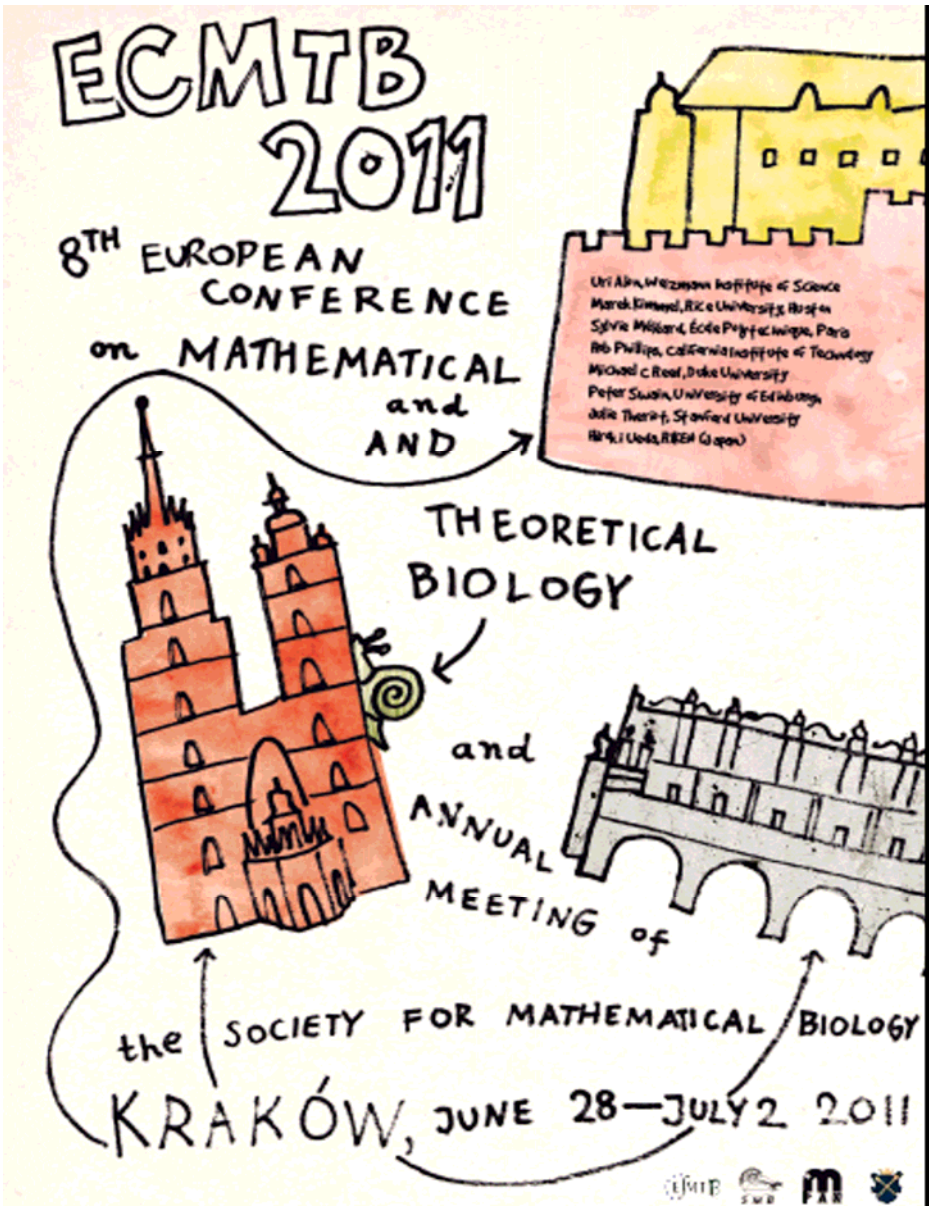
European Communications in Mathematical and Theoretical Biology
July 2010, No. 12

ECMTB Communications



ESMTB European Society for Mathematical and Theoretical Biology

A European Forum for Information, Presentation and Exchange
Official Communication Bulletin of the ESMTB
European Society for Mathematical and Theoretical Biology

