecture Notes on Biomathematics and Bioinformatics'95

Dynamic Models for Coastal Water Ecosystems[12]

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Spatially explicit simulation models have been recently proposed [1] as a tool that can be useful in analyzing interactions among adjacent habitats or ecosystems. These grid–based spatial models were developed to be used in simulation ecological processes within a dynamic, heterogeneous landscape/seascape. The fundamental aspects to the structure of the models observed therein concern the problems of the so–called space averaging in continuum mechanics [2], the scaling up the output of local models for input into models of larger spatial domain [3] as well as the coupling of physical and biological models which usually have quite different spatial and temporal scales [4].

To formulate properly the hydro–biological part of these models, the space averaging technique has been applied to the initial set of conservation laws, including, besides the continuity, the momentum and the energy equations, the migration and the diffusion equations for the species and the substances involved in the ecosystem. The application of this general approach shows that the substantial additional terms present at the transport equations if one has to work out space–averaged models in which the physical and the biological transport processes are considered. These terms, appeared within the modelling, show the presence of additional fluxes between the spatial scales caused by the scaling up itself. The new terms need additional closing relations for their determination, and the conservation law for the angular momentum is suitable for this purpose. Consequently, the water ecosystem appear in spatial dynamic models as continuum having internal rotational degrees of freedom.

For the physical and the biological models usually being in consideration for the Black Sea internal shelf regions, the proper conservation laws and the corresponding spatial dynamic models describing transport of pollutants as well as ecosystem self–restoration are obtained by using the methods of nonequilibrium thermohydrodynamics and the space averaging technique. The results of numerical analyses based on spatial models are tested against the results obtained within a simple numerical model assuming the fluid without internal rotations [5]. The results obtained for the Black Sea ecosystems conform to the data known from the field experiments (KAMCHIA'77-79, the Bourgas Bay eutrophycation). The developed here analytical techniques and numerical methods as well as the worked out program code can be used to create new software tools for the study and the management of both coastal waters and marine ecosystems.

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Nonlinear Signal Processing in Bioenergetics[13]

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Chaotic time series data are observed in experiments on biological systems, in clinic practice, in sports medicine, etc. Each physical parameter measured in physiology and medicine has values that are changing either periodically having nonlinear and noisy behavior, or nonperiodically and at all chaotically. In all the cases, the desired "clean" signal is effected by the environment through which it passes on its way from the source to the measurement device or by properties of measurement process itself. As the organisms are very complex systems, many causes have influence on the measured parameter.

Our aim is to review briefly the new methods for nonlinear signal processing with respect to possible applications in medicine, physiology, and bioenergetics. In the analysis of signals we assume that a dynamical system is in the form of a differential equation or a discrete–time evolution rule is responsible for the observations. The number of degrees of freedom or, equivalently, the dimension of the state space of a dynamical system is the same as the number of first–order equations required to describe the evolution. We consider methods for:

- separating signal of interest from contaminations ("noise reduction");
- constructing an appropriate phase space for the data in which the full structure of the strange attractor associated with the chaotic observations is unfolded;
- evaluating invariant properties of the dynamics such as dimensions, Lyapunov exponents, and topological characteristics;
- model making for diagnosis, prediction, and other goals.

The emphasis throughout the review is on the tools one has for the realistic study of measured data in order to bring these tools into general use among physiologists and medical scientists. Much of the progress in studying complex and chaotic systems has rested on advanced data acquisition devices and computational tools based on underlying rigorous mathematics. A number of analysis tools guided by this mathematics and realizable on existing computers constitute the core of the review. An attempt is made to concord the requirements upon both the data acquisition system and the computational tool as a consequence of properties of the algorithm as well as of the dynamical system itself.

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Analysis and Modeling Blood Pressure Wave

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Recent experiments indicate participation of the argine vasopressine (AVP) in the blood pressure control. This peptid modifies the course of the blood pressure wave.

A model can assist in the testing the above phenomenon.

The data used in modeling were obtained in an experiment perfomed on conscious rats. The rats were chronically instrumented with femoral arterial catheters for the blood pressure measurements. During the experiment the arterial catheter was connected to a transducer, an amplifier and an A/C converter connected to a PC computer.The data were stored on a disk of PC.

