EDITORIAL

Dear Society members, dear friends of mathematical and theoretical biology.

This is the ***10th edition*** of the "Communications in Mathematical and Theoretical Biology" after its first appearance January 2000. Before it carried the name "Biomathematics Newsletter" and brought 19 editions from June 1988 on – this is exactly 20 years ago and three years earlier as the foundation of our Society in 1991. We hope that the meanwhile performed edition of only one issue per year has been accepted by the reader, because any short term announcements and monthly information can better be communicated via our website www.esmtb.com, where since more than one year the ***ESMTB InfoLetter*** has been established, containing up-to-date information about forthcoming conferences, workshops, schools and open positions.

➔ You can post information in the InfoLetter by sending the relevant text to info@esmtb.org. Please, use this opportunity to increase communication within our Society.

With this issue we are going to present, for the first time, the outcome of the newly offered annual ***Reinhart Heinrich Award*** for the best doctoral thesis from any area of Mathematical or Theoretical Biology (see the box to the left). We are happy to announce, that the Awarding Committee this time has selected two prize winners (ex-aequo), namely ***Barbara Boldin*** and ***Antonio Politi*** (see the laudations on them and the abstracts of the 3 best candidates from *page 10* on). We decided not to print the extended abstracts of all the other 8 applicants within in this issue, since we already had 3 earlier contributions for the section *Further Recent Thesis* (see *page 21*), but we want to thank them for their participation in this first round, hoping that we can expect a similar response for the second round (applications to be sent until ***30th September 2008***).

This summer we hope to have many of us meeting at the triennial *European Conference on Mathematical and Theoretical Biology* ***ECMTB'08*** between 29th June and 4th July in Edinburgh (whose staircase-logo we chose for the cover page – for further details, including the invitation to the ***General Assembly of ESMTB***, see *pages 4-5*). In particular, there will be the opportunity to present candidates for the five new Board Members that have to be elected within this year for the next period 2009-2012. Finally, let us mention the call for Summer School organizers (*page 3*) and the list of contributions on *Perspectives of Theoretical and Mathematical Biology* that have been published in our official Society Journal *JMB* during the last two years (see *page 4*).

For the Editorial Board,
Wolfgang Alt (president of ESMTB)

****

The **closing date** for submissions to the next issue of the Communications *(ECMTB # 11)* has been postponed to **December 31th, 2008.** Please send, preferably by e-mail, any information, reports or other material to the managing editor

Wolfgang Alt*, Theoretische Biologie, IZMB, Universität Bonn, Kirschallee 1-3, D-53115 Bonn, Germany*
wolf.alt@uni-bonn.de

Those who are interested in the Society or want to have more information, please visit our Society website at
www.esmtb.org
The page can be used by members to pay their fee, or, by not-yet-members to register. Thanks!

CALL FOR MEMBERSHIP FEES 2008

http://www.esmtb.org

ESMTB membership includes automatic and free subscription to the **print edition** of the
Journal of Mathematical Biology
-- The official journal of the Society --

Please register at www.esmtb.org and send your payment of the required annual fee for 2008 by bank draft transfer or electronically (PayPal).

Membership Fees per year**:**

a. The **Individual Annual Membership Fee** is:

- 50 Euro (full member)
- 40 Euro (ISTMB, JSMB, NVTB, SFBT, SMB full member)
- 25 Euro (student, developing country or Eastern European member)
- 20 Euro (student SMB member)

b. The **Institutional Annual Membership Fee** is:

- 200 Euro

Details for bank draft transfer:
Bank: Dresdner Bank
Account Name: ESMTB
Account Number: 04 076 801 01
Bank Code No.: 850 800 00
SWIFT-BIC: DRES DD FF
IBAN: DE 18 85080000 0407680101
Bank Address:
Dresdner Bank, Dr. Kuelz-Ring 10
D-01067 Dresden, Germany

Further information:
Dr. Andreas Deutsch, ESMTB treasurer
Center for Information Services and High Performance Computing
Dresden University of Technology

Andreas.Deutsch@tu-dresden.de

SOCIETY NEWS

REQUEST FOR SUMMER SCHOOL ORGANIZERS

To pursue the purpose of the European Society of Mathematical and Theoretical Biology (ESMTB), promoting theoretical approaches and mathematical tools in biology and medicine, one of the most successful actions has been the organization of summer schools. *European Summer Schools on Mathematical and Theoretical Biology* have been organized by various groups in France, Italy, Spain, Austria and other European countries since the foundation of our Society in 1991. They have become a well-recognized event within the growing interdisciplinary community of young researchers and students in mathematics applied to the biosciences. The various themes of these Schools have covered quite a large range of modelling and analysis in relevant fields of modern biology such as ecology, cell biology, physiology, and molecular biology, as well as in medical applications (*see also pages 27-29*).

To go on with the profitable task of summer school organization the ESMTB requests the participation of local groups of our community willing to carry out one, or a series, of these events. The applicants are expected to take care by themselves of local organization while they will be strongly supported by the Society in everything else along the lines described in the following points:

- **Organizational training:** A representative of the applicant group will be invited to participate in a previous summer school to interact with the organizers and so getting experienced enough to manage all different organizational aspects.
- **Subject choice:** The Society is sounding out our community to get a list of hot topics worth including in summer schools at the corresponding level.
- **Scientific Committee composition:** The Society will support the appointment of prominent researchers in the school topic.
- **Lecturers' pool composition:** The Society will support the appointment of adequate teachers.
- **Financial support:** The Society will help in getting funding from European programs and also it will provide some direct funding.
- **Promotion of the events:** The Society will use its entire means to advertise the events among young members of our community.

Interested groups are encouraged to contact us sending a message to any one of the ESMTB Board members.

Rafael Bravo de la Parra,
Madrid, Spain
rafael.bravo@uah.es

~~~~~~

AFRICAN SOCIETY FOR BIOMATHEMATICS (ASB)

The African Society for Biomathematics was formed on Friday 4, January 2008, during a special session of the *Marrakesh International Conference and Workshop on Mathematical Biology*. We adopted a constitution, formed a steering committee, and committed ourselves to an *inaugural conference in Cape Town starting the 27th of January 2009*. Elections for our first president and other officers of the ASB will take place at this conference. Interested persons should visit the website at
http://euromedbiomath.free.fr/asb/

Henri Laurie
University of Cape Town, South Africa
on behalf of the Steering Committee

In the mean time, the Steering and the Advisory Committee have been formed. For the latter there are two ESMTB members in duty:
Pierre Auger (IRD Bondy, France)
Odo Diekmann (Utrecht Univ., The Netherlands)
~~~~~~

ESMTB Financial Support Offer:
Travels to Mathematical/
Theoretical Biology Meetings

2007 was the start of a new ESMTB initiative. ESMTB was able to financially support meeting participations of 12 ESMTB members with an amount of 500 EUR each. Applications came from ESMTB members representing seven different countries (Russia: 3, UK: 3, Germany: 2, France: 1, Spain: 1, Turkey: 1, India: 1). This successful initiative will continue in 2008.

Application details will be available soon and published on the society website www.esmtb.org.

Andreas Deutsch
ESMTB treasurer
Dresden, Germany

~~~~~~

Perspectives in Mathematical and Theoretical Biology
List of articles in our official journal, the Journal of Mathematical Biology, that are devoted specifically to the scopes of ESMTB

Luigi Preziosi:
Hybrid and multiscale modeling.
JMB 53(6): 977-8 (2006)
Hans Westerhoff:
Mathematical and theoretical biology for systems biology and then - *vice versa*
JMB 54(1): 147-50 (2007)
Steve Coombes:
Mathematical Neuroscience
JMB 54(2): 305-7 (2007)
Miguel Herrero:
On the role of mathematics in biology
JMB 54(6): 887-9 (2007)
Bindi Brook and Sarah Waters:
Mathematical challenges in integrative physiology *JMB* 55 (in press, 2008)

Peter Jagers:
A plea for stochastic population dynamics
JMB (to be submitted)

Helen Byrne, Nottingham, managing editor

ECMTB'08:
European Conference on Mathematical and Theoretical Biology 2008
Edinburgh (Scotland) 29 June – 4 July 2008

The triennial meeting of the ESMTB is now a well-established fixture on the Mathematical Biology International Conference Circuit. Previous meetings have been held in Alpe-D'Huez, Lyons, Heidelberg, Amsterdam, Milan and Dresden. Following in the path of these historical cities, this year's meeting will take place in Edinburgh, capital city of Scotland, where a warm welcome awaits all participants.

The Scientific Themes of the meeting include Cell-cell interaction and tissue engineering, Developmental biology, Systems biology & metabolic engineering, Mathematics for genomics and proteomics, Complex biological networks, Biosimulation in medicine, Cancer Modelling, Epidemiology, Evolution, Ecology, Neuronal systems and behaviour and Biological environment and Climate Change. Once again, in line with previous meetings, the plenary speakers - Ellen Baake, Vincenzo Capasso, Lisa Fauci, Neil Ferguson, Mats Gyllenberg, Sir David Lane, Franziska Michor, Mayan Mimura, Hans Othmer, Luigi Preziosi, James Sneyd, Frank Tobin, John Tyson - promise a wide range of interesting and exciting state-of-the-art talks.

The minisymposium call for proposals has led to the acceptance of 40 minisymposia and already over 160 participants have registered for what promises to be a very dynamic and stimulating meeting. The deadline for submission of contributed talk and poster abstracts is coming up fast - *Friday 14th March* - and the organisers and Scientific Committee Members are expecting a busy few weeks refereeing all the proposals before the list of accepted talks is published in late April.
A wealth of mathematical biology research and a warm Scottish welcome (perhaps not weather!) awaits everyone in Edinburgh in July!

Cead Mille Failte!
One Hundred Thousand Welcomes!
http://www.maths.dundee.ac.uk/ecmtb08
ECMTB08 Local Organising Committee
~~~~~~

Invitation to all Society members for the GENERAL ASSEMBLY of ESMTB
organized during the Edinburgh Conference
on ***Tuesday, 1st July 2008, 18:15 h***

TOPICS (preliminary):

- Report by the president
- Presenting the winners of the first Reinhart Heinrich Doctoral Thesis Award 2007
- Report by the treasurer
- Discussion of prominent issues
- Presentation of candidates for the election of 5 new Board members (for the period 2009-2012)

We – already from now on – are collecting proposals of new ***candidates for the Board!***

Any member of the Society can propose a candidate by just sending name and country of the suggested ESMTB member (plus the support by at least one other member) to the president: Wolfgang Alt (wolf.alt@uni-bonn.de)

In case you are not at the Edinburgh Conference, send the candidate proposal until ***25th June 2008*** please.

Minutes of the ESMTB Board Meeting

Torino, 2 March 2007

Meeting starts at 10:15 am.

Present: Wolfgang Alt (WA, chair), Carlos Braumann (CB), Rafael Bravo de la Parra (RB), Andreas Deutsch (AD), Christine Jacob (CJ), Eva Kisdi (EK; minutes), Luigi Preziosi (LP), Hans Westerhoff (HW), Oleg Demin (non-voting counsellor).
Absent with apology: Helen Byrne (HB), Jean-Christophe Poggiale (JP).

Welcome and Adoption of agenda
WA welcomes *Oleg Demin* to the Board, who is attending for the first time as East-European counsellor. The proposed agenda is accepted.

1. Report by the President and review of Board responsibilities

WA reports on the letter received from Ari Laptev, president of the European Mathematical Society (EMS), enquiring about possible links between ESMTB and EMS (see the full text of the letter in Communications #9). ESMTB is an institutional member of EMS and there is certainly space for joint conferences and other activities. WA will reply describing our Society's activities, suggesting that ESMTB organises a symposium at the next Congress of EMS, inviting EMS to participate in our upcoming Conference in Edinburgh, and inviting further suggestions for joint actions.

Reviewing Board responsibilities, WA urges to pay more efforts to supporting summer/winter schools (RB takes lead) and to matters of education (JP, CJ). A database of mathematical biology programs and course modules at the Master level should be made available on the Society's website and input of such information invited via the InfoLetter. Outreach to other scientific societies should be improved (CJ).

2. Report by the Treasurer

Financial data
According to the balance sheet of 31 December 2006, the Society's bank account has 5,290 euros; this does not contain the assets of the Dresden 2005 Conference and a sum of about 5,000 euros on the Society's PayPal account. All revenues are from membership fees, which total 8,325 euros. The regular expenditures include the Communications, flyer, JMB subscription for members, membership fees in ICIAM and EMS, and domain registration for www.esmtb.org (these total 9,064 euros in 2006). In addition, the Society supported the Sarajevo Summer School on Mathematical Techniques in Modelling Physiological Systems (September 10-22, 2006) with 2,000 euros. The Society paid tribute to Prof. Reinhart Heinrich, who passed away unexpectedly in October 2006 (obituary in Communications #9), with a flower arrangement and inscription (200 euros).

Estimated revenues for 2007 are 9,000-10,000 euros, whereas regular expenditures (as listed above) will be 5,926 euros (the main difference compared to 2006 is a decrease in the amount paid for JMB to Springer). The Board has already committed to support the FEBS Advanced Course on Systems Biology and the CPMD2 conference with a minimum of 1,000 euros each (the actual support depends on the number of new members joining the Society via these events), and the Marie Curie Training Series "Mathematical Modeling of Human Physiological Systems with Biomedical Applications" with 1,500 euros. As new initiatives, travel support and a new prize for PhD theses will be announced this year (see below).

It is foreseen that the membership fees, which have been unchanged since 2002, will have to increase in the foreseeable future, but the positive balance permits delaying this decision to be effective in 2009 at the earliest (5 votes in favour, none against). RB proposes introducing a special institutional membership for developing countries.

Membership development
The Society's membership is consolidating, ESMTB had 200 paying members in 2006.

Travel grant
ESMTB introduces a travel grant to give partial support to Society members (especially student members) who present their work at mathematical biology meetings. In the first year (2007), up to ten persons will be supported with a maximum of 500 euros each. The call for applications will appear in the InfoLetter. Applications are to be sent to AD by 31 May 2007. The Board deputes AD and RB to make the decisions.