EDITORIAL

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

Noctice that currently we are within the 20th year of the European Society for Mathematical and Theoretical Biology (ESMTB). From its birth till now our Society has undergone a very lively development. ESMTB promotes theoretical approaches and mathematical tools in biology and medicine in a European and wider context. This is reflected in supporting relevant Conferences and Workshops, helping to set up European Summer or Winter Schools and providing traveling costs for students. Moreover, the **new Website** of our Society (www.esmtb.org) offers material for downloading and actual information, as does the **ESMTB Infoletter**, regularly distributed to all members, and the yearly appearing **European Communications:** we are glad to present you the latest *12th edition* issue here, featuring an overview about a series of past activities and further perspectives.

This edition appears quite late in the year, because the decision on the ***Reinhart-Heinrich Doctoral Thesis Award 2009*** again took longer than expected: The awarding committee was pleased to receive 17 high-quality applications from young scientists (see *page 11*). After a pre-selection of 6 candidates with excellent theses on most interesting topics, the committee finally nominated two of them as winners (see the laudations together with the extended summaries of all 6 theses from *page 13* on).

The forthcoming ***8th European Conference on Mathematical and Theoretical Biology ECMTB'11*** will take place in ***Krakow, Poland, 28 June – 2 July 2011.*** ECMTB'11 will bring together scientists and students from all over the world to discuss recent advances in modeling ideas and analysing methods. ECMTB'11 will also be the 2011 annual meeting of the Society for Mathematical Biology. The conference is designed for researchers who are active in or interested in this fast growing field where experimental biology and medicine, biochemistry, computational biology, mathematics, computer science, physics and various fields of technology merge. Participants from East-European countries are particularly welcome; for further information see *page 9* and website: http://www.impan.pl/~ecmtb11/

The society depends on the activities of its members. So please think already now about how you can contribute to the next Communications, for example, by presenting your *Research Group*, by writing reports on *Past Activities* (as conferences, workshops, summer school) or by just sending your opinion, critique or suggestions.

Thanks a lot for your active support over the years.

The editorial board

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Please send by e-mail any information, reports or other material for the next Communications *(ECMTB # 13)* as soon as available, best until **February 28th, 2011,** 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 2010

http://www.esmtb.org

ESMTB membership includes free electronic subscription of the official journal of the Society
Journal of Mathematical Biology
and reduced low subscription rates to the **print edition** (25 Euro) as well as for several other journals.

Please register at www.esmtb.org and send your payment of the required annual fee for 2010 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: Commerzbank
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:
Commerzbank, Dr. Kuelz-Ring 10
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Dresden University of Technology

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SOCIETY NEWS

Minutes of the ESMTB Board Meeting
Marseille, 21 March 2009

Meeting starts at 10:05.

Present: Carlos Braumann (CB, chair), Andreas Deutsch (AD), Miguel Herrero (MH), Peter Jagers (PJ), Eva Kisdi (EK; minutes), Daphne Manoussaki (DM), Jean-Christophe Poggiale (JP), Andrea Pugliese (AP), Hans Westerhoff (HW), Wolfgang Alt (WA, advisor), Ryszard Rudnicki (RR, advisor).

Absent with apology: Christine Jacob (CJ)

1. Round of welcome

CB welcomes the new members of the Board and welcomes WA and RR as invited advisors to the Board. All present briefly introduce themselves. CB thanks Past President WA and all members of the previous Board who have finished their term, and thanks JP for organising the Board meeting in Marseille.

The Board votes if WA (Past President) and RR (organiser of ECMTB'11 and representative of the new EU countries) are invited as permanent advisors to the Board for the term 2009-2011: accepted with 9 yes, 0 no and 0 abstention from Board members present, CJ expressed consent via email.

2a. Review of current activities by the Past President

WA is invited to give a review of the previous Board's work, the last Board meeting in Edinburgh, current activities, responsibilities that previous Board members have offered to continue with also in the future, and those tasks that need to be reassigned to present Board members.