The first step in a model creation was a statistical analysis of the measurements. A stationarity test based on the number of runs showed that this wave is stationary. The FFT analysis indicates that in the frequency domain one may select three basic frequency components. The first $f_1 = 7.4$ Hz corresponds to the heart rate, the second $f_2 = 2.5$ Hz corresponds to the frequency of respiration, and the third $f_3 = 15$ Hz may reflect the resonance frequency of the blood vessel vibrations.

The first and second frequency component are most interesting from physiological point of view. In particular, changing of this frequency components after the injection of AVP is very important.

The model we present belongs to the class of autoregresion (AR) models. The value of the blood pressure in the actual moment is modeled as a linear combination of several selected values from preceeding time moments.

A current version of model allows to describe the pressure wave with the use of four parameters. Two of them describe the component related to the heart frequency. Two other show how strong the actual value of pressure depends on values from preceeding time moments. The number of parameters can be incresed to include the respiratory components in the model.

This model has two advantages. First, it allows for a statistical analysis of changes of frequency compenents. It leads to better understanding of the mechanism of the modification of the blood pressure via AVP. Second, this model can be applied to predict of the pressure course. Experiments with this model show that the course of wave can be predicted even for 2 heart periods forward with very small error. It can be applied in clinical fields. It makes it possible to detect the differences between the pressure normal course (which is predicted) and the actual (pathological) course.

This kind of a model can be applied for analysis of other biological data. It is easy to notice that periodical triends can be observed in many biological signals.It can also be useful in pharmacology to create models of drugs dynamics.

Spectral Analysis Techniques of Stationary Point Processes and their Applications to Neurophysiological Problems

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Our intention in this work is to use spectral analysis techniques of stationary point processes in the study of a complex physiological system. Estimates of the spectral density functions can be obtained by smoothing the periodogram statistics. These estimates are shown to be consistent.

Certain parameters of the point processes both in time and frequency domains can be estimated by using the estimates of spectral density functions. In the frequency domain we can obtain an estimate of the coherence coefficient which provides a measure of the linear relationship between the components of the point process. In the time domain we can find an estimate of the cross-intensity function by using the inverse Fourier transform. This is an important function and provides a measure for the conditional probability of having an output event when an input event occurs.

Estimates of the spectral density functions, the coherence coefficients and the cross-intensity functions are illustrated by analysing four data sets from the field of Neurophysiology. The data sets are described as follows:

1. Spontaneous activity of the complex physiological system.
2. Response of the complex system when is affected by the presence of a gamma motoneuron.
3. Response of the complex system when is affected by the presence of an alfa motoneuron.
4. Response of the complex system when is simultaneously affected by a gamma motoneuron and an alfa motoneuron.

The main results which are obtained from the analysis described above are as follows:

- When the complex system is affected by a stimulus its periodic character is destroyed completely.
- The effect of the gamma motoneuron on the system is more likely to happen when an input event is about 15msec away from an output event.
- The effect of an alfa motoneuron makes the system fire for a very short period and then blocks it for about 30 msec.
- When both stimuli affect simultaneously the complex system, then the effect of the gamma motoneuron is reduced by the presence of the alfa motoneuron.

A Program for Human-Eye Data Processing

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The paper presents an approach for data processing of human-eye iris digital image. The informtion for the left and right eye is collected by a CCD-camera, digitised by a frame-grabber and stored as two separate files on a PC hard disk driver.

The program, written in C, based oon the level of brightness black & white image analysis is a part of a complex system, which is in the process of being worked out.

Diagnosing by the iris is an ancient method used in the modern medicine as a suppoorting method for quick differential diagnosis. Using contemporary technical equipment such as persoonal computer-based analysis and data storage system, medical doctors will be able to improve the decision-making process and to create an electronic archive of the history of the decease.

The program also gives suggestions about possible causes of dark or light spots in the iris and can be useful for the educatiion of beginners.

Keywords: Data processing, iris diagnosis, frame-grabber, image analysis, programming in C language.

Fast and Accurate Sensitivity Analysis for Large-Scale Non-Linear Models

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In this talk we discuss applications of automatic differentiation to sensitivity analysis of complex nonlinear models.