3. Journal of Mathematical Biology

Special issues
Three special issues of the Journal of Mathematical Biology (JMB) covering computational biology will appear in 2007-2008 (Computational molecular biology, edited by P. Clote, finalized in spring 2007, to appear in 2007; Computational oncology, edited by M. Chaplain, submission deadline in March 2007, to appear in 2008; Computational cell biology, edited by WA, AD and LP, submission deadline in June 2007, to appear in 2008). HW proposes a further special issue on computational biology of rhythms (cell cycle etc). Special issues could focus on the computational aspects of physiology, sequence analysis, neurology, immunology, image analysis, etc. Further proposals can be sent to WA.

Perspectives in Mathematical and Theoretical Biology
The Perspectives series has started with the first piece published in the 2006 December issue of JMB as part of the 2-page material provided by ESMTB. These contributions are edited by HB. At least until the Perspectives have become established with a clear identity, drafts are circulated among board members to establish whether they are appropriate; board members have 2 weeks to respond. HB will develop guidelines for authors. A short invitation for contributions will be placed in JMB, and the Board also continues to invite authors.

Mission Statement
The revised Mission Statement for the official journal of ESMTB, namely of JMB, is final as printed in Communications #9 (p. 10).

Other matters related to JMB
New editors-in-Chiefs will take office from 2008 and from 2009, replacing Alan Hastings and Odo Diekmann, respectively. The Board discusses possible candidates and also suggestions for new editors. HW proposes that JMB makes use of Springer's online submission handling system in order to avoid occasional delays in manuscript handling.

4. The Society's webpage, the InfoLetter, and the Communications

AD is in charge of the website and the InfoLetter. The InfoLetter launched in August 2006 and is emailed monthly to all paying members. It announces news including conferences, workshops and schools as well as

on open positions. Announcements are to be sent to info@esmtb.org. The website has improved information and help facilities and now also offers all issues of the InfoLetter for download. The next step of website development will be to introduce a troubleshooting system.

WA reports on the status of the Communications. As announcements are now quickly published via the InfoLetter, the Communications can expand its coverage on past activities and should keep its journals & books section; it hopes to receive more current theses as well, also in connection with the prize announced (see below). Currently, the Communications are printed in 300 copies and mailed to all paying members. The Board and the General Assembly at the next ECMTB conference may discuss whether we continue with the print publication.

5. The Reinhart Heinrich Doctoral Thesis Award

The Society announces the Reinhart Heinrich Doctoral Thesis Award by ESMTB to reward the best PhD theses in mathematical and theoretical biology. The prize will be awarded annually and will include a diploma, an invited lecture at the European Conference on Mathematical and Theoretical Biology, an annual membership of the Society and a travel grant. The detailed description and call for applications will be worked out and advertised by AD, WA and HW.

6. ECMTB'08 in Edinburgh

The 7th European Conference on Mathematical and Theoretical Biology will be held in Edinburgh, 29 June - 4 July 2008 for a maximum of 520 participants. Main organiser Mark Chaplain informs the Board by email on the conference preparations. The Board proposes 14 members to the scientific committee in addition to the 7 British members selected by Chaplain, and draws up a list of themes as key topics of the conference. The structure of the conference will be similar to the previous ECMTB conferences with plenary talks (mostly settled by Chaplain already), minisymposia (call will be announced in early autumn), contributed sessions, and posters.

The Board votes that conference proceedings should be published (6 yes, 0 no and 2 abstentions) along the lines proposed earlier to improve quality (see the minutes of the Amsterdam board meeting in Communications #9). WA, AD, CJ, EK and HW will be responsible for the proceedings.

7. East European affairs

Oleg Demin (Russia, non-voting counsellor) shares his insights on why East European membership and participation has declined since the early nineties: the economic situation became more difficult, there are language problems, and Russian scientists publish often in Russian journals. Travel grants and possibilities for short presentations could improve participation at scientific conferences. Demin is asked to write a survey of mathematical biology research in the countries of the former Soviet Union for the Communications, and a short version for the Perspectives series in JMB.

8. EU 7th Framework Programme and support for conferences and summer schools

LP reports on the possible opportunities in the 7FP. Unfortunately, there seems to be no funds to support large conferences or summer schools outside initial training networks (the latter must include employment of young scientists). Notwithstanding the financial difficulties, WA urges that the Board should help to organise more summer schools. RB will look for other opportunities, and the board members responsible for schools and education (WA, RB, CJ, JP, HW) will possibly hold a dedicated meeting in the autumn of this year.

9. Diverse

The next board meeting is scheduled for late February - early March 2008 in Évora, Portugal. The meeting ends at 16:55.

Eva Kisdi
Secretary of ESMTB

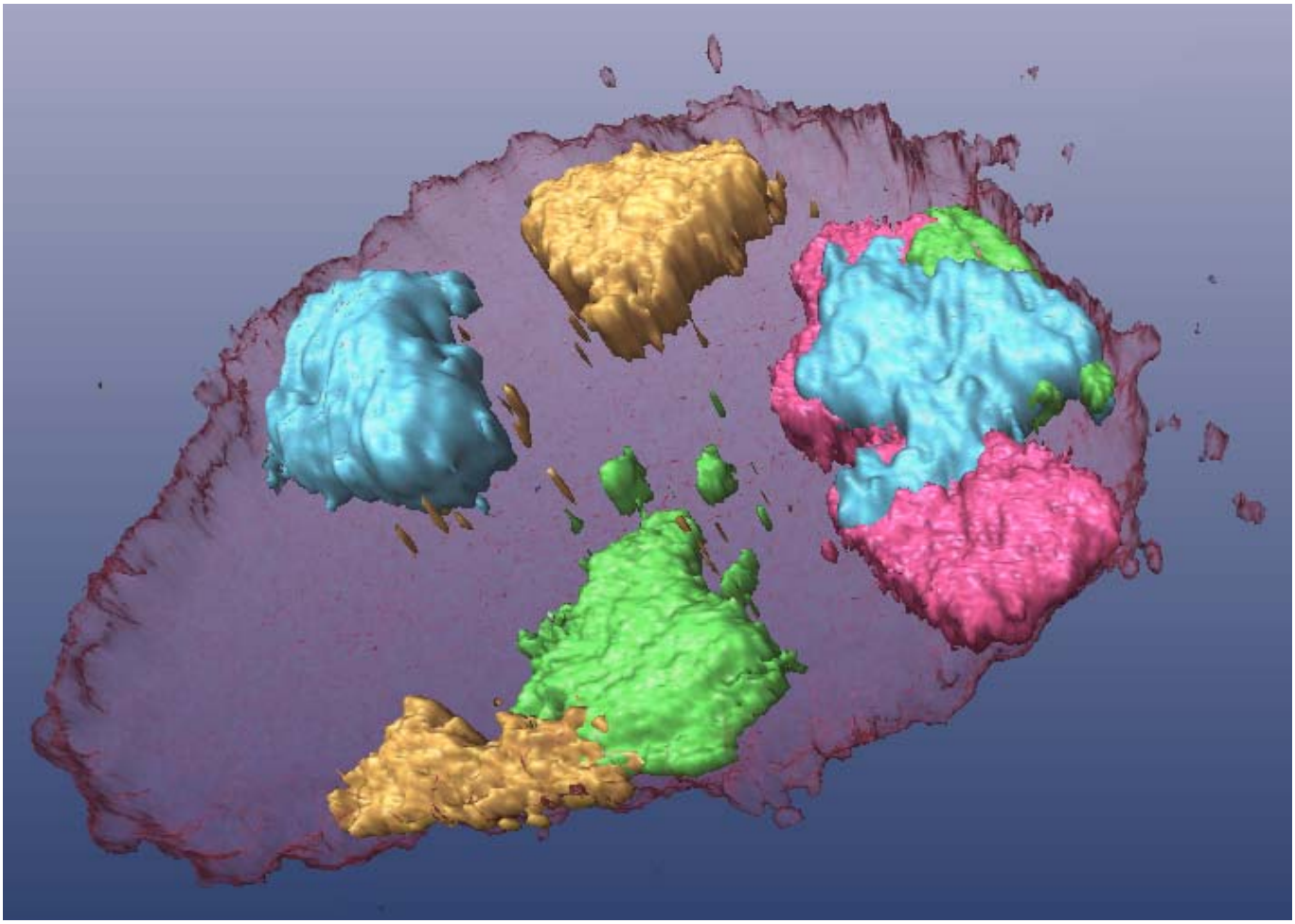
Research Group "Biomedical Computer Vision" University of Heidelberg

BIOQUANT, IPMB
Dept. Bioinformatics & Functional Genomics
German Cancer Research Center (DKFZ)
Heidelberg, Germany

The research group „Biomedical Computer Vision" (BMCV) headed by *Karl Rohr* is part of the Department for Bioinformatics & Functional Genomics at the University of Heidelberg and the DKFZ (director: *Roland Eils*). The group develops methods and algorithms for computer-based analysis of biological and medical images, in particular, cell microscopy images and medical tomographic images. One main aim is to derive quantitative information about the shape, motion, and function of cellular as well as subcellular structures. The current main research topics are image registration, tracking and classification, as well as segmentation and quantification.

Image Registration

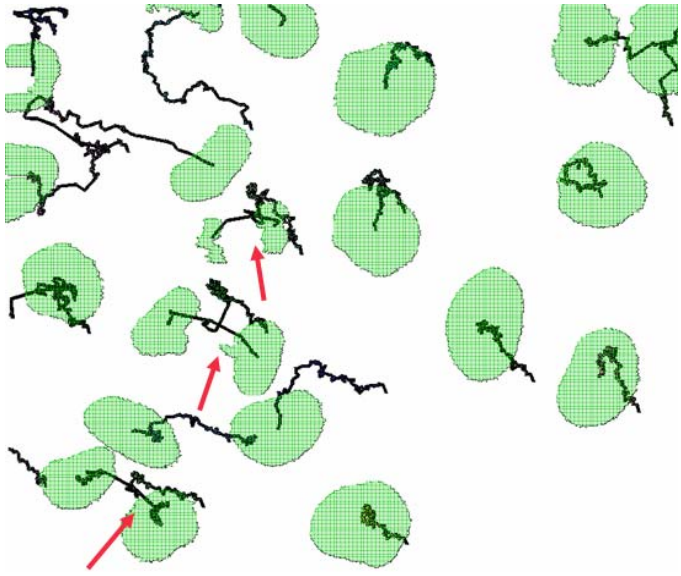
Accurate quantification of biomedical images often requires to geometrically align the data. The task of finding an optimal geometric transformation between corresponding image data is known as image registration and generally one has to use non-rigid or elastic deformation models. We have developed elastic registration approaches which can be applied to different application domains. The algorithms either use point features (landmarks), intensity information, or a combination of both information. We have successfully applied our approaches to medical tomographic images, gel electrophoresis images, and cell microscopy images. In the latter case, we have considered the registration of multi-channel 3D confocal images of different cells for



shape normalization as well as the registration of 4D (3D+t) images of moving cells for accurate computation of protein particle movement. The work is carried out in cooperation with experimentally working groups at LMU Munich, the University of Amsterdam (SILS), the Curie Institute (Paris), and Cold Spring Harbor Laboratory (NY, USA). Funding has been provided within the EU project 3DGenome and the DFG project ELASTIR.

Tracking and Classification

Another field of study in our group is the analysis of 2D and 3D multi-cell time-lapse images generated by high-throughput RNAi experiments with the aim to understand the process of mitosis (cell division). Based on confocal fluorescence microscopy cell-array images the task is to determine the influence of genes on cell division and thus to identify gene function. To analyze these large-scale cell phenotype screens we have developed an automated approach for segmentation, tracking, and classification of cell nuclei into different mitotic phases. This enables to automatically determine the duration of cell cycle phases. In particular, our tracking algorithm is able to cope with splitting cells. Classification of cells is based on a support vector machine classifier. The work is carried out in collaboration with the EMBL Heidelberg within the EU project MitoCheck. Beyond that, we have also developed automatic approaches for the tracking of virus particles in cooperation with the Dept. of Virology at the University of Heidelberg.



Segmentation and Quantification

We are also investigating approaches for the segmentation and quantification of structures in 2D and 3D biomedical images. In particular, we are studying model-based and differential approaches. Examples for applications are the quantification of vessels and landmarks in medical images, the quantification of spots in gel electrophoresis images, and the quantification of cellular as well as subcellular structures in microscopy images. We collaborate with groups at the DKFZ and the newly established BIOQUANT center. Recent work includes the segmentation and quantification of virus-infected cells in images from siRNA high-throughput screens with the aim to identify relevant cellular factors for virus replication. This work is carried out within the BMBF (FORSYS) project VIROQUANT in cooperation with the Dept. of Molecular Virology at the University of Heidelberg.

For further information, please visit
http://www.dkfz.de/tbi/projects/bmcv

Karl Rohr
k.rohr@dkfz.de

Reinhart Heinrich Doctoral Thesis Award 2007

In 2007, the year after the sudden death of our recognized colleague and teacher Reinhart Heinrich (see ECMTB 9: 3-4, 2007) the ESMTB announced for the first time the Reinhart Heinrich Doctoral Thesis Award to be presented annually to the *best doctoral thesis from any area of Mathematical and Theoretical Biology*. Until the required date, 30th September 2007, the awarding committee obtained the applications by ***11 young European scientists*** who had recently finished their PhD. Here we present the final

Decision by the Awarding Committee

The committee is impressed by the quality of the received applications. The feeling is that the prize has attracted the right people. Just looking at the submissions shows that today concepts of mathematical biology are applied to a multitude of fascinating biological problems. Most of the eleven applicants have received multiple awards and already have a remarkable list of publications in high-ranked journals. The applicants present a range of research topics that are so broad, that it seems to be difficult to compare them definitively.

Judging from the submitted extended abstracts the committee selected a **shortlist of 3 best candidates**, which were *Barbara Boldin (Amsterdam)*, *Tiago Paixao (Lissabon)* and *Antonio Politi (Berlin)*. After looking at their full theses, the committee found out that the Doctoral Thesis Prize 2007 should be awarded ex-aequo twice to

- ***Barbara Boldin*** and
- ***Antonio Politi***.

with ***Tiago Paixao*** on the third place.