- The previous Board held five board meetings in 3 years (Bonn 2006; Amsterdam 2006; Turin 2007; Evora 2008; Edinburgh 2008). Board members were frequently in contact by email, which provided fast and efficient way of discussing matters arising inbetween board meetings. The Society has changed its Statutes to allow for a Board member to be elected twice consecutively, and AD was re-elected in the electronic ballot organised in the fall of 2008. WA proposes to the new Board to nominate AD as election candidate for Treasurer, EK for secretary and CB for President.

- ESMTB has established the Reinhart Heinrich Doctoral Thesis Award, which was first awarded to two winners during the ECMTB'08 conference in Edinburgh. For this year's award, WA has received 14 applications, of which 6 have been asked to submit the full thesis. The Awarding Committee has already chosen three finalists, and the winner will be announced within a few weeks from the Board meeting.

- ESMTB has successfully launched the series "Perspectives in Mathematical and Theoretical Biology" in the Journal of Mathematical Biology, and Helen Byrne will continue to edit submissions to the Perspectives with advice from the current members of the Board. The contract ESMTB has with Springer Verlag on publishing JMB as the official journal of the Society will have to be renewed this year.

- ESMTB has supported several summer schools and is going to collaborate with EMS (European Mathematical Society) in organising and supporting further schools. In the previous Board, summer schools and related activities were the responsibility of Rafael Bravo de la Parra, the new Board needs to assign this task to one of its members (see below).

- WA will continue as the main editor of the ESMTB Communications, the editorial board however needs new members to replace past board members Helen Byrne and Luigi Preziosi. Luigi Preziosi had also the responsibility for keeping contact with EU Framework Programmes and other funding agencies, so that the new Board has to reassign this task (see below).

- Conferences: SMB will join the ECMTB'11 Conference in Krakow. The status of the Proceedings from ECMTB'08 (Edinburgh) needs to be clarified and the publication process be speeded up (EK to contact ECMTB'08 organiser Mark Chaplain). The Third Conference on Computational and Mathematical Population Dynamics (CMPD3) seeks support and offers reduced price to Society members.

2b. Report by the Treasurer

AD gives an overview of the past 6 years as he has served as Treasurer since 2003, and outlines plans for the next period.

Membership

- Membership has been consolidated and is steadily growing (2003: 91 paying members from 26 countries, 5 countries have five or more members; 2008: 258 paying members from 41 countries, 15 countries have five or more members). 2005, the year of the last joint conference of ESMTB and SMB, had an exceptionally high membership figure (319 paying members).

  Membership payments accumulate gradually during each calendar year so that (in years without a summer conference) about half the members pay only in the second half of the year. AP proposes to send renewal notices at the beginning of each year. CB will call the attention of SMB members to the benefits of joint membership with ESMTB.

- The Treasurer has worked on making membership benefits significant and visible to all members[1].

- Membership survey: AD will carry out a survey among the Members of the Society in 2009 asking which Society services they appreciate and what suggestions they have for service development.

- The best way to pay membership fees is via bank transfer, other modes attract a fee paid by the Society. The Society's bank account is located in Dresden, and is difficult to move. AD suggests that the function of the Treasurer could in the future be made a service rather than an elected post, such that the account does not have to be moved when the Board changes.

Financial situation

- In 2008, the Society's revenues, exclusively from membership fees, were EUR 8,345. Expenditures totalled

[1] Newly introduced benefits include the Reinhart Heinrich Prize, travel grants, and the monthly Infoletter; benefits continue to include full subscription to JMB, free copies of the Communications, reduced journal subscription rates, reduced fees at selected conferences and schools, and support to summer schools. The Society website serves up to date information together with the Infoletter.

EUR 14,782 and included the payment to Springer for members' copies of JMB, the printing and distribution costs of the Communications, the Reinhart Heinrich Prize, support to a summer school, travel grants, EMS and ICIAM membership fees, flyers and posters, domain registration and bank account fees. For 2009, revenues are estimated to be 10,000 euros whereas expenditures may be as much as 24,500 euros.

- Membership fees are not changed in 2009. As seen above, the Society membership fees do not cover the expenditures. The Society however has had extra income from the Dresden conference ECMTB'05, which can currently finance the expenditures. The Technical University of Dresden provides an assistant to the Society currently for free, even though this amounts to ca 20 working hours / week or EUR 15,000 a year.