Any nonlinear computational model operating with real variables requires some kind of local approximation. To analyze or optimize mathematical models numerical methods require sensitivities, i.e. partial derivatives of intermediate or final results with respect to input parameters or other intermediate values.

The derivatives can obtained by means of automatic differentiation — a non-approximative method allowing fast and exact evaluation of derivatives of any degree. In contrast to the method of divided differences automatic differentiation method does not incurr any truncation errors and the only errors introduced are those associated with using floating point arithmetic. Especially in applications where second- and higher-order derivatives are needed, the ability of automatic differentiation to avoid truncation errors plays a major role.

The reverse mode of automatic differentiation yields the gradient of a given function at a time and storage cost that is independent of the number of variables the function depends upon. This means that, irrespective of the number of parameters in our model, we obtain the whole set of sensitivities at a only a small multiple of the runtime of the program that evaluates the underlying model. This property in particular makes sensitivity analysis of large-scale models possible.

ADOL-C and ADOL-F packages for automatic differentiation of C and FORTRAN codes are presented. Theoretical and practical approaches to the parallelization and vectorization of the derivatives' evaluation code are also discussed.

Computer Program for Performing Whole-Cell Voltage-Clamp Experiments

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The routine performance of patch-clamp whole-cell experiments is the generation of several successive voltage pulses by special stimulator, applying them as a command voltage to the investigated cell and observing the evoked current using a recording oscilloscope. The program SWT (Step Wave cell Tester) automates this process, using DAC to generate stimulus signal, and fast AD conversions to obtain the oscillogram of the response current. The stimulus could consist of up to 5 voltage pulses. The amplitudes and the durations of these pulses could be easily changed, and the obtained stimulus waveform could be simultaneously monitored. There could be more than one value for specific level or duration. In this case multiple experiments (one for each value) are performed automatically. The oscillogram of the evoked current can be acquired during given stimulus pulse or multiple consecutive pulses. The time resolution could be up to 10 microseconds and precision is 0.04% of the full range (for 12 bit ADC-DAC board "Labmaster TL-1" Axon instruments). The data could be stored in files, and simple procedures of data processing are available such as cursor measurements, current – voltage relationship curves, etc. Very useful option is the subtraction and the addition of currents obtained under similar conditions, e.g. estimation of the current blocked by some toxin. A special mode is introduced to ensure simultaneous visual control of the leak current and giga-seal formation.

A Dynamical Model of Synaptic Transmission by Acetylcholine[14]

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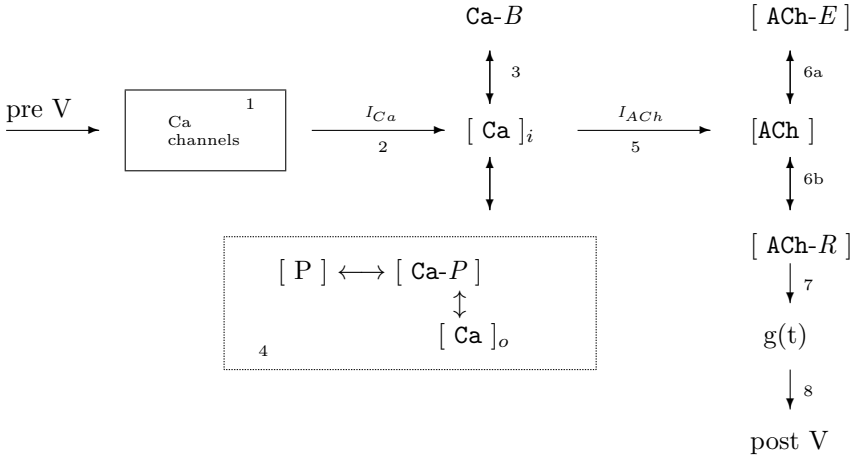
The process of synaptic transmission is schematically described as follows [2]:
– the presynaptic voltage opens specific Ca channels in the presynaptic membrane;
– the increased $[\mathtt{Ca}^{2+}]_i$ releases the ACh vesicles in the synaptic cleft;
– the ACh binds the receptors in the postsynaptic membrane, which are ion channels too;
– the postsynaptic current causes depolarisation of the postsynaptic membrane.
To allow for the next pulse to be transmitted, the following phenomena occur:
– the presynaptic Ca channels close or inactivate, depending on the value of the potential;
– the free $\mathtt{Ca}^{2+}$ in the cell is extruded by plasma-membrane Ca pumps;
– the ACh is hydlolysed by ACh esterase.