For both prize winners there is a laudation formulated. Afterwards, the **extended abstracts** of all three best candidates are printed. Subsequently, under the section *Recent Theses* some more extended abstracts are published, which were sent to the editors independently of the Reinhart Heinrich Award. Information for the next round can be found on the inside cover page and the Society Website www.esmtb.org.

Laudatio for *Baraba Boldin*

Barbara Boldin, born 1976 in Slovenia, got her Diploma (2000) and Master in Mathematics (2003) from the Faculty of Mathematics and Physics in Ljubljana. After changing to the Department of Mathematics at the University of Utrecht (The Netherlands) she finished 2007 her PhD under the supervision of *Odo Diekmann* and *Marc Bonten* with a Doctoral Thesis on ***Mathematical aspects of infectious disease dynamics*** (see the extended abstract below).

This thesis develops a general theoretical framework with novel contributions and uses it to shed light on a wide variety of biological theories and applied issues, thus showing the power and generality of

Mathematics. It possesses a remarkable breadth of coverage within the field of Mathematical Biology: not only does this thesis provide a mathematical analysis of the trans-critical bifurcation around the "reproduction value" *R0=1* with some generally applicable results for a wide range of models, it also addresses through mathematical modelling a number of important, applied issues, such as the efficacy of prophylactic antibiotic treatment against MRSA *(methicillin resistent staphylococcus aureus).*

Summarizing it can be said that Barbara Boldin offers an impressive thesis on epidemiology containing both general results and a pretty broad range of detailed applications. The results on generic invasion bifurcations look very interesting and useful. The application areas (concerning the virulence of intensive care pathogens) raise interesting questions and she seems to have dealt with these in ways that will have more general application.

Laudatio for *Antonio Politi*

Antonio Zaccaria Politi, born 1975 in Florence (Italy) and currently working at the Department of Mathematics, University of Auckland (New Zealand), got his Diploma in Biophysics (2000) at the Humboldt University in Berlin with *Reinhart Heinrich* as his supervisor, then finished 2007 his PhD under the auspices of *Thomas Höfer* with a Doctoral Thesis on ***Systems Biology Perspectives on Calcium Signaling and DNA Repair*** (see the extended abstract below).

This thesis is an exciting work that extends and improves formerly obtained results on Ca-oscillations and their applications in physiology and medicine. The idea to include also the IP_3 kinetics came form experiments and turned out to be successful for explanation and further predictions with the aid of ODE/PDE modelling. In the first part of the thesis, the analysis is taken to quite a high level, showing that the conclusions are independent of the precise model formulation, but result as a consequence of the general sign structure of the models. Furthermore, the predictions that are maid to discriminate between positive and negative feedback and its subsequent experimental corroboration are extremely nice.
The second part treats a different question concerning the molecular details of the DNA repair process, namely assembly kinetics of the nucleotide excision repair machinery. Similar modelling tools are used here in order to again obtain experimentally related results of pathway formation.
Thus, the thesis presents very interesting and challenging models, with strong analysis and with strong connection to experiments. In both areas non-trivial biological insights have been obtained and new experiments have been motivated for further research in the important field of systems biology, where his adviser, Reinhart Heinrich, was a pioneer. Antonio Politi's work is a classic example of Reinhart Heinrich's ability to inspire and guide students to achieve their own landmark research.

Brief laudatio for *Tiago Paixao*

With his thesis ***The Stochastic Basis of Somatic Variation*** (see the extended abstract below) Tiago Paixao presents an impressive work on one of the most important problems in the current "evo-devo" discourse, namely the explanation of genetic variability of isogenic cell populations. By using a consistent framework of stochastic modelling he shows, how the variability induced by an "interior environment" can produce experimentally observed gene expression patterns, and he checks the criterion, whether the observed traits can be (biochemically) regulated and thus appear as potentially selected outcomes in evolution.

Mathematical aspects of infectious disease dynamics

Thesis by *Barbara Boldin*

Extended abstract

This thesis is about model formulation, analysis and interpretation of four questions arising from biology or medicine.

The first of these questions concerns introductions of new populations into existing communities. Suppose that a new population is introduced into a steady community. It is known that when the basic reproduction ratio of the invader R_0 exceeds value 1 the invader is able to grow, while the invasion fails when $R_0 < 1$.What happens when R_0 passes the critical value 1?

In Chapter 2 we provide the answer to this question, assuming that populations are characterized by finitely many characteristics (also called *i*-states) and that the dynamics is described as a deterministic process, either in the form of a parameterized system of differential equations or in the form of a parameterized map. We observe that population invasion models, regardless of the biology that underlies them, take a specific form, which significantly simplifies the centre manifold analysis and implies that the transition through $R_0 = 1$ corresponds to a transcritical bifurcation.

In the biological context we distinguish two types of transcritical bifurcation, according to whether the positive branch of equilibria is subcritical or supercritical. In Chapter 2 we provide a formula that enables us to distinguish between the two, qualitatively very different, scenarios. Our general formulation allows us to make a uniform study of population invasions in ecology, adaptive dynamics and epidemiology, which is demonstrated by several examples.

The theme of Chapter 3 is the evolutionary dynamics of virulence. Pathogens reproduce and are subject to natural selection at several different, but intertwined, levels. Viruses, for instance, compete for uninfected target cells within a single infected host and also at the host population level by competing for susceptible hosts. But while an increased reproduction inside a host may enhance transmission at the host population level, it may also increase host's mortality and consequently decrease transmission to new hosts. Thus, the following question arises: how are these conflicting tendencies balanced in the course of evolution and to what extent do the two levels of reproduction influence the outcome of evolution?

In Chapter 3 we deal with this question while relating the between-host characteristics, such as transmissibility and the disease induced death rate, to the dynamics inside a host. We couple the two levels of reproduction by incorporating the possibility of superinfection and study the evolution of the pathogen's within-host reproduction rate. We introduce a superinfection function $\varphi = \varphi(p,q)$, giving the probability with which pathogens with trait q, upon transmission to a host that is already infected by pathogens with trait p, `take over' the host. We consider three cases according to whether the function $q \rightarrow \varphi(p,q)$ (i) has a discontinuity, (ii) is continuous, but not differentiable, or (iii) is differentiable in $q = p$. We find that in case (i), where a slightly better within-host competitor has a large advantage in taking over the host, the within-host selection dominates in the sense that the outcome of evolution at the host population

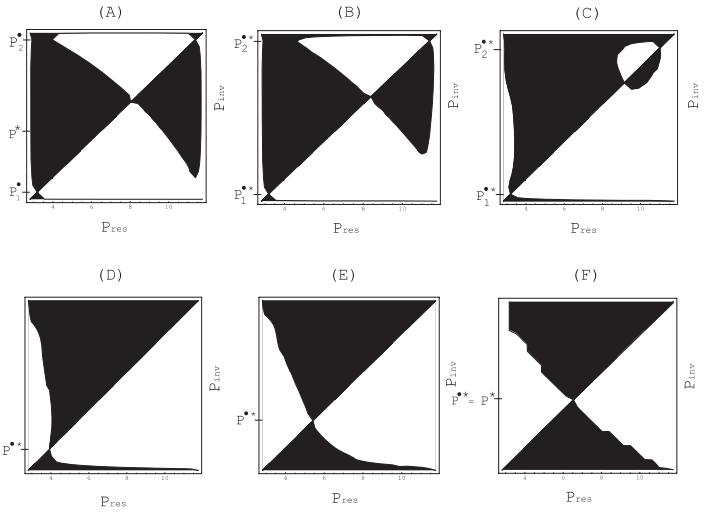


Figure 1. Examples of pairwise invasibility plots (PIPs) given by the superinfection model. For details see page 75 of the PhD thesis.

level coincides with the outcome of evolution in a single infected host. In case (iii), it is the transmission to susceptible hosts that dominates the evolution to the extent that the singular strategies are the same as when the possibility of superinfections is ignored. In case (ii), both forms of reproduction contribute to the value of a singular trait. We show that case (ii) is the biologically most relevant case: indeed, when φ is derived from a branching process variant of the submodel for the within-host interaction of pathogens and target cells, the superinfection functions fall under case (ii). We furthermore demonstrate that the superinfection model allows for evolutionary branching and steady coexistence of pathogen traits (at the host population level) on the evolutionary time scale. Branching points encountered in the superinfection model are of a degenerate, asymmetric type.

In Chapter 4 we investigate the dynamics of pathogens typically found in intensive care units, such as *Pseudomonas Aeruginosa* and methicillin-resistant *Staphylococcus Aureus* (MRSA).

Nosocomial infections are typically preceded by asymptomatic carriage at several body sites. Pathogen dynamics thus includes within-host transmission as well as transmission among patients. Different routes of transmission create a complex epidemiology, which is furthermore complicated by rapid patient turnover and small population sizes, typical for ICUs. We present two models that incorporate several colonization sites and evaluate the effects of barrier precautions (improved hygiene, use of gloves and gowns etc.) and of administration of non-absorbable antibiotics on the prevalence of colonization in ICUs. We find that the effect of the controversial, though widely used, antibiotic prophylaxis can only be substantial if the patient-to-patient transmission has already been reduced to a subcritical level by barrier precautions. Taking into account that the very use of antibiotics may increase selection for resistant strains and may thereby only add to the ever increasing problem of antibiotic resistance, our findings hence represent a firm theoretical argument against the routine use of topical antimicrobial prophylaxis for infection control.

The last chapter of the thesis deals with the within-host dynamics of enterotoxigenic *Escherichia Coli* (ETEC) in piglets. ETEC can attach to the intestinal microvilli and often leads to post-weaning diarrhoea, a disease that results in severe deterioration or even death in newly weaned piglets. We present a model describing the microbial dynamics in the intestine of a single piglet and investigate two scenarios.

To begin with, we derive an explicit expression for the amount of shed bacteria in the case a piglet is infected by a single dose of ETEC. We do so by using a very interpretation-oriented approach, namely, we characterize the bacteria in the intestine by the number of times they attach to the wall of the intestine. Since piglets often come into contact with faeces containing the bacteria, we furthermore investigate the case where a piglet is reinfected with a fraction of the shed bacteria. For the analysis of this second scenario we make use of the theory of positive operator semigroups. In both, the single infection and the reinfection case, we determine the Malthusian parameter and investigate whether we observe convergence to a stable distribution of bacteria in the intestine (in other words, we investigate whether we observe asynchronous exponential growth of the bacteria in the intestine). We furthermore discuss how the results, and the ways in which we analyze the two cases, are related to each other.

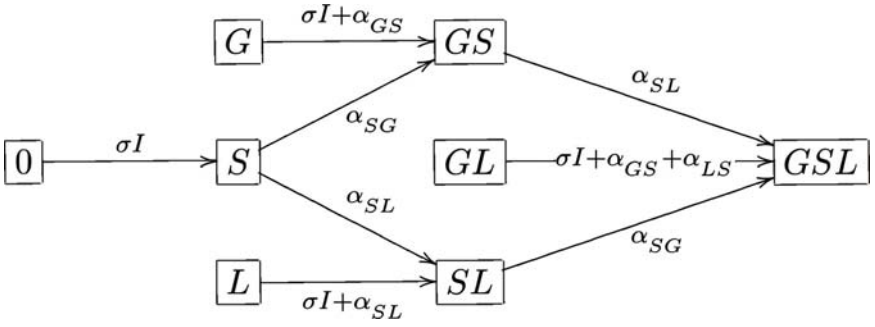


Figure 2. Dynamics of an individual's colonization status. For details see page 94 of the PhD thesis.

Further reading:

1. B. Boldin: Introducing a population into a steady community: the critical case, the center manifold and the direction of bifurcation, *SIAM Journal on Applied Mathematics*, Volume 66 (2006), Issue 4, pp. 1424-1453

2. B. Boldin, M.J.M. Bonten, O. Diekmann: Relative effects of barrier precautions and topical antibiotics on nosocomial bacterial transmission: results of multi-compartment models, *Bulletin of Mathematical Biology*, Volume 69 (2007), No. 7, pp. 2227-2248

3. B. Boldin, O. Diekmann: Superinfections can induce evolutionarily stable coexistence of pathogens, *Journal of Mathematical Biology*, Volume 56 (2008), No. 5, pp. 635-672
4. B. Boldin: Mathematical aspects of infectious disease dynamics, PhD Thesis, University Utrecht, the Netherlands (2007). ISBN: 978-90-9022069-7.