- Questions arise if the membership fee should be increased now and if the expenditures could be cut back. AD proposes that the Board waits until the new Springer contract has been negotiated and the Membership survey results are in, so that a clearer picture of future expenditures arises. CB proposes to limit the number of travel grants (e.g. to 12 grants, support attending ECMTB).

- WA raises the question if printed copies of the Communications need to be sent to each member or the Communications should be distributed electronically. Electronic copies are available to all via the Society website. Printing in small numbers increases the cost per copy, which cautions against making the distribution of printed copies optional. The Communications will appear in print this year and the membership survey will help to make the decision for the future.

- CB will urge ECMTB'08 organiser Mark Chaplain to submit the financial report of the conference and clarify revenue contribution.

- The Society awarded 15 travels grants in 2008. The travel grants need to be better announced especially in the new EU-countries and in developing countries.

Journal of Mathematical Biology

Downloads of JMB articles from the Springer website have markedly increased. The computational biology special issues of JMB expanded the journal's coverage. The contract with Springer will be renewed this year.

2c. Overview of other current matters

JP has submitted the change of Statutes to the Prefect's Office in France (the Society is subject to French law) and collects updated information of the Board for the same office.

European Biomathematics curricula will be collected on an interactively updated website JP is developing. The Board briefly discusses the promotion of this site when ready.

AP will be the current Board's contact person to JMB for the "Perspectives in Mathematical and Theoretical Biology" section (edited by Helen Byrne). AD will update the description of the Society appearing in JMB.

3. ECMTB'11

RR presents the current status of the ECMTB'11 conference to be held in Krakow.

RR plans the dates 29 June – 3 July 2011 (Wednesday-Sunday). Board members suggest moving the conference away from the weekend, e.g. Tuesday – Saturday (28 June – 2 July).

RR reviews the conference venue, the local organising and scientific committees, and proposes to invite one Polish plenary speaker. Expenditures and conference fees are discussed (there is considerable uncertainty due to the changes in currency exchange rates). The structure of the conference and the Proceedings from the conference are discussed next.

AD proposes that tutorial sessions could be organised before the conference. WA reminds of organising a mentor programme similar to the one ECMTB'05 had. AD urges the organisers to include the social programme (such as the conference dinner) in the registration fee, which proved successful in Dresden.

The Board compiles a list of key topics and draws up a draft for the Scientific Committee.

[Elections are conducted at this point because HW needs to leave shortly. See election records below. HW leaves after the elections.]

Further discussion of the conference centres on the special events (awarding the Reinhart Heinrich Prize of ESMTB and the Okubo Prize of SMB; discussion forum; General Assembly of ESMTB; special session for the 20th anniversary of ESMTB; exhibitions), recruiting new Society members via the conference, financial support to the conference and space requirements.

4. Elections

The elections are conducted by WA.
CB is nominated as candidate for President. AP and DM are nominated as candidates for Vice President. 9 members of the Board are present and vote.

Results of the ballot electing the President: 8 yes to CB, 0 no, 1 abstention.
CB accepts the post of President.

Results of the ballot electing the Vice President: 4 votes for AP, 3 votes for DM, 2 abstentions.
AP accepts the post of Vice President.

EK is elected as Secretary with 8 yes, 0 no, 1 abstention.
AD is elected as Treasurer with 8 yes, 0 no, 1 abstention.

The Board votes to request Rafael Bravo de la Parra and Barbara Boldin as the new cash auditors of the Society: 9 yes, 0 no, 0 abstention.

5. Assignment of specific tasks and responsibilities

Vincenzo Capasso will continue to represent ESMTB at ICIAM, and Mats Gyllenberg will be asked to continue to represent ESMTB at EMS[2].

Specific tasks are distributed among Board members as follows:
Co-editor of the Communications: AP
Contact person towards Springer: AD, PJ
Evaluation of travel grant applications: DM, MH
Funding: HM, DM
Website: AD
Promotion, outreach, members' benefits, membership development: CJ, HW; RR towards new EU-member countries
Education, curriculum database: JP, CJ
Summer schools: DM

The committee evaluating theses submitted for the Reinhart Heinrich Prize consists of CB, WA, AD, Edda Klipp, David Rand and Andre de Roos (no new members).