In this work we formulate a mathematical model of synaptic transmission based on the above scheme. In the formulation of the model some ideas have been borrowed from previous mathematical models of synaptic transmission [1], [3].

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Medical Multiple Distributed Systems

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When administrative integration of two or more computerised organisations takes place, integration of the information flow has to be organised. The switching of central or regular computers into a common network requires provision of common software environment within which simultaneously function and interact applied systems, such as centralised or distributed database systems, possible rule base systems, image data base systems, even multimedia data base systems, time-sharing by representative processes a number of common sites, single or multiple CPU each, within one or more computer networks. Such complex structures of software systems, we call multiple distributed systems. When the organisations are medical clinics, wards or other medical centres, and the interacting applied systems manage and process medical information, for the purposes of diverse health care domains, e.g., administration, human and material resources planning, resources distribution, patients medical histories data management, general diagnostics support, etc., we speak about medical multiple distributed systems. The study focuses both (1) at the contribution of the medical implementation to the development of the multiple distributed systems software technology, the consistency and integrity checking of devised set of approaches, methods, and solutions, and (2) at the contribution of the advanced distributed system software technology to the medical information management needs. An example for computer network and corresponding information flow integration of Obstetrics and Gynaecology Clinic and Paediatrics Clinic within a multiple distributed system is presented for medical sciences studies involving prenatal information.

Robust Compensator Control of Nonlinear Fermentation Processes[15]

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Fermentation processes involve living micro-organisms, their dynamic behaviour is often badly understood, strongly non-linear and non stationary. The model parameters do not remain constant over long periods, due to metabolic variations and physiological dimofications. Continuous fermentation processes are very perspective ones with their effectiveness and productivity. In continuous cultivation of micro-organisms the bioreactor is continuously fed with the substrate influent. The rate of outflow is equal to the rate of inflow and the volume of culture remains constant. The concentrations of biomass, substrate and product (in the case of biosynthesis) in the liquid leaving are equal to those in the well-mixed bioreactor. Because of the very restrictive on-line information the control of these processes is often reduced to regulation of one or more variables at a desired values in the presence of some perturbations

The paper deals with the robust compensator control of continuous fermentation processes described by a set of two and three non-linear differential equations. The first model describes anaerobic waste water treatment process (methane fermentation) and the second one deals with general biosynthesis process model.

For the design purposes the non-linear models are transformed into linear ones with interval parameters. Robust state space compensators are designed by the internal model principle. The effectiveness of the algorithms designed is performed by a lot of simulation experiments.

[15]For the full version of this paper see Lecture Notes on Biomathematics and Bioinformatics'95, M. Candev (Ed.), DATECS Publishing, Sofia, 1995.

Inconsistency Problems in the Information Systems Integration[16]

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A **data warehouse** (DW) is a *subject oriented*, **integrated**, *time variant, collection of data* that is used primarily to aid organizational decision making. The MetaGroup Survey exhibited that while in the year 1993 only 5% of Fortune 1000 Companies had DW Projects, in the year 1994 it was already 90%. The DW projects enable users to more easily perform very popular and much demanded **data mining** (*knowledge discovery*) which naturally presents new system requirements (usually : 1000 – 10 000 MIPS, 1 000 – 10 000 IO/s, 50 GB – 5 TB) in the field of the commercial processing.

Multiple databases may be used to store **knowledge** (obtained by totally different *information sources*) about the same slice of reality. Naturally one may try to get the complex information as a *result* of **integrating** knowledge from these different databases. And, also naturally, one is immediately faced with the *problems* of **inconsistency** [1] (in the sense of classical logic), which are amplified if one admits *temporal information* (**temporal logic**) and *uncertainty* (**fuzzy logic** and **possibilistic logic**). We concentrate on he following problems:

- the integration of the data/knowledge bases with different priorities (hierarchically organized, centralized or decentralized, federated etc.)
- the temporal inconsistency (its classification and resolution)
- the integration of the data/knowledge bases with different kinds of fuzziness (vagueness, degree of truth) and of uncertainty (probabilistic, possibilistic, degree of belief).