Current address:

Barbara Boldin
Department of Mathematics and Statistics
FIN - 00014 University of Helsinki, Finland
barbara.boldin@gmail.com

The full thesis is available at:
http://igitur-archive.library.uu.nl/dissertations/2007-0905-204659/index.htm

~~~~~~

Systems Biology Perspectives on Calcium Signaling and DNA Repair

Thesis by *Antonio Zaccaria Politi*

Extended abstract

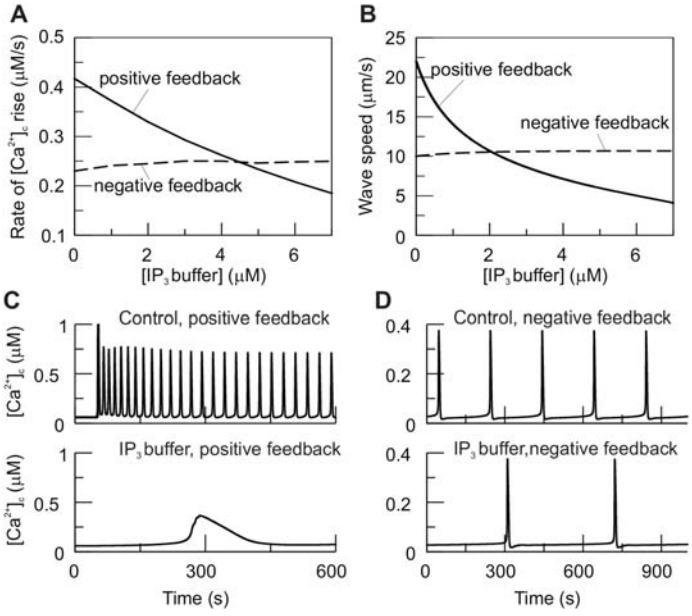
This work deals with two paradigms of cellular signaling: a change in the intracellular Ca^{2+} concentration represents one of the first steps in the transduction of incoming stimuli; the ability to properly respond to external injuries and repair damaged DNA is an essential component for life. The approaches used to investigate Ca^{2+} signaling and DNA repair bear common points. The mathematical models we developed are based on systems of ordinary differential equations or, when spatial resolution was required, on partial differential equations. The study of such models, using dynamical systems and bifurcation theory, and parameter identification tools, allowed to asses system properties, such as efficiency in the signal processing, specificity of the response, and design principles behind the different pathways. A close collaboration with experimentalists made it possible to directly compare model predictions and experimental data, and to test different mechanistic hypothesis.

The first part of the thesis focuses on the phosphoinositide-dependent Ca^{2+} signaling. Hormones that act through the Ca^{2+}-releasing messenger, inositol 1,4,5-trisphosphate (IP_3), cause intracellular Ca^{2+} oscillations, which have been ascribed to Ca^{2+} feedbacks on the IP_3 receptor (IP_3R). Recent studies have shown that IP_3 levels oscillate together with the cytoplasmic Ca^{2+} concentration. To investigate the functional significance of this phenomenon, mathematical models of the interaction of both second messengers have been developed. The models account for both positive and negative feedbacks of Ca^{2+} on the phosphoinositide metabolism, mediated by Ca^{2+} activation of phospholipase C and IP_3 3-kinase, respectively. The theoretical analysis shows that each of these Ca^{2+} feedbacks substantially expands the range of oscillation frequencies of a core oscillator based on Ca^{2+} and IP_3R dynamics, compared to Ca^{2+} fluctuations obtained with clamped IP_3. The action of the feedbacks depends on the turnover rate of IP_3. To shape the oscillations, positive feedback requires fast IP_3 turnover, whereas
~~~~~~

negative feedback requires slow IP_3 turnover. This suggests to perturb the IP_3 turnover in order to study the feedbacks: Whereas increasing the IP_3 turnover by overexpressing IP_3 metabolizing enzymes gives no information on the underlying feedbacks, slowing the IP_3 dynamics with an IP_3 binding protein can reveal positive feedback (Fig. 1). This theory has been tested in chinese hamster ovary cells by transiently expressing an IP_3 binding protein. The overexpression of this fusion protein exerted a dose-dependent suppression of agonist-induced Ca^{2+} oscillations that is consistent with an oscillator model including positive feedback of Ca^{2+} on IP_3 generation. This prominent role of the IP_3 dynamics in modulating Ca^{2+} oscillations demanded a more deeper analysis of the fate of the IP_3 precursor, phosphatidylinositol 4,5-bisphosphate (PIP_2). To this end, we constructed a detailed model for the phosphoinositide pathway based on measured metabolite concentrations. The model illustrates the importance of futile (de)phosphorylation cycles for regenerating PIP_2 during stimulation, an essential property to support long-lasting Ca^{2+} signals. Alternatively, when futile cycling is weak, the presence of positive feedback of Ca^{2+} on the IP_3 production also allows to regenerate the PIP_2 pool. Taken together, the experimental data and theoretical analysis presented in this thesis indicate that IP_3 oscillations are an essential component of the Ca^{2+} oscillator, they are physiologically important for supporting the efficient frequency encoding of hormone dose and the long-lasting Ca^{2+} signals observed in many cell types.

Figure 1: Slowing of the IP_3 turnover with an IP_3 buffer. (A) The maximal rate of $[Ca^{2+}]_c$ rise during a Ca^{2+} spike decreases as a function of IP_3 buffer concentration in the positive-feedback model (solid line), while it is barely affected in the negative-feedback model (dashed line). (B) The intracellular wave speed decreases as a function of IP_3 buffer concentration in the positive-feedback model (solid line), while it only slightly increases in the negative-feedback model (dashed line). (C) High IP_3 buffer concentration abolishes oscillations in the positive-feedback model (D) Oscillations persist in the presence of IP_3 buffer in the negative-feedback model.

The second part of the thesis is devoted to nucleotide excision repair (NER). It is a versatile DNA repair mechanism that can remove different type of lesions, such as UV light induced pyrimidine dimers and bulky adducts caused by chemical agents. It requires the concerted action of many different proteins that assemble at sites of damaged DNA. Despite our detailed biochemical knowledge about NER, many questions concerning its dynamic behavior remain unanswered, in particular, it is controversial whether repair factors are assembled sequentially or in a random way at the site of damage, or whether they exist as a holocomplex. Therefore, to understand the mechanisms underlying the protein assembly and the performance of repair, a mathematical model, delineating hallmarks and general characteristics of NER, has been developed. First, the binding and dissociation kinetics of repair factors are related to the structural properties of the system, such as the sequential order in which the factors enter repair. Second, using *in vivo* kinetic data for the recruitment of three different protein factors at local damaged nuclei, the model parameters are determined and the dynamic behavior of the repair process is scrutinized in detail (Fig. 2). The observed saturation of NER is predicted to rely on the high engagement of the recognition factor in repair. Furthermore, the model predicts a quiescent phase, where the amounts of factors involved in repair remains high and constant for a long time period, a forecast that has been



validated experimentally. The theoretical analysis of repair performance indicates that a sequential assembly process is remarkably advantageous in terms of repair efficiency and can show a marked selectivity for the damaged substrate. Alternative mechanisms for repairosome formation, including random assembly and preassembly, can readily become kinetically unfavorable. Based on the model, new experiments are proposed to gain further insight into the early and late steps of this complex process and to critically test model predictions.

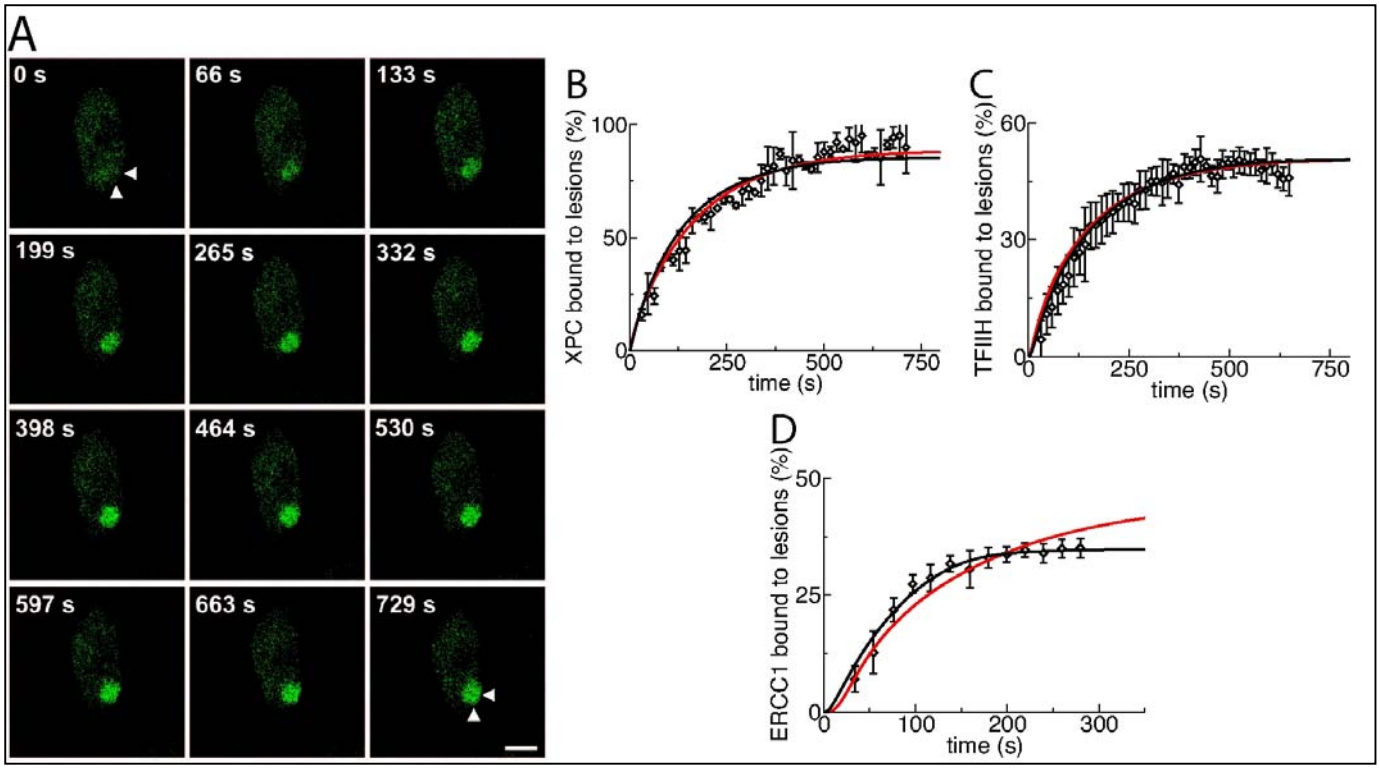


Figure 2: (A) A fluorescently labeled repair protein accumulates at the site of local damage, this provides the binding kinetics. (B)-(D) Binding kinetics of three repair proteins in experiments (dots) and for two alternative models (solid lines).

Current address:

Antonio Politi
Department of Mathematics
University of Auckland
Private Bag 92019
Auckland, New Zealand

The full thesis will soon be available at:
http://edoc.hu-berlin.de/browsing/dissertationen/

The Stochastic Basis of Somatic Variation

Thesis by *Tiago Paixao*

Extended Abstract

The factors that contribute to phenotypic variation are typically divided into two classes: genetic variation and environmental factors. Because of preponderance of genetics, molecular biology has ascribed most phenotypic variation to genetic variation, the so called genetic reducionism. However, ever since the beginning of molecular biology, numerous observations of phenotypic variation could not be explained by genetic factors (since they were made on isogenic unicellular organisms) and were hard to attribute to environmental factors (since these organisms were cultured in the exact same medium). As such, the manifestation of non-genetic individuality, the fact that distinct isogenic cells behave differently under the same environmental conditions, as been a long standing challenge, albeit an overlooked one.
In this thesis we propose that this phenomenon is attributable to stochastic events within the cell itself. In fact, the low numbers of molecules present within a cell leads to a high variance in the rate of molecular encounters, and since the cell functions through molecular reactions, which depend on such encounters, this means that kinetic rates can be interpreted as stochastic variables. This is especially relevant in gene transcription since one of the reagents, the chromosome itself, is frequently present in one or two copies. In fact, the stochastic nature of gene transcription has been implicated in the fluctuations of protein numbers in single cells. As such, in this thesis, we investigate the role of intracellular stochastic events in creating this somatic variation and its implications and potential adaptive value for an isogenic population of cells. We essentially address two manifestations of somatic variation: stochastic monoallelic expression of cytokine genes and the heterogeneity of protein copy numbers per cell.

The phenomenon termed stochastic monoallelic expression of genes refers to the observation that isogenic populations of T cells express certain genes in a specific allelic pattern. In fact, these cells express interleukin genes preferentially from one of its alleles, albeit a small percentage of cells express the gene from both alleles. Moreover, unlike other monoallelically expressed genes (such as antigen receptors and autossomal imprinted genes) the allelic expression pattern did not seem to be stable, since culturing a population of cells expressing from the same allele would eventually reconstitute the original allelic expression pattern. Also, and in contrast with these classical monoallelic expressed genes, the mechanism and function of this phenomenon is unknown and highly debated.
It had already been established that the frequencies of cells in each of the subpopulations of allelic expression pattern (no expression, only from one of the alleles and from both alleles) were consistent with an independent stochastic process (hence the denomination “stochastic monoallelic expression”), meaning that there was no evidence to postulate an active mechanism of repression of one allele when the other was transcriptionally active. The most parsimonious explanation for this phenomenon is that the two alleles undergo random uncorrelated bursts, which seldomly coincide (resulting in biallelic expression), due to the low number of transcription factors. A more elaborate hypothesis is that the two loci are differently accessible to the transcription factors, because they undergo independent epigenetic modifications in each cell.
In order to gain quantitative insights into the mechanism of monoallelic expression of cytokine genes, we modelled the two candidate mechanisms above. We made use of a widely spread model for stochastic gene expression in which each allele switches independently and stochastically between transcriptionally active and inactive states as the transcription factors necessary for attracting the RNA polymerase associate and dissociate at its promoter. This constitutes essentially a two state cyclic markov chain. When the allele is transcriptionally active the corresponding protein is produced deterministically thereby following a piecewise differential equation. We ask the model to reproduce the observed allelic expression pattern

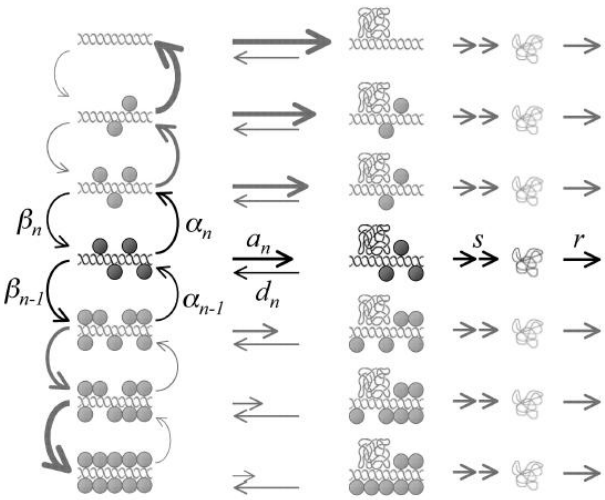


Figure 1. Reversible chromatin modification model of allele expression. This model is an extension to the Cook et al. model in which the rate at which the allele becomes transcriptionally active depends on its chromatin state.

frequencies of cells and the randomization dynamics, i.e., the dynamics of recovering the steady state expression pattern frequencies after isolation of one of the subpopulations (cells expressing one of the alleles). We find that this model can reproduce the observed data but under unrealistic parameter regimes, specifically in terms of the average time between transcriptional bursts and burst duration.