[2] As it turned out, Gyllenberg was unable to attend the May 2009 EMS meeting of the Presidents; instead, RR represented ESMTB there.

6. Diverse

CB proposes that the Technical University of Dresden could be invited as the official sponsor of ESMTB, such that their sponsorship would amount to maintaining the Society's website.

The CMPD3 conference is awarded support of 1000 euros plus any income the Society obtains via the conference.

J. F. Rodriguez (Lisbon) has approached the Society asking help to organise the conference "The Mathematics of Darwin's Legacy". The Board delegates PJ and EK to be co-organizers of this conference.

EMS has invited ESMTB to propose and co-organise summer schools. The biannual series "The Helsinki Summer School on Mathematical Ecology and Evolution" is proposed along with individual schools on a variety of subjects in biomathematics in the intervening years. The latter could include a biomechanics school organised by MH and schools DM intends to co-organise with other scientific societies.

The next Board meeting will be organised by DM in Crete, around October 2009.
The meeting ends at 18:00.

Eva Kisdi
ESMTB Secretary

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A Summer School and Workshop on Mathematical Modelling of Cancer Growth and Treatment
15-28 August 2010,
Mathematical Biology Group
University of Dundee

This event is the last in a series of 4 previous summer schools all funded by the European Union Marie Curie Conferences and Training Course programme.

The Summer School is scheduled for 15-25 August. The Workshop will follow immediately afterward: 26-28 August.

The Summer School will take place at The Westpark Conference Centre, Dundee:
http://www.westpark.co.uk/

For more details see the Summer School website:

http://www.maths.dundee.ac.uk/summerschool2010

Confirmed Summer School Lecturers/Instructors:

H. Byrne, University of Nottingham
J. Clairambault, INRIA, Paris-Rocquencourt
A. Deutsch, Technische Universität Dresden
A. D'Onofrio, European Institute of Oncology, Milano
D. Drasdo, INRIA, Paris-Rocquencourt
H. Enderling, Tufts University School of Medicine, Boston
A. Marciniak-Czochra, University of Heidelberg
L. Preziosi, Politecnico di Torino
P. Macklin, University of Dundee
A. Matzavinos, Iowa State University
I. Ramis-Conde, INRIA
B. Ribba, Ecole Normale Superieure de Lyon
J. Tyson, Virginia Tech

Confirmed Workshop Speakers:

A. Ciliberto, IFOM-IEO, Milano
V. Cristini, MD Anderson Cancer Center, Houston
J. Lowengrub, UC Irvine
S. McDougall, Heriot-Watt University
N. Monk, University of Nottingham
M. Owen, University of Nottingham
J. Sherratt, Heriot-Watt University
M. Swat, Indiana University
Z. Szymanska, ICM Warsaw
S. Webb, Strathclyde University

Summer school:
Mathematical ecology and evolution
Finland, 22-29 August 2010

The Helsinki Summer School on Mathematical Ecology and Evolution 2010 invites applications from students and young researchers to attend the one-week intense program of five topics at the research frontier:

Evolutionary game theory (Karl Sigmund) Bifurcation analysis (Yuri Kuznetsov) Stochastic differential equations (Carlos Braumann) Population genetics (Reinhard Bürger) Stochastic models for epidemics (Tom Britton)

The school will be held between 22 and 29 August 2010 in Turku, Finland, organised by the Biomathematics Group of the University of Helsinki and endorsed by EMS and ESMTB.

For more details see http://
wiki.helsinki.fi/display/huippu/mathbio2010.

Welcome
Eva Kisdi and Petr Ondracek

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KEPLER AWARD for European Young Scientists (KEYS)

Award:
The European Academy of Sciences (EAS) announces an award for highly talented young scientists successfully working in European Universities or Research Institutions.
The award is granted to an international team of young scientists, selected in a competition for a workshop, planned and organized by the team and covering interdisciplinary topics chosen by the applicants in a field selected by EAS.
The award consists of financial and organisational support to run the workshop.
The starting Kepler workshop is dedicated to Modelling and Simulation in the Life Sciences and is planned to take place in Heidelberg (Germany) in 2010/11, in cooperation with the Heidelberg Academy of Sciences and Humanities (HAW), the State Academy of Baden-Württemberg.