While in the case of the first two problems, the formalism of the classical (predicate) logic ought to be sufficient, the last problem requires application of some variants of the many-valued logics. We present a general framework within which these problems can be treated and give generic solutions for some well-defined classes of problems.

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[16]This work was supported by ICS AS CR.
For an extended abstract see Lecture Notes on Biomathematics and Bioinformatics'95, M. Candev (Ed.), DATECS Publishing, Sofia, 1995.

Some Aspects of Age-Dependent Population Dynamics

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The classical Gurtin-MacCamy model involving the McKendrick-Von Foerster partial differential equation is considered. Some simplification is suggested, and applications are shown for several specific species: squirrels, bats and voles. The main technique is to reduce the model to a system of ordinary differential equations, which are far more tractable than the original classical model.

Mathematical Modelling of Anaerobic Digestion Process in CSTR Mode

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Anaerobic digestion is one of the most perspective treatment processes in the last few decades, mainly because of its high productivity. A lot of models dealing with different aspects of the process are known, and all of them are based on multiple stage shemes of description, which involved respectively hydrolisis, acidification and methanization (or parts of them).

Due to the very complex nature of this process and the lach of any reliable sensors for on-line measuring of state variables the study and control of such a process is very difficult yet. That is why, based on some of his last works in this paper the author presents an approach for modelling of one easy measured and controlable in real time variable as pH, which is one of the most important factors for normal running of the process.

Different models, derived by the using of the simplest one and two stage sheme presentation of the anaerobic digestion in CSTR mode, which is the most broadly for industrial purposes, are proposed. Discussions of both applicability and limitations of these new models are also presented. Some of the models are simulated by using well-known RK methods for numeric integrations. The real data for identification in case of Hook & Jeevs gradient method and the criterium of the square error integration are also used.

Genetic Networks and Evolution — the Impact of Nonlinearity[17]

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The basic mechanism of gene control at the level of transcription is realised by protein/DNA interactions. These interactions are concentration-dependent and obey the law of mass action. A number of DNA-binding proteins have been described modifying the activity of a gene. These trans-factors bind to specific DNA sequences designated as cis elements, thus forming regulatory complexes. Due to such interactions the genes are integrated into networks of mutual interrelations. A genetic network is formed due to the presence of either physically linked genes with one common control cis element (**operons**) or to a cis element common to several physically separated genes (**regulons**). The genetic network of such a set of genes may be represented by a matrix $\parallel \sigma_{i,j} \parallel$ fixing the interaction between the i-th trans factor and the j-th cis element. Using a Jacob-Monod repression circuit and applying the law of mass action, a non-linear differential equation for the synthesis of mRNA is obtained. It was found later that trans factors may be both repressors and activators. An equation common to both repressors and activators can be derived. The synthesis of mRNA, the programming of ribosomes and the synthesis of the trans protein can be described by a nonlinear system of three differential equations. The system is stable within some regions of the parameter space, while transitions outside these regions show abrupt changes leading either to a chaotic unstable state or to a new, quite different, steady state. This shows that the parameters of the matrix defining a genetic network are of primary importance for the behaviour of the cellular system by fixing its steady state. Thus, the matrix of the genetic network represents an additional information as important for a given species, as the information in the coding sequences of DNA. A number of parameters may play a crucial role: the equilibrium constants, threshold concentrations, supercoil density of chromatin fibers, half-life time of mRNAs etc. The nonlinearity of the system segregates the parameter space into many zones of stability and zones of unstable chaotic behaviour — a zone of lethality for a living system. These considerations imply that small gradual *Darwinian* changes in the parameters of a living species are the driving mechanism providing changes for the natural selection. As long as these changes remain within the zones of stability, they will only slightly modify a species, a situation which may remain for a long period of stability or *stasis*. However, when the parameters reach the border of the stability zone, extremely small changes will lead either to instability (death) or to the transition into a new stability zone — the abrupt emergence of a new species and a new period of stasis.

[17]For an extended abstract see Lecture Notes on Biomathematics and Bioinformatics'95, M. Candev (Ed.), DATECS Publishing, Sofia, 1995.