As such, we mathematically formalize the alternative model which relies on epigenetic modifications that control locus accessibility. In order to do so, we extend the previous model so that it includes another class of states which control the probability of activating gene expression. In this model, modifications can be stochastically added or removed from the locus and the number of modifications determines the probability of activating gene transcription at that locus. This extends the previous model since the probability of activating gene expression of the previous model is now affected by this extra regulatory layer conferred by the locus accessibility control mediated by the modifications and consists of one of the first models of chromatin dynamics. We found that this model can indeed reproduce both the basal frequencies of cells in each allelic expression state and the randomization dynamics of the population under very general parameter regimes. We did found that, in order for the model to reproduce the observed data, the transition rates between the locus accessibility states need to display cooperative behaviour, such that the steady state distribution of accessibility states becomes bimodal.

We conclude by arguing that the phenomena of stochastic monoallelic expression might not serve any function per se but is under indirect selection for the trait of having a low number of expressing cells, which, given this mechanism of regulation of gene expression, leads to predominant monoallelic expression.

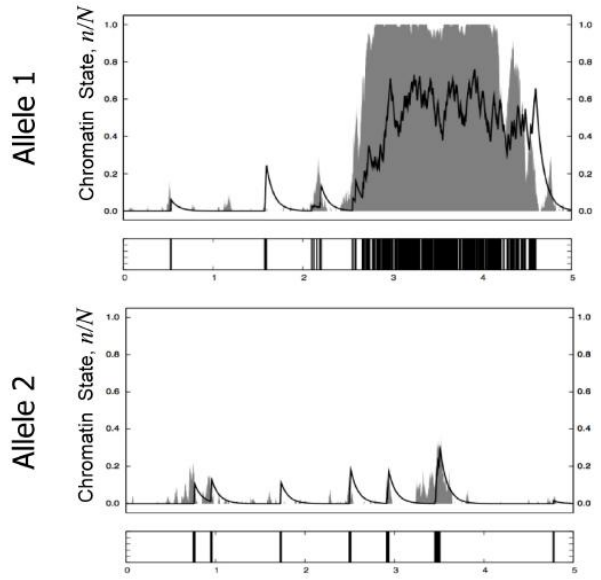


Figure 2. Representative time series obtained by simulation of the reversible chromatin modification model of allele expression.

We then turn our attention to another manifestation of somatic variation: heterogeneity of protein copy numbers. In fact, populations of isogenic cells exhibit a remarkable heterogeneity in terms of protein copy numbers.

This somatic variation of protein copy numbers could potentially be explained by the stochastic nature of gene expression. However, the shape of the distribution of protein copy numbers per cell that is typically observed in isogenic cells is the lognormal distribution, which can hardly be explained by traditional models of gene expression since these models often predict

poissonian distributions for the distributions of protein copy numbers. We demonstrate that this distribution can be explained by several common multistep motifs that permeate the cell's metabolism. We model, using stochastic differential equations, several multistep mechanisms where an element needs to undergo several modifications or steps in order to become functional. We show that, given enough of these steps, mechanisms such as accumulation of posttranslational modifications, regulatory cascades or transcription activation by multiple transcription factors, lead to a multiplicative propagation of the noise and hence to a lognormal distributed final product. We also show that this convergence towards the lognormal is independent of the specific distribution of the fluctuations of the components of these mechanisms making the lognormal distribution an attractor. We also show that this particular shape is extremely versatile in reproducing population response curves when individual cells are responding in a all-or-none fashion.

Since our proposed mechanism for the origin of this heterogeneity allows for a regulation of the characteristics of the population distributions of specific protein copy numbers, it creates the possibility for selection on these traits. We then seek the implications of this stochastically driven variation for the cell population. We analyze how the fact that protein levels are heterogeneous in isogenic populations affects the response of the population. We model several common signalling networks and analyze how these mechanisms affect the distribution of responses of the population. We identify the conditions under which these mechanisms constrain the underlying heterogeneity, making the population response more homogeneous, or exacerbate it creating the possibility of creating new forms of heterogeneity in the population, such as determining whether a cell responds or not, its level of response and the timing and dynamics of this response. We also note the implication that these new forms of heterogeneity that come from the distributed nature of the signalling machinery components have on ability to identify models based on average response data from the population.

Because the proposed mechanisms entail that protein levels in each cell is a fluctuating trait we try to investigate whether the structure of these fluctuations might have any adaptive value. By formalizing a model in which cell growth is dependent on a molecule whose levels fluctuate in each cell, we show how the structure of these fluctuations can lead to somatic adaptation, providing a basis for selection of different fluctuation generating mechanisms. By modelling the fluctuations of this molecule as a stochastic differential equation and integrating it with population dynamics, we were able to show that different fluctuation characteristics, such as steady state distributions with more variance or faster fluctuation rates, confer different growth characteristic, hence conferring differential fitness. This is possible by introducing a semi-analytical framework to deal with the two modelling levels displayed in this process: fluctuations at the level of the single cell and population dynamics of the population.

Fig 4

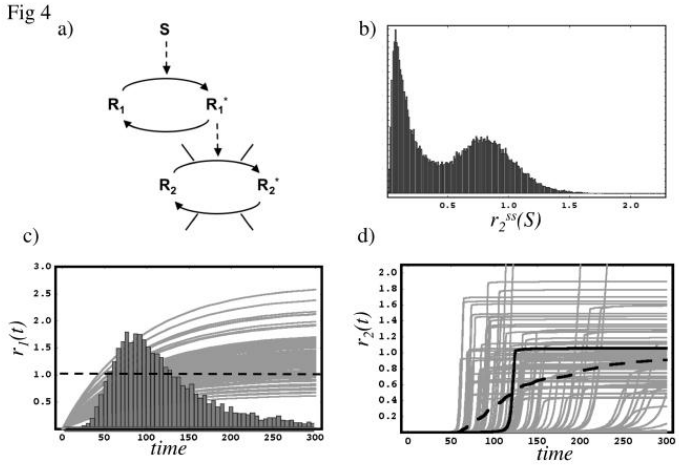


Figure 3. A mutual activation module. a) diagram of the mechanism. b) Steady state as a function of signal strength. Thick continuous line represents the steady state for a nominal total protein amount (*r1T=1*) and thinner lines represent 2-fold increase and decrease of that value. Dashed lines represent unstable steady states. c) Distribution of the critical signal strength beyond which the system jumps to the higher steady state for a population distributed as a lognormal with parameters *m=log(1)* and *s=0.25*. d) Several kinetic trajectories for the same population. Continuous black line represents the average cell of this population and dashed line the average of all trajectories.

Finally, we show how a stochastic environment can lead to heterogeneity within the cell. By coupling one of the signalling modules discussed above with population dynamics, we show that the individual history of each cell can itself lead to somatic variation of thresholds of activation of cells. Furthermore we show how a mechanism of this sort can be used by a cell population as a homeostatic mechanism to regulate cell numbers.

This thesis provides a new way to look at cell populations and lineages. It provides a way to understand the origin of somatic variation through the stochastic effects inherent to any biological system. Moreover, it shows how this somatic variation is shaped by cellular mechanisms and its impact on the population's fitness. As such, it shows how genetic factors can be tuned for cell populations to take advantage of the fitness advantage that the somatic variation confers in certain situations or to minimize its effects when it is more desirable to have a uniform behaviour across the population. Hence, we provide arguments for the possibility of selection of particular mechanisms as shapers of somatic variation by demonstrating how their ability to shape somatic variation depends on parameters that are encoded on the genome and the differential fitness value of these alternatives.
In essence, this thesis extends the concept of environmental factors as determinants of phenotypic variation to include the intracellular environment and the stochasticity there present as generators of cellular individuality.

We argued that stochastic effects inherent to the cells metabolism generates non-genetic individuality in an isogenic population and entails a new form of "determinism" based not on the deterministic dynamics of the single cell but on the evolution of a probability distribution of the underlying mechanisms. We showed the implications of this at several levels: at the level of gene expression, signal transduction and population dynamics. We have shown how a population of cells could use this spontaneous heterogeneity to their benefit in dealing with stochastic environments or as a regulation mechanism. Moreover, we argue that this heterogeneity creates a link between populations of isogenic cells and their environment. In fact, our work shows that the environment can have a determinant role in shaping and maintaining this heterogeneity within a cell population.

Current address:

Tiago Paixao
University of Houston
Dept Biology and Biochemistry
4800 Calhoun Road
Houston TX 77004
tmsearap@mail.uh.edu

FURTHER RECENT THESES

Mathematical Modelling of Evolutionary Ecology

Daniel John Lawson
Imperial College London
daniel.lawson@imperial.ac.uk

Supervisor: Henrik Jeldtoft Jensen

The process of evolution is both trivial to understand and yet fraught with complexity. We analyse the evolutionary process from the very simplest starting point - that of a number of individuals reproducing with mutation and dying, without selection, in an arbitrary type space. We consider adding selection and analyse the transition from the neutral case to the `nearly neutral' regime, extending smoothly to strong selection. In the absence of interaction, strong selection allows for classical approaches to evolution to be used, and stochasticity is not important. However, by `switching on' interactions, stochasticity again becomes a vital part of evolutionary modelling, providing a link between short (ecological) timescales, and long (evolutionary) timescales.

A number of surprising results are found for neutral evolution, such as natural clustering forming short lived `species'. The implications for the definition of a species and hence diversity are considered in light of the findings. The case of neutral phenotype evolution is solved by considering a simplified model containing all the essential features. Additionally, the problem is mapped to a Field Theory, which in the infinite population limit allows the description of Neutral Evolution as a `Super Brownian Motion', that is a diffusion of -interacting- particles with a non-trivial distribution. The analysis of the nearly neutral case shows that the effectively neutral regime can be `larger' in terms of a selection parameter than previous results indicate. The discrepancy is due to what is considered small - the effect of each allele mutation (as in previous work), or the total possibility for selection on a type.

Finally, more realistic models are considered, with selection, interaction and real space introduced. The complex version of the model is given the name ``Tangled Nature'' and many results are already known about its behaviour for comparison. Simulation results are presented, with mean-field arguments to support generalisation of observations. We find that a satisfying definition of `species' emerges from the effects of interaction, and thus described diversity due to neutrality as fundamentally different to diversity due to selection.

Thesis available from:
http://www.ma.ic.ac.uk/~djl2/Lawson_Thesis_150107.pdf

Further Reading:

`Neutral Evolution in a Biological Population as Diffusion in Phenotype Space: Reproduction with Local Mutation but without Selection.'
Daniel John Lawson and Henrik Jeldtoft Jensen.
Phys. Rev. Let., 98:098102, 2007.

`The species-area relationship and evolution.'
Daniel Lawson and Henrik Jeldtoft Jensen.
J. Theor. Biol., 241:590-600, 2006.

`Diversity as a product of interspecial interactions.'
Daniel Lawson, Henrik Jeldtoft Jensen, and Kunihiko Kaneko.
J. Theor. Biol., 243:299-307, 2006.

`The Tangled Nature model of Evolutionary Ecology: An overview.'
Simon Laird, Daniel John Lawson and Henrik Jeldtoft Jensen.
Mathematical Modeling of Biological Systems (II), Birkhäuser Boston, Eds. A. Deutsch et al, 2007.

From individual to collective motion of self-propelled particles:
The role of particle shape, orientational ordering and clustering.

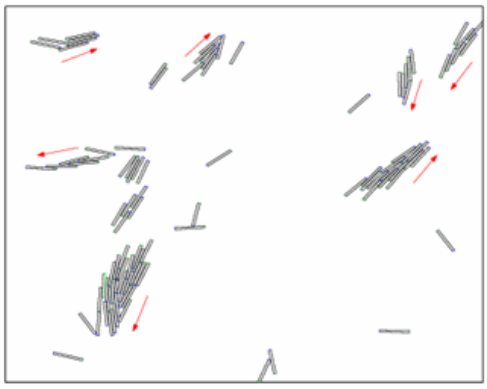
Fernando Peruani
Center for Information Services and High Performance Computing (ZIH)
Technische Universität Dresden, Germany
peruani@mpipks-dresden.mpg.de

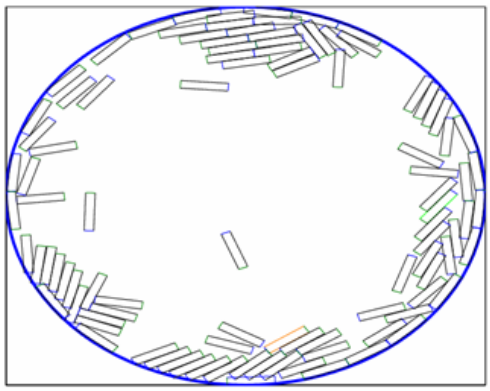
Supervisor: Andreas Deutsch (Dresden) and Markus Bär (Berlin)

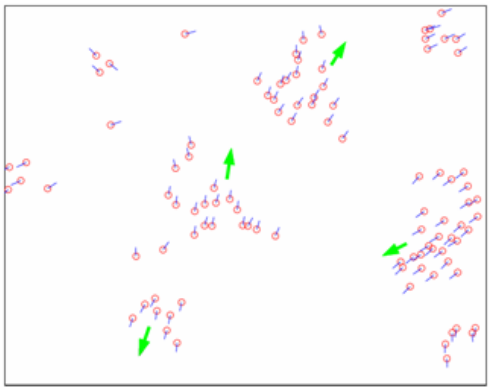
Self-propelled particles (SPPs) are non-equilibrium systems and as such they are not forced to obey the fluctuation-dissipation theorem. Moreover, SPPs can exhibit fluctuations in the direction of motion uncorrelated from those in the speed. In this Thesis it is shown that uncorrelated fluctuations lead to a non-Brownian motion characterized by expressions for the mean square displacement and diffusion coefficient that differ from the classical results by additive corrections. It is also indicated that such effects have been observed in cell motility experiments.