Help for the local organisation will be provided.
The basic financial grant for this workshop will be 10.000 €.
The proponents of the winning team will be invited to become Kepler fellows of EAS for 5 years and to cooperate with members of the Academy.

Aims:
This award has the goal to stir the cooperation of young researchers in Europe interested in research crossing the borders of disciplines and states. By offering communication and cooperation with its members the interactions between generations is going to be enhanced. Fellows will have the right and are expected to take part in scientific activities of the EAS.

Application:
The teams, participating in the competition, should have at least two, but not more than four members, they have to be interdisciplinary and its members should come from institutions located at least in two European countries.
The applicants should not be older than 35 years and not yet in a permanent position as professors. All members of the team should have received the doctoral degree and successfully published papers.
The proposed list of supported participants should include at least two thirds from European countries (either EU or associated states). The list of proposed participants may include senior scientists, who are supposed to be financially self supported.
The application has to follow the instructions given in www. eurasc.org,
where further information can be found.

Expected date for the supported workshop would be not later than march, 2011.

The deadline of applications for the following **second** Kepler Award will be in April, 2011.

Vincenzo Capasso, Milano

First announcement of ECMTB'2011

8th European Conference on Mathematical and Theoretical Biology 2011

http://www.impan.pl/~ecmtb11/

The joint triennial meeting of the European Society for Mathematical and Theoretical Biology (ESMTB) and the annual meeting of the Society for Mathematical Biology (SMB) will be held in

Kraków, June 28 - July 2, 2011

Previous ESMTB meetings were held in Alpe-D'Huez, Lyons, Heidelberg, Amsterdam, Milano, Dresden, and Edinburgh; previous SMB meetings were in San Jose, Toronto, Vancouver, and Rio de Janeiro.

Call for abstracts and minisymposia

Minisymposium proposals are solicited. Each minisymposium should be organized in a block of 2 hours, each of which consists of five talks. (Example: One 40-min lecture and four 20-min communications).
We also solicit contributed talks and posters. Titles and abstracts should be submitted via the conference website. All submitted abstracts will be evaluated by the Scientific Committee.

Approved talks will either be a
20-min communication or
a contributed lecture of 30 or 40 min.

Mentoring program

The ECMTB will offer a mentoring program, which matches junior and senior scientists with similar research interests. Prospective mentees or mentors may sign up via the conference web site or directly via email to the Mentor Scheme Coordinator.

Key topics and sections

* Immunology
* Cancer
* Bio-imaging
* Cellular Systems Biology
* Cell and Tissue Biophysics
* Neurosciences
* Molecular Dynamics
* Medical Physiology
* Regulatory Networks
* Developmental Biology
* Epidemics
* Education
* Conservation Biology
* Bioengineering
* Population Dynamics
* Ecosystems Dynamics
* Evolutionary Ecology
* Population Genetics
* Genetics and Genomics
* Bioinformatics and System Biology
* Miscellaneous

Deadlines

Nov. 1, 2010 - Registration opens
Dec. 1, 2010 - Minisymposium proposals
Feb. 1, 2011 - Proposals for talks and posters
Feb. 1, 2011 - Hotel reservation starts
Apr. 15, 2011 - Early registration closes
June 1, 2011 - Late registration closes

Important information will be released:
Jan. 15, 2011 - Acceptance of minisymposia
March 20, 2011 - Acceptance of abstracts
June 10, 2011 - Programme online

Ryszard Rodnicki, Kraków, Poland

"Perspectives in Mathematical Biology"

***Review articles**, so far published as 'last pages' in several issues of JMB, devoted to the general scopes of our Society (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 & Sarah Waters:
Mathematical challenges in integrative physiology JMB 56(6): 893-6 (2008)

Vincenzo Capasso:
Multiple scales and geometric structures: additional sources of randomness
JMB 59(1): 143-6 (2009)

Wolfgang Alt:
Model-supported data analysis: some biological principles and examples (5 pages)
JMB DOI 10.1007/s00285-009-0310-7 (2009)

Amaury Lambert:
Population genetics, ecology and the size of populations JMB 60(3): 469-72 (2010)

Peter Jagers:
A plea for stochastic population dynamics
JMB 60(5): 761-4 (2010)

Eva Kisdi & Stefan A.J. Geritz:
Adaptive dynamics: a framework to model evolution in the ecological theatre
JMB 61(1): 165-9 (2010)

The **European Mathematical Society Ethics Committee** is now born with first goals:

Initially, the Ethics Committee will focus on unethical behaviour in mathematical publications as, for example, inadequate citations, inflated self-citations and dishonest refereeing.