Experiments with the Danish Eulerian Model[18]

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The two-dimensional Danish Eulerian Model has been developed during the 80'ies. More than 70 chemical reactions (some of them photochemical) are involved in the model. The space domain of the model covers the whole of Europe. It has been discretized by using a (32×32) equidistant spatial grid. The concentrations and the species calculated by the model were compared both with measurements taken over land and with measurements taken over sea. The model has also been run by using finer grids; as, for example, a (96×96) grid. The experiments indicated that in general the model calculates rather reliable results. However, it is also clear that the results might be improved if a three-dimensional version of the model is developed. Three-dimensional air pollution models are very time-consuming. Therefore the development of a reliable three-dimensional version of an air pollution model is a very challenging task. The efforts to solve some of the numerical problems arising during the development of a large three-dimensional air pollution model (with non-linear chemical reactions) will be discussed in this paper.

[18]For the full version of this paper see Lecture Notes on Biomathematics and Bioinformatics'95, M. Candev (Ed.), DATECS Publishing, Sofia, 1995.

Relationship Between Emission Sources and High Ozone Concentrations

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"Elevated ozone in rural areas is believed responsible for crop losses of 1 to 2 billion dollars annually".

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While the ozone layer in the stratosphere is shielding the Earth's surface from radioactivity, high ozone concentrations in the troposphere have damaging effects on plants, animals and humans, when they exceed certain critical levels. This is why it is necessary to resolve successfully three tasks: (i) to determine in a sufficiently accurate way the critical levels of the ozone concentrations, (ii) to reduce the ozone concentrations to the critical levels and (iii) to develop reliable and robust control strategies by which the ozone concentrations can be kept under the critical levels. Both the second and the third tasks are very expensive. Therefore, it is necessary to reduce (as much as possible) the economical costs of these actions. Mathematical models can be used in the search of an optimal solution of the tasks listed above.

A mathematical model for studying air pollution levels in Europe (the Danish Eulerian Model, [1]) will be shortly disscussed. The model consists of a system of 35 partial differential equations and leads to huge computational tasks, when it is handled numerically. Therefore it is necessary to use big modern high-speed computers (with vector and/or parallel capabilities).

The Danish Eulerian Model has been used to run various scenarios in order to study some of the relationships between emission sources in Europe and high ozone concentrations. Modern visualization techniques have been applied to illustrate better the effects of different emission reductions used in the scenarios on the ozone concentrations and to draw some conclusions.

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Key words: High concentrations, damaging effects, critical levels, control strategierrs, mathematical models, high-speed computers, visualization.

Growth Modeling of Yeast Citric Acid Producer Using Interval Analysis[19]

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It is well known the ability of some microorganisms to produce citric acid at external defined conditions. The yeast growth of the population in special nutrient media for this acid production is considered. By this reason the growth is not limited by the substrate. The biomass accumulation depends just on cell abilities. This phenomenon could be described by one differential equation:

$$\frac{dx}{dt} = k_1 \left(1 - \frac{x}{k_x}\right) x, \tag{7}$$

where x is the biomass concentration, and k_1 and k_x are kinetic coefficients.

In cause of insufficient reproducibility of the biological experiment, interval data for biomass concentration are used. The parameters k_1 and k_x are estimated using interval analysis in the following sense. It is sought an approximation of the set of all values of the parameters which, when substituted in (7), produce a solution x lying within the interval experimental data.

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FOUNDATION EVRIKA

EVRIKA foundation was established to promote the development of youth technical and scientific creativity and the dissemination of technical scientific and economic knowledge; to help young people adopt technical and scientific knowledge and skills and encourage youth economic enterprise; to assist education, specialization and training, as well as for other non profit purposes.

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Geographic and Historical Data, Social Events

BIOMATH-95 offers you the opportunity to learn about Bulgaria, Sofia and its surroundings. The Conference site is a nice hotel in the mount Vitosha situated at about 1400 m above the see level. The hotel can be reached by car in 30 min from the center of Sofia. It is a rest house, belonging to a big electrical plant. The name of the hotel is ELPROM-TRAFO (E-T).

Sofia is the capital of Bulgaria, its largest and most active town and the country's main economic and cultural centre. The position of the town is outstandingly beautiful. It stands at a height of ca 550 m (1800 feet) at the foot of Mount Vitosha, whose lower slopes are already being invaded by the spreading south-western suburbs. Vitosha gives Sofia not only its splendid scenery, but also its bracing air and pure water.