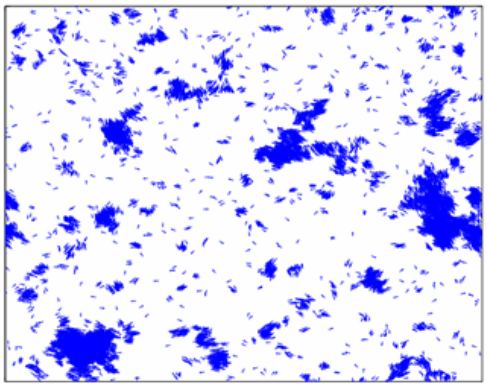
Interacting SPPs represent another fascinating kind of systems with remarkable differences with equilibrium system. For instance, while in equilibrium two-dimensional systems with continuum symmetry long-range order is forbidden, SPPs can develop such long-range order. Though it is well known that two-dimensional SPPs with local polar interactions can exhibit such transition to orientational order, a recurring question refers to alternative physical mechanisms that lead to collective motion in SPPs. In this Thesis it is shown that a self-propelling force together with volume exclusion are sufficient to cause collective migration. This is clearly illustrated through a model for self-propelled rod-shaped particles. In particular, it is indicated that the emerging collective patterns depend on the particle elongation. For instance, it is shown that for a given density there is critical particle aspect ratio that triggers non-equilibrium clustering. It is also suggested that those effects might play a major role in the collective motion of gliding bacteria such as myxobacteria.

Volume exclusion represents an apolar interaction. This rises the question how the results known for SPPs with polar interactions change when the interactions become apolar. This issue is addressed in this work and it is shown that though SPPs with apolar interactions can also achieve long-range order, the character of the transition highly depends upon particle density.









Finally, it is shown that the ordering dynamics in SPPs with either polar or apolar interactions can be described with the same continuum theory.

Timescales and spatiotemporal populations dynamics

Tri Nguyen-Huu
Laboratoire de Microbiologie, Géochimie et Ecologie Marines, Université Aix-Marseille II, France, September, 2007
tri.nguyen-huu@ens-lyon.fr

Supervisor: Rafael Bravo de la Parra (Madrid)

Population dynamics describe numerical evolution of living organism populations with mathematical models. The processes which rule this evolution are numerous and vary from a molecular scale to the environmental scale. The growing number of processes and parameters taken into account has led to very complex models which cannot be easily used or analysed. Aggregation of variables methods allow reducing complexity of mathematical models by building simplified models governing fewer variables. Those methods take advantage of timescales differences between the different processes to reduce continuous time models as well as discrete time models.

We first use those methods to study spatial host-parasitoids models on a square grid of patches. Those models are composed of a non-linear local interaction submodel (the Nicholson-Bailey model) and a dispersal submodel. Dispersal consists in k events of elementary dispersal on the nearest neighbours. When k is large, dispersal is fast compared to local processes. It is then possible to build a reduced model, called aggregated model. We study the influence of parameter k on global dynamics and persistence of the system. When k is small, spatial structures appear and the dynamics is persistent, even when local interaction submodel is instable. When k is large enough, dynamics of the complete model (non-reduced model) and the aggregated model are qualitatively the same. We found that the threshold value over which both dynamics are qualitatively equivalent is relatively low: less than 10% of the size of a side of the grid. This indicates that aggregation methods can be useful in many cases, even when dispersal is a relatively local process. Results obtained allow proposing an explanation to synchronism observed for different populations of a same species located on different places. Dispersal can promote synchronism without any environmental correlations, even if dispersal occurs at a local scale. Results are then extended to a host-parasitoid model on a chain of patches, with host density-dependent dispersal for parasitoids. There is functional emergence for this model, which can be studied with the aggregated model.

We then develop a model of a virus in a marine environment to study the "plankton paradox": plankton dynamics violate the principle of competitive exclusion. The model consists of five differential equations governing the three different states of bacteria (susceptible, infected and recovered), the virus concentration and the substrate concentration. It uses parameters measured in a chemostat experiment. This model presents slow and fast processes, which allows building an aggregated model. It is then possible to perform a mathematical analysis which proves that two species can exist at the same time. To obtain the coexistence of more species, it appears to be necessary to introduce spatial heterogeneity.

References

Nguyen Huu, T., Lett, C., Poggiale, J.C., Auger P. (2006), Effect of movement frequency on global host–parasitoid spatial dynamics with unstable local dynamics, *Ecol. Model.*, **197(3-4)**: 290-295

Nguyen Huu, T., Lett, C., Auger, P. Poggiale, J.C. (2006), Spatial synchrony in host–parasitoid models using aggregation of variables, *Math. Biosci.*, **203(2)**: 204-221

Nguyen Huu, T., Lett, C., Auger, P. (in press), Effects of density-dependent dispersal on the stability of host-parasitoid associations in a chain of patches, *Ecol. Comp*.

Auger P., Lett C., Nguyen Huu T., Poggiale J.C. (2004) Rencontre du non linéaire 2004. Dynamique spatiale d'un système hôte-parasitoïde.

Verhulst and the logistic equation for population dynamics

Nicolas Bacaër
Institut de Recherche pour le Développement
32 avenue Henri Varagnat,
93143 Bondy, France
bacaer@bondy.ird.fr

In 1838, the Belgian mathematician Pierre-François Verhulst published an article in which he introduced (with different notations) the now well known logistic equation for population growth

$$dP/dt = r*P*(K-P)/K \qquad (1)$$

(Verhulst, 1838). He used this equation to fit population data from several countries including Belgium. The article does not say which values for r and K he obtained. But it appears from the table he shows that he based his computations for Belgium on the following assumptions derived from real data:
$P(1815) = 3{,}494{,}985$; $P(1824) = 3{,}816{,}249$
$P(1833) = 4{,}142{,}257$.

With these three points (notice that the model has three parameters: r, K and a constant of integration), one easily finds $K = 8.43$ million for the asymptotic population. Indeed, if $P0$, $P1$ and $P2$ are populations at time $t0$, $t1 = t0+T$ and $t2 = t0+2T$, then $K = P1*(P0*P1+P1*P2-2*P0*P2)/(P1*P1-P0*P2)$.

In 1845, Verhulst published another article on the same subject, in which he introduced the name "logistic" and explained in more detail how to estimate the parameters. This time, he used slightly different assumptions derived from a more careful analysis of real data:
$P(1815) = 3{,}627{,}253$; $P(1830) = 4{,}247{,}113$
$P(1845) = 4{,}800{,}861$. (2)

He obtained $K = 6.58$ million (Verhulst, 1845), a result much smaller than the previous one. Verhulst returned to the subject in a short note the next year (Verhulst, 1846) and finally in a longer article published in 1847. In these two documents, he suggested there was a flaw in the "derivation" of the logistic equation and used instead (still with different notations) a model of the form

$$dP/dt = r*P*(K-P)/P = r*(K-P) \qquad (3)$$

(Verhulst, 1847). Using the same data (2), he obtained $K = 9.44$ million, a result again quite different from the previous two results. For this second model,

$K=(P1*P1-P0*P2)/(2*P1-P0-P2)$.

The logistic equation (1) was reintroduced several decades later by different people without knowing about Verhulst's work (Lloyd, 1967). It was used for the individual growth of animals, plants, humans and body organs (Robertson, 1908), for the growth of populations of micro-organisms (McKendrick & Kesava Pai, 1911), or like Verhulst for the growth of human populations such as the population of the United States (Pearl & Reed, 1920). Verhulst's work was finally noticed (Pearl, 1922, p.249) and the term *"logistic"* became widely used. Debates concerning the meaning of the logistic equation lasted many years (for the details of the story, see Kingsland, 1985, pp.64-97), the conclusion probably being that it is not a fundamental law and that it can be used for short term projections but not for long term projections.

In 1976 however, volume 13 of the *"Dictionary of Scientific Biography"* contained a notice on Verhulst with the following summary of Verhulst's work on population (Pelseneer, 1976):

"Verhulst showed in 1846 that the obstacles increase in proportion to the ratio of the excess population to the total population. He was thus led to give the figure of 9,400,000 as the upper limit for the population of Belgium (which, in fact, has grown to 9,581,000 by 1967). Verhulst's research on the law of population growth makes him a precursor of modern students of the subject."

Notice that this paragraph refers to model (3) and not to model (1), even though Verhulst is now remembered only because of model (1). Besides, given the variability of Verhulst's results for the maximum population *K*, it seems that the comparison of only one of them with the present population of Belgium has little meaning. The previous quote has also been misleading for later references to Verhulst. Since 1996 for example, one of the most popular web sites on the history of mathematics (O'Connor & Robertson, 1996), citing Pelseneer (1976), tells the story in a slightly modified (and updated) way:

"The non-linear differential equation describing the growth of a biological population which he deduced and studied is now named after him. Based on his theory Verhulst predicted the upper limit of the Belgium population would be 9,400,000. In fact the population in 1994 was 10,118,000 and, but for the affect of immigration, his prediction looks good."

Notice in this quote that "his theory" refers to the logistic equation, which Verhulst himself thought to be incorrect. Moreover, the numerical result of model (3) is attributed to model (1), giving the impression of a rehabilitation of the logistic equation for long term population projections. In a recent book (Iannelli, Martcheva & Milner, 2005, p.5), we find a close variant with a further update:

"Based on his theory, Verhulst predicted that the carrying capacity for the population of Belgium would be *9.4* million people. The total population of Belgium as of January 2000 is *10.24* million people, a difference of only *0.84* million people - mostly due to immigration."

A similar story is told in the book (Istas, 2005, p.10). As Ronald Fisher once wrote about Mendel's work (Bennett, 1965, p.6):

"The History of Science has suffered greatly from the use by teachers of second-hand material, and the consequent obliteration of the circumstances and the intellectual atmosphere in which the great discoveries of the past were made. A first-hand study is always instructive, and often ... full of surprises."

Thanks to the World Wide Web, first-hand studies are now greatly simplified. The journals containing Verhulst's 1845 and 1847 articles have been scanned by the library of the university of Göttingen in Germany and can be downloaded from the library's website. As for the 1838 article, an English translation can be found in (Smith & Keyfitz, 1977).

Finally, here is a short ***biography of Verhulst*** (Quetelet, 1850, 1867; for recent discussions, see e.g. Mawhin, 2002, Delmas, 2004, Ausloos & Dirickx, 2006, and Bacaër, 2008):

1804: born in Brussels.

1822-1825: studies at the University of Ghent, PhD in mathematics.

1829: publication of his translation of John Herschel's "Treatise on Light".

1830: after the revolution which leads to the independence of Belgium, interested in politics, history and "political arithmetics".

1834: starts teaching mathematics at the Ecole Royale Militaire.

1835: publication by his former teacher Quetelet of "Essai de physique sociale", the starting point of Verhulst's studies on population growth.

1835-1840: professor at the Université Libre in Brussels.

1841: publication of his mathematical treatise on elliptic functions. Elected to the Royal Academy of Belgium.

1848: president of the Academy.

1849: dies in Brussels (probably of tuberculosis).

References:

Ausloos, M., Dirickx, M. (Eds), 2006. The Logistic Map and the Route to Chaos: From the Beginnings to Modern Applications. Springer-Verlag, Berlin.

Bacaër, N., 2008. Histoires de mathématiques et de populations. Editions Cassini, Paris. (to appear)

Bennett, J.H., 1965. Experiments in Plant Hybridisation. Oliver & Boyd, Edinburgh.

Delmas, B., 2004. Pierre-François Verhulst et la loi logistique de la population. Mathématiques et Sciences Humaines 167, 51-81. http://www.ehess.fr/revue-msh/pdf/N167R893.pdf

Iannelli, M., Martcheva, M., Milner, F. A., 2005. Gender-structured Population Modeling: Mathematical Methods, Numerics, and Simulations. SIAM, Philadelphia.

Istas, J., 2005. Mathematical Modeling for the Life Sciences. Springer, New York.

Kingsland, S.E., 1985. Modeling Nature. University of Chicago Press.

Lloyd, P.J., 1967. American, German and British antecedents to Pearl and Reed's logistic curve. Population Studies 21, 99-108.

Mawhin, J., 2002. Les héritiers de Pierre-François Verhulst: une population dynamique. Académie Royale de Belgique, Bulletin de la Classe des Sciences, 349-378.

McKendrick, A.G., Kesava Pai, M., 1911. The rate of multiplication of micro-organisms: A mathematical study. Proceedings of the Royal Society of Edinburgh 31, 649-655.

O'Connor, J.J., Robertson, E.F., 1996. Pierre François Verhulst. The MacTutor History of Mathematics archive. http://www-history.mcs.st-andrews.ac.uk/Biographies/Verhulst.html

Pearl, R., Reed, L.J., 1920. On the rate of growth of the population of the United States since 1790 and its mathematical representation. Proceedings of the National Academy of Sciences 6, no.6, 275-288.

Pearl, R., 1922. The Biology of Death. Lippincott, Philadelphia.

Pelseneer, J., 1976. Verhulst (Pierre-François). In: Gillispie, C.C. (Ed.), Dictionary of Scientific Biography, vol.13. C. Scribner's sons, New York, p.616.

Quetelet, A., 1835. Sur l'homme et le développement de ses facultés ou Essai de physique sociale. Bachelier, Paris. http://gallica.bnf.fr/ark:/12148/bpt6k81570d

Quetelet, A., 1850. Pierre-François Verhulst. Annuaire de l'Académie royale des Sciences, des Lettres et des Beaux-Arts de Belgique 16, 97-124. English transation in: Miner, J.R., 1933. Pierre-François Verhulst, the discoverer of the logistic curve. Human Biology 5, 673-689.

Quetelet, A., 1867. Sciences mathématiques et physiques au commencement du XIXème siècle. C. Mucquardt, Bruxelles. http://gallica.bnf.fr/ark:/12148/bpt6k99395b

Robertson, T.B., 1908. On the normal rate of growth of an individual and its biochemical significance. Archiv für Entwicklungsmechanik der Organismen 25, 581-614.

Smith, D.P., Keyfitz, N., 1977. Mathematical Demography: Selected Papers. Springer, New York.

Verhulst, P.-F., 1838. Notice sur la loi que la population poursuit dans son accroissement. Correspondance Mathématique et Physique, vol.X, 113-121.

Verhulst, P.-F., 1845. Recherches mathématiques sur la loi d'accroissement de la population. Nouveaux mémoires de l'Académie Royale des Sciences et Belles-Lettres de Bruxelles, vol.XVIII, 1-45. http://gdz.sub.uni-goettingen.de/no_cache/dms/load/img/?IDDOC=77222

Verhulst, P.-F., 1846. Note sur la loi d'accroissement de la population. Bulletins de l'Académie Royale des Sciences et Belles-Lettres de Belgique, vol.XIII, 1ère partie, 226-227.

Verhulst, P.-F., 1847. Deuxième mémoire sur la loi d'accroissement de la population. Mémoires de l'Académie Royale des Sciences, des Lettres et des Beaux-Arts de Belgique, vol.XX, 1-32. http://gdz.sub.uni-goettingen.de/no_cache/dms/load/img/?IDDOC=74013

PAST ACTIVITIES

3rd Annual Vanderbilt Integrative Cancer Biology Center Workshop:
Mathematical modeling and clinical oncology, the road to convergence.
15 - 19 July 2007
Vanderbilt University, Nashville, TN, USA

The annual workshops organised by Dr. Lourdes Estrada and Prof. Vito Quaranta (both at the Cancer Biology department of Vanderbilt University) have the remarkable feature that, asides from the usual sessions, talks, keynotes and posters (which it also has, and rather good ones at that) it offers also the chance to interact with biologists. This interaction comes from the group projects to which all participants (including the organisers) are assigned. In this year's edition four groups where created in which equal number of experimentalists (biologists and medical doctors) and theoreticians (mathematicians or computer scientists) where put together in order to come with the sketch of a model of some relevant cancer related phenomenon. My group combined biologists from Vanderbilt's own Medical Center with engineers, mathematicians and computer scientists from farther afield. The experimentalists interest in exploring the potential dual role of TGF-Beta in preventing and promoting prostate cancer led to a Cellular Automaton model whose early results were shown at the end of the workshop. The results in all these groups confirmed how much can both groups of people (experimentalists and theoreticians) gain by working closely together. For that reason I would encourage any PhD student or postdoc in mathematical biology to attend the next edition which will take place in Toronto in August 2008.

David Basanta
TU Dresden, Germany

Graz Summer School and Workshop: Biomedical Modeling and Cardiovascular-Respiratory Control: Theory and Practice"

Overview

The Graz summer school and workshop " **Biomedical Modeling and Cardiovascular-Respiratory Control: Theory and Practice"** was held *from July 22 to August 4, 2007*, at Schloss Seggau near Graz Austria and organized by the Institute for Mathematics and Scientific Computing, University of Graz. Principal organizers were *Mostafa Bachar*, *Jerry Batzel*, and *Franz Kappel*.

This event is the first in a series of four schools sponsored by the Marie Curie Conferences and Training Courses Program as described at the end of this report.

Graz event scientific focus

The focus of the summer school segment of the Graz event was on providing the school participant with an understanding of the theory and practice of modeling physiological control systems with a primary application of studying clinical problems related to the cardiovascular and respiratory control systems. Instructors included mathematicians, bioengineers, and life scientists from academia and industry as well as medical clinicians. Courses, teachers, and presenters are listed at the web page.

Web page:

http://www.uni-graz.at/biomedmath/graz/index.html

Structure of the event:

The Graz event included an eleven day summer school followed by a three day scientific workshop on the same scientific theme. The summer school component was aimed primarily toward PhD students and new Post-Docs.

After the 11 day summer school training period, the students of the school took part in a three day scientific workshop on Cardiovascular and Respiratory Modeling. This workshop was designed as if it could stand alone as a scientific event and included presentations from 16 scientists actively involved in research in the focus theme of the event. Contributions from students were also included.

A major reason for combining the school and workshop was that it allowed students to apply what they learned, become exposed to the state of the art in research, learn about presentation, meet potential collaborators, and make contacts for the future.

Outcome of the event:

55 students from 20 countries attended the event along with 9 teachers and 16 presenters at the workshop. A virtual library was established with course notes, workshop talks and related resources, as well as a virtual round table to discuss the future direction of research at the web page:

http://www.uni-graz.at/biomedmath/library.html

The combined summer school and workshop structure appeared to be an effective way for students to develop interest and skills in the areas of research presented in the event.

A Marie Curie Training Series of four summer school/workshop events

The Graz event is the first of four scientific events sponsored by The Marie Curie Conferences and Training Courses Program with each event combining a summer school and an associated workshop on the same topic. These events will be held sequentially between 2007 and 2010.
This series of events entitled "**Mathematic Modeling of Human Physiological Systems with Biomedical Applications"** (**BioMedMath 07-10)** is organized by the University of Graz in partnership with the University of Copenhagen, the Biomathematical Laboratory Rome, and the University of Dundee.

A general **BioMedMath 07-10** linking and reflecting all four events can be found at:

http://www.uni-graz.at/biomedmath/info.html

The ***primary scientific reason*** for the events in **BioMedMath 07-10** is to advance, through training and communication, mathematical modeling essential for studying human biomedical and clinical problems at primarily the organ and system level with an emphasis on control mechanisms and clinical problems arising from deficiencies in these control mechanisms. To further advance this field of research this sequence of events will seek to promote the development of a network of researchers in related biomedical modeling areas. The format of each event, consisting of a focused school followed by an associated scientific workshop, will aid in establishing links between prospective researchers and current researchers, research institutions, and key organizations such as the SMB and the ESMTB.

Next events

- **Copenhagen 2008: "Stochastic Differential Equation Models with Applications to the Insulin-Glucose System and Neuronal Modeling,"**

The Copenhagen summer school and workshop will take place *from August 3 to August 16, 2008*, at Middelfart Kursuscenter 2 hours from Copenhagen. It is organized by the Department of Mathematical Sciences, University of Copenhagen. Principal organizers are *Susanne Ditlevsen* and *Michael Sørensen*.

This event will focus on stochastic issues in physiological modeling. The school aims to concentrate on the possibilities offered by stochastic calculus for the solution of relevant biological problems. Stochastic models of the glucose-insulin system and neuronal functioning will be presented as applications. The associated workshop will have the same themes.

The school will have specific courses on stochastic integrals, statistical methods for diffusion processes, simulation of diffusion processes, stochastic neuronal models, and stochastic differential equation models for the glucose-insulin system.

The web-page is still under construction, but will soon be open for applications:

http://www.math.ku.dk/~susanne/SummerSchool2008

- **Acireale, 2009: "Parameter Estimation in Physiological Models"**

This event will be dedicated to parameter estimation and qualitative study of mathematical models, both deterministic and stochastic. The school will address mathematical modeling and statistical estimation in a single framework with applications to human physiology and clinical issues. The associated workshop will also have parameter estimation issues as its theme.

- **Dundee, 2010: "Mathematical Modeling of Cancer Growth and Treatment"**

The focus of the school will be the use of ordinary and partial differential equations in modeling the biology/pathology of cancer growth as well as modeling applications related to the development of clinical treatment. The associated workshop at the end of the school will focus on practical matters such as multi-scale modeling, numerical and computational aspects of systems of DE's and application to anti-cancer drug design and development.

~~~~~~

ELSO 2007
6th International Congress of the European Life Scientist Organization
1 – 4 September, 2007, Dresden

ELSO 2007 had invited experimental as well as theoretical life scientists to Dresden, Germany, and an enthusiastic, young audience of almost 1500 participants gathered September 1-4, 2007. Already previous ELSO meetings had proven to be a stable attractor in the field-space spanned by developmental, molecular and cell biology. This year, 180 talks were delivered and 600 posters presented and discussed along with so-called bio-clips (www.bioclips.com) until deep into the nights.

Among the highlights from a theoretical perspective were the keynote lecture by *Eric Wieschaus* (Priceton) and the mini-symposium on systems biology. Eric Wieschaus reinforced the mysteries of robust patterning of the early fly embryo by presenting fresh data on single molecule counts of Bicoid proteins per nucleus along the anterior-posterior axis of the embryo. He used mathematical models also accounting for data on nuclear-cytoplasmic shuttling and demonstrated that the observed precision in positioning the front of target gene expression (Hunchback) could not be explained by the known cooperativity of transcriptional activation. The mini-symposium on systems biology included a lecture by *Frank Jülicher* (Dresden) on the role of transcytosis for
~~~~~~

morphogen transport and gradient formation. He presented a compelling interplay of theory and experiments. Moreover, in the same mini-symposium, *Bela Novak* (Budapest) discussed a model of mitotic exit in budding yeast and convinced at least part of the audience that corresponding passages in biology textbooks need to be rewritten.

The other side of the participation-coin, however, meant that many of the rooms turned out to be too small for holding the parallel mini-symposia. It was a pitty that the otherwise excellent facilities of the congress center didn't give more flexibility in room space and seats. Along with the latest science, ELSO has a remarkable tradition in career development efforts including the Early Career Award presented at the meeting, Career Mentoring Lunch, Funding Showcase and Open Floor Debate on the unaccounted European career structures.
Continuing a success story, the **ELSO meeting** will reconvene **in Nice on the French Riviera** from *August 30 to September 2, 2008*.

For upcoming details, please see www.elso.org/index.php?id=elso2008

Lutz Brusch
Technische Universität Dresden

ANNOUNCEMENTS

SBMC 2008
Systems Biology of Mammalian Cells
May 22-24, 2008
Kulturpalast Dresden
www.sbmc08.de

SBMC 2008 will present cutting edge experimental, theoretical and computational approaches to unravel the design principles underlying a wide range of regulatory processes in mammalian cells, including cell organization, metabolic pathways, genetic and signaling networks, tissue morphogenesis and development, and pathogenetic mechanisms.

Submission deadline for SBMC posters and talks: *31.03.2008*

SBMC is organized by HepatoSys, the Federal German research initiative for Systems Biology of hepatocytes.

Organizing committee:
Marino Zerial
Andreas Deutsch
Ute Heisner
Hemann-Georg Holzhütter
Ursula Klingmüller

ECMI 2008
University College London
30 June - 4 July 2008
www.ecmi2008.org

All participants in ICIAM07 are warmly encouraged to attend the biennial conference of the European Consortium for Mathematics in Industry which will be held in central London in 2008. The plenary talks will cover a wide range of applied mathematical topics and there will be a strong industrial presence particularly from the financial district in the City of London. Highlighted themes of the meeting are Socio-economic interactions, Medicine, Sport and Leisure, Uncertainty and Risk, Optimisation and Control as well as more traditional industrial sectors.
There will be receptions each evening and then there are the theatres and other attractions of central London to enjoy.
If you would like to receive further bulletins about this conference please contact
lucy.nye@ima.org.uk .

John Orbury
Chair, Organising Committee, ECMI2008

Computational Cell Biology Course
June 27 - July 17, 2008
Cold Spring Harbor Laboratory, New York

Organizers: *Tim Elston, Chris Fall, Greg Smith, Les Loew, John Tyson*

The course will cover the computational modeling of cellular processes including intracellular signaling, Ca2+ signaling in particular, gene expression, cell cycle, molecular motors and motility and other topics. Lecturers will include both experimentalists and theoreticians.

The course is focused on advanced graduate students and postdocs, although retraining faculty would also be appropriate. We welcome mathematically inclined or interested biologists as well as biologically inclined researchers with a quantitative background. Please see the Cold Spring Harbor course website for details.

http://meetings.cshl.edu/courses.html

~~~~~~

Summer School Copenhagen 2008
Stochastic Differential Equation Models with Applications to the Insulin-Glucose System and Neuronal Modeling

August 3 to 16, 2008
Middelfart Kursuscenter
(2 hours from Copenhagen)

Department of Mathematical Sciences
University of Copenhagen. Principal organizers: *Susanne Ditlevsen* and *Michael Sørensen*.

An **eleven day summer school** is followed by a **three day scientific workshop** on the same scientific theme. The summer school component is aimed primarily toward Ph.D students and Post-Docs.

The focus is on stochastic issues in physiological modeling. The school aims to concentrate on the possibilities offered by stochastic calculus for the solution of relevant biological problems. There is an increasing need to extend mathematical models of biological systems to models capable of describing more complex variations in the dynamics. In general, stochastic effects influence the dynamics, and may enhance or diminish or even completely change the dynamic behavior of the system. Real biological systems will always be subject to influences that are not fully understood or that cannot be explicitly modeled, and random noise offers a tractable way of taking account of these mechanisms. A natural extension of a deterministic differential equations model in continuous time is given by a stochastic differential equations model, where relevant parameters are modeled as random processes of some suitable form. This approach assumes that some degree of noise is present in the dynamics the process.
The stochastic modeling methods are applied to the glucose-insulin system and neuronal functioning. This will illustrate the advantages and highlight the problems of the stochastic modeling approach. The associated workshop will have the same themes.

The **School** will have specific courses on stochastic integrals, statistical methods for diffusion processes, simulation of diffusion processes, stochastic neuronal models, and stochastic differential equation models for the glucose-insulin system.

The **Workshop** aims at raising awareness of these matters and building a bridge between the biological problems and the possibilities offered by the theory of stochastic calculus. The goal is to gather experienced researchers within the two research areas, as well as young researchers, who will have opportunities to discuss and present their specific problems, and hopefully engage in new collaboration projects.

http://www.math.ku.dk/~susanne/SummerSchool2008

See also the full **Summer School concept and program** on *pages 28-29.*
~~~~~~

GCB 08
German Conference on Bioinformatics 2008
September 9-12, 2008
Deutsches Hygiene-Museum Dresden
www.biotec.tu-dresden.de/gcb2008/

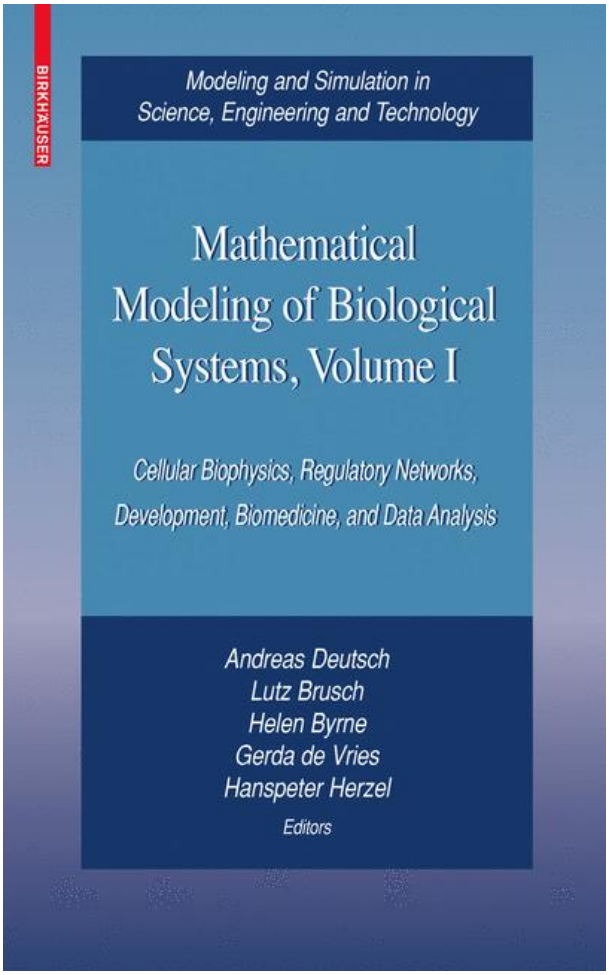
The German Conference on Bioinformatics is an annual, international conference devoted to all topics in bioinformatics. Its tradition reaches back to 1985, and recent conferences have attracted more than 200 participants from all over the world.
The 2008 conference is organized by the Technische Universität Dresden and the venue is the Deutsches Hygiene-Museum Dresden.