Vitosha is a beloved place for tourism for the inhabitants of Sofia. The famous Bulgarian writers, Ivan Vasov and Aleko Konstantinov, often climbed Vitosha. Aleko Konstantinov (literature pseudonim: Stastlivetsa – The Lucky Man) organized in 1895 the first group of tourists from Sofia to climb the Black Peack. The hut Aleko and the hotel Stastlivetsa are given his name, resp. pseudonim. Seldom biological plants can be found on Vitosha, that are unique for the European flora. Such is the famous Vitosha tulp, a beautiful jellow flower. "Vitosha tulp" is also the name of a long ski track in the region of Aleko hut. Exellent ski facilities are available almost 5 months in the year.

Dragalevci is the most convenient starting point for climbing the Cherni Vrah (Black Peack (7513 feet, 2290 m) the highets point of mount Vitosha. Vistosha has an almost conical form with a diameter of about 20 km. The area has been inhabited since most remote antiquity. It was named Scomius or Scombrus from the anciets — meaning a steep mountain. The name Vitosha is of tracien origin and means "with two peaks" In the Roman time Vitosha was covered with numerous fortresses. A characteristic feature of Vitosha are the moraines left behind by an ancient glacier, now forming a river of large boulders which runs down the mountain from its summit almost to its base. Gold-washing was formerly practised here: hence the name Golden Bridge of a nice part of Vitosha with the ending of a huge stone river strting in the region of peack Black

Rock (Cherna Skala). From Dragalevci there is a lift, which first stage finishes near hotel E-T, and its second part finishes near hotel Stastlivetsa.

Dragalervci Monastery is the oldest monastery in Bulgaria. It was built in the reign of Tsar Ivan Alexander (1331–71) The only part of the original structure which survives is the church, which is decorated with fine 15th and 17th century frescoes.

The Vitosha's Golden Bridge region, mentiond above, is easily reached from the town of Boyana. Boyana is famous with its Boyana Church.

The Boyana Church was built in 1250 by Sevastokrator Katoljan, who ruled over the teritory in the Sofia area. The frescoes in the church belong to different periods, but the most interesting are those painted in 1259. The unknown artist –**"Bulgarian Giotto"**, responsible for these paintings can stand comparison with the greatest masters of the Italian Renaissance. To measure his achievements we need only reflect that these frescoes were painted seven years before the appearance of the first works of Giotto, one of the earliest masters of the Italian Renaissance. The spectator is struck at once by the live lines of the figures, which have broken completely free of the hieratic attitudes of byzantine art. The master of Bojana had taken the step in the history of painting which marks the beginning of a new age.

During the conference an excursion is planned to the town of Koprivstitsa, situated about 100 km in direction east from Sofia.

Koprivstica is a small town, huddling in the highest-lying valley of the Sredna Gora Mountains, and could hardly be compared to the remaining settlements in the country. Koprivshtitsa is a unique museum under open skies, an architectural and historic reserve. It still preserves its original National Revival period (18th-19th c.) appearance and hundreds of houses have been declared architectural monuments. Arranged chiefly in groups, these old buildings, together with the bridges, fountains and high stone walls, form pictures and unusual architectural ensemble. There are also many historic sights. The native places of outstanding revolutionaries, public figures, writers and poets are now museums.

The excursion to the town of Koprivstica will give you an impression of the unspoilt beauty of the Bulgarian countryside. Koprivstica was founded by boyars who left Tarnovo after the fall of the second Bulgarian kingdom. Although three times damaged by fire (in 1793, 1804 and 1810), the town quickly recovered after each ordeal, and in the 19th century achieved a

high level of artistic development. Koprivstica has preserved its oldworld character and is now officially recognised as a unique museum under open skies, an architectural and historic reserve. It still preserves its original National Revival period (18th-19th c.) appearance and hundreds of houses have been declared architectural monuments Arranged chiefly in groups, these old buildings, togeder with the bridges, fountains and high stone walls, form pictures and unusual architectural ensemble. There are also many historic sights. The native places of outstanding revolutionaries, public figures, writers and poets are now museums.

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