Areas of interest at the German Conference on Bioinformatics 2008 are:
Sequence Analysis and Comparative Genomics
Analysis of Functional Genomics Data
Structural Bioinformatics
RNA/DNA Structure
Molecular Interactions and Drug Design
Systems Biology
Biochemical and Genetic Networks
Textmining and Ontologies
Image Analysis

Deadline for submission of contributions:
May 16, 2008

Local organizers:
Andreas Beyer
Andreas Deutsch
Bianca Habermann
Michael Schroeder
Pavel Tomancak

NEW BOOKS AND JOURNALS



Mathematical Modeling of Biological Systems, Volume I
Cellular Biophysics, Regulatory Networks, Development, Biomedicine, and Data Analysis

Deutsch, A. / Brusch, L., both Technical University of Dresden, Germany / *Byrne, H.*, University of Nottingham, UK / *de Vries, G.*, University of Alberta, Edmonton, Canada / *Herzel, H.*, Humboldt-Universität zu Berlin, Berlin, Germany (Eds)

This two-volume, interdisciplinary work is a unified presentation of a broad range of state-of-the-art topics in the rapidly growing field of mathematical modeling in the biological sciences. Highlighted throughout the work are mathematical and computational approaches to solving central problems in the life sciences, ranging from the organizational principles of individual cells to the dynamics of large populations.

The chapters of Volume I are thematically organized into the following main areas: Cellular Biophysics; Regulatory Networks; Developmental Biology; Biomedical

Applications; Data Analysis and Model Validation.

2007. XVIII, 382 p. 120 illus. Hardcover
ISBN 978-0-8176-4557-1
Modeling and Simulation in Science, Engineering and Technology
www.birkhauser.com/978-0-8176-4557-1

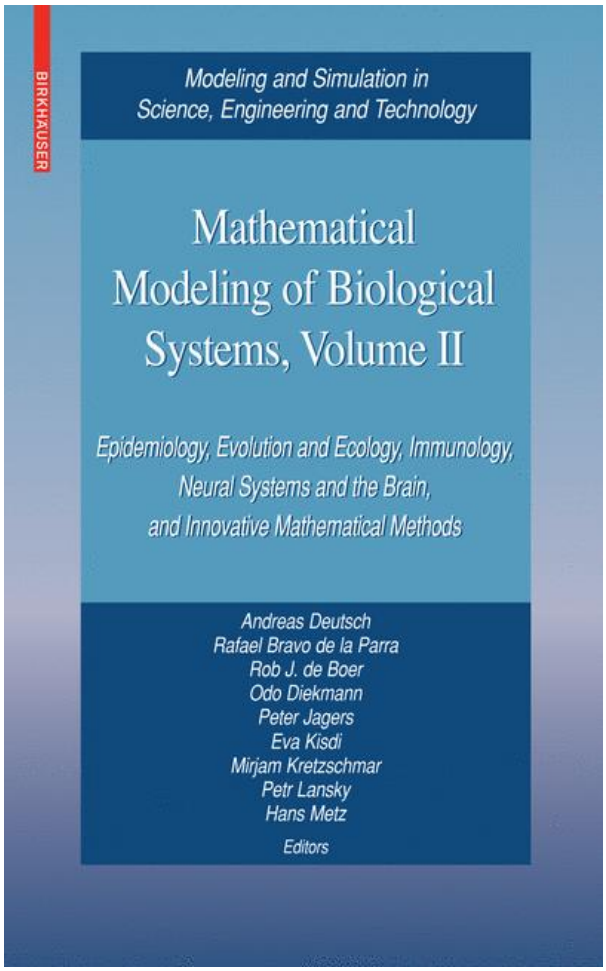
~~~~~~

Mathematical Modeling of Biological Systems, Volume II
Epidemiology, Evolution and Ecology, Immunology, Neural Systems and the Brain, and Innovative Mathematical Methods

Deutsch, A., Technical University of Dresden, Germany / *Bravo de la Parra, R.*, University of Alcala, Madrid, Spain / *de Boer, R.J. / Diekmann, O.*, both Utrecht University, The Netherlands / *Jagers, P.*, Chalmers University of Technology, Göteborg, Sweden / *Kisdi, E.*, University of Helsinki, Finland / *Kretzschmar, M.*, University of Bielefeld, Germany / *Lansky, P.*, Academy of Sciences of the Czech Republic, Prague, Czech Republic / *Metz, H.*, University of Leiden, The Netherlands (Eds)

The chapters of this volume are thematically organized into the following main areas: Epidemiology, Evolution and Ecology, Immunology, Neural Systems and the Brain, Innovative Mathematical Methods and Education.
Both volumes will be an excellent reference text for a broad audience of researchers, practitioners, and advanced students in this rapidly growing field at the intersection of applied mathematics, experimental biology and medicine, computational biology, biochemistry, computer science, and physics.

2008. XVIII, 390 p. 119 illus. Hardcover
ISBN 978-0-8176-4555-7
Modeling and Simulation in Science, Engineering and Technology
www.birkhauser.com/978-0-8176-4555-7



Modeling Complex Living Systems
A Kinetic Theory and Stochastic Game Approach

N. Bellomo, Politecnico di Torino, Italy

Using tools from mathematical kinetic theory and stochastic game theory, this work deals with the modeling of large complex systems in the applied sciences, particularly those comprised of several interacting individuals whose dynamics follow rules determined by some organized, or even "intelligent" ability. Traditionally, methods of mathematical kinetic theory have been applied to model the evolution of large systems of interacting classical or quantum particles. This book, on the other hand, examines the modeling of living systems as opposed to inert systems.

2008. XII, 220 p. 37 illus. Hardcover
ISBN 978-0-8176-4510-6
Modeling and Simulation in Science, Engineering and Technology
~~~~~~

www.birkhauser.com/978-0-8176-4510-6
Modelling in Medicine and Biology VII
edited by *C. A. Brebbia*
Volume 12 in WIT Press's WIT Transactions on Biomedicine and Health.

Proceedings of the *Seventh International Conference on Modelling in Medicine and Biology*, which was held in The New Forest, UK, *September 10-12, 2007*. The conference also incorporated a seminar on Environmental Electromagnetic Fields. The papers from the conference present the latest developments in simulations in medicine. The papers are organized into the following chapters: Cardiovascular systems; Biomechanics; Computational fluid dynamics; Intracranial pressure dynamics; Exposure to electromagnetic fields; Skin and membranes; Data acquisition and analysis; and Computer simulation.

Full contents details on the book can be found at http://www.witpressusa.com/acatalog/9781845640897.html

~~~~~~

Journal of Computational Biology
ISSN 1066-5277
10 Issues Annually

New "Open Option" for Journal of Computational Biology

A peer-reviewed journal providing a forum for the communication of technical issues associated with the analysis, management, and visualization of cellular information at the molecular level. Includes papers on genomics, mathematical modeling and simulation, distributed and parallel biological computing, designing biological databases, pattern matching and pattern detection, linking disparate databases and data, new tools for computational biology, relational and object-oriented database technology for bioinformatics, biological expert system design and use, reasoning by analogy, hypothesis formation and testing by machine, and management of biological databases.
Formerly: Journal of Theoretical Medicine
has been renamed into
Computational and Mathematical Methods in Medicine

According to the new name this journal seeks to promote genuine interdisciplinary collaboration between those interested in the theoretical and clinical aspects of medicine and to foster and encourage the application of mathematics to problems arising from the biomedical sciences. Areas of interest include gene therapy, cell kinetics, pharmacokinetics, chemotherapy, oncology, developmental biology, wound healing, physiology, heart modelling, cardiovascular and lung dynamics, neurobiology, computational neuroscience, biomechanics, biomedical statistics, image analysis, epidemiology, immunology, time series analysis, extracellular matrix properties and signalling, and tissue engineering. This list is not exclusive and papers in other biomedical disciplines are encouraged, particularly in the emerging areas of multiscale modelling in medicine, systems biology and translational research.

An ideal paper will combine theory with experiment and papers published will range from theoretical modelling papers to experimental clinical papers.

The Journal also welcomes the submission of rapid communications - offering researchers the opportunity to pose problems to the mathematical medicine community and comment on topical issues and current research.

All published research articles in this journal have undergone rigorous peer review, based on initial editor screening and anonymous refereeing by independent expert referees.
~~~~~~

Central European Journal of Biology (CEJB)

Excellent research in life sciences continues to accelerate in Poland, the Czech Republic, Hungary, Russia and other countries of the region. Our journal is fast becoming the leading publication on the best research done in life sciences in Central and Eastern Europe. We are inviting you to read the journal:
www.springerlink.com/content/1644-3635/,
which is freely available by the end of December 2007. More information about the journal can also be found below.

The CEJB is a broad scope biological journal published by Springer and Versita. For further information feel free to visit our website at http://versita.com/science/lifesciences/cejb/

~~~~~~

EPIDEMICS
is a new journal publishing papers on infectious disease dynamics in the broadest sense. Its scope covers both within-host dynamics of infectious agents and dynamics at the population level, particularly the interaction between the two.
Areas of emphasis include: spread, transmission, persistence, implications and population dynamics of infectious diseases; population and public health as well as policy aspects of control and prevention; dynamics at the individual level; interaction with the environment, ecology and evolution of infectious diseases, as well as the population genetics and molecular evolution of infectious agents.

The journal is open for submission of papers which will be published online as accepted. The first print issue is officially planned for launch at **EPIDEMICS**[1] - the inaugural conference in the field. **Submit papers here...**

JOURNAL EDITORS

Sebastian Bonhoeffer, *ETH, Zürich, Switzerland*
Neil Ferguson, *Imperial College London, UK*
Hans Heesterbeek, *University of Utrecht, The Netherlands*
Eddie Holmes, *Pennsylvania State University, USA*
Gabriel Leung, *University of Hong Kong, Hong Kong*

~~~~~~

HFSP Journal
Frontiers of Interdisciplinary Research in the Life Sciences

Editor-in-Chief
Arturo Falaschi
ICGEB, Trieste and SNS, Pisa

http://hfspj.aip.org/

The *HFSP Journal* is a new journal which aims to foster communication between scientists publishing high quality, innovative inter-disciplinary research at the interface between biology and the physical sciences.

It aims to publish high quality, innovative interdisciplinary basic research at the frontier of biology over a wide range of organizational levels (from the molecular level to population biology) using principles strategies or technologies from the more quantitative disciplines as physics, chemistry, mathematics, engineering, or informatics.

An example of a recently published article:
The origin of modern terrestrial life
Patrick Forterre and Simonetta Gribaldo

International Journal of Biomathematics
(IJB) ***Forthcoming 2008***

World Scientific
http://www.worldscinet.com/ijb/mkt/aims_scope.shtml

The goal of this journal is to present the latest achievements in biomathematics, facilitate international academic exchanges and promote the development of biomathematics. Its research fields include mathematical ecology, infectious disease dynamical system, biostatistics and bioinformatics.
The *International Journal of Biomathematics* is published quarterly.

Editor-in-Chief
Lansun Chen
Acade Academy of Mathematics and System Sciences, Academia Sinica, Anshan Normal University, China
E-mail: lschen@math.ac.cn

Co-Editor-in-Chief
Karl Sigmund
Universitaet Wien, Strudlhofgasse, Austria
E-mail: karl.sigmund@univie.ac.at

Editors (selection out of the complete list):
Edoardo Beretta *(Universita di Urbino, Italy)*
Odo Diekmann *(University of Utrecht, Netherlands)*
Mats Gyllenberg *(University of Helsinki, Finland)*
SA Levin *(Princeton University, USA)*
Avidan U Neumann *(Bar-Ilan University, Israel)*
Juan J Nieto *(IMAT-USC Santiago de Compostela, Spain)*
Y Takeuchi *(Shizuoka University, Japan)*

~~~~~~

BioMed Central Blog
Wednesday Jan 16, 2008

Biology Direct launches new Mathematical Biology section

We are delighted to announce the launch of the new Mathematical Biology section of *Biology Direct*, over seen by the Section Editor Andrei Yaklovev, and supported by an international Editorial Board.

Biology Direct, founded by David J Lipman, Laura Landweber, and Eugene Koonin, operates a unique open peer review system, whereby reviewers' comments and authors' responses are published alongside the final article, making the process of peer review open, rather than anonymous.

Biology Direct was launched in 2006 and has since published over 75 articles; nearly half of which have been accessed over 2,000 times, and seven articles have been highlighted on the literature evaluation service Faculty of 1000 Biology.

Biology Direct is tracked by Thomson Scientific and is on course to receive its first impact factor in 2008. As an open access publication, all articles are freely and immediately available online, maximising the visibility of the author's work, and copyright is retained by the author.
~~~~~~