"This includes plagiarism, duplicate publication, dishonest refereeing, and other violations of the professional code."

The Committee will be responsible for the following three tasks:

1. To raise the awareness of the problem by prearing a code of practice.
2. To encourage journals and publishers to respond to allegations of unethical behaviour in a conscientious way.
3. To provide a mechanism whereby researchers can ask the Committee to help them pursue claims of unethical behaviour.

The members are, for the moment:

Professor Arne Jensen (chair of the committee)
Department of Mathematical Sciences
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DK-9220 Aalborg Ø, Denmark
matarne@math.aau.dk

Jean-Paul.Allouche@lri.fr
Adolfo.Quiros@uam.es
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Radu.Gologan@imar.ro
Christine.Jacob@jouy.inra.fr
Garth Dales: garth@maths.leeds.ac.uk

Christine Jacob, Paris

Reinhart-Heinrich Doctoral Thesis Award 2009

Again, the awarding committee obtained a long list of applications, this year from ***17 young scientists***, who had recently finished their PhD thesis. The theses represent a broad and interesting range of actual research topics in our growing field of Mathematical and Theoretical Biology. For example, metabolic network modeling and reaction kinetics have been presented four times (by *Albert Gevorgyan, Sergio Grimbs, Saowalak Kalapanulak* and *Anna Lena Nöthen*), the same holds for gene regulatory models (by *Aysam Gürler, Orsolya Kapuy, Treenut Saithong* and *Stefan Zeiser*), also population dynamics and phylogenetics have been brought onto scene (by *Peter Kálmán Molnár, Ivo Siekmann* and *Mareike Fischer*) and neurophysiology was treated by *Ondrey Pokora*.

The committee pre-selected six candidates, whose theses were found to be all excellent. Therefore, it was not easy to separate them and make a special choice. Finally, however, a comparison of rankings brought the following decision:

The awarding committee nominates ***two winners*** of the RH Award 2009

- ***Stefan LEGEWIE*** *(Berlin, Germany)*
- ***Max WOLF*** *(Groningen, Netherlands)*

The other selected candidates are:

- *Haralambos HATZIKIROU (Dresden)*
- *Alexander SKUPIN (Berlin)*
- *Orsolya KAPUY (Budapest)*
- *Yael ARTZY-RANDRUP (Tel-Aviv)*

Thanks goes to all for their stimulating work and gentle cooperativity!

Stefan LEGEWIE
s.legewie@dkfz-heidelberg.de

Systems biological analyses of intracellular signal transduction

The promotion took place at the Institute for Theoretical Biology, Humboldt University of Berlin
Advisors: Hanspeter Herzel (Berlin), Jens Timmer (Freiburg)

Laudatio:
Stefan Legewie's thesis is a a tour-de-force of modelling networks, with a great variety of application, huge amount of information, very

complete, amazingly competent. One of the new ideas is to fully incorporate feedback modeling into Molecular Systems Biology.
Legewie has investigated cell fate decisions by studying the dynamics and structural properties of various signaling pathways. He has combined new ways of theoretical analysis of signaling cascades, such as MAPK pathway, TGFbeta pathway and caspase pathways, with health relevant processes such as tumor suppression and oncogene cooperation. He has studied the regulation mechanisms on various levels, i.e. within the pathway, transcriptional, post-translational, or by miRNA, and thereby, given an impressively comprehensive view on cellular decision making. Although the work is primarily theoretical, he stayed closely at the experimental data and provided new interpretation of experimental facts.

It can be seen as a somehow independent argument for the quality of Legewie's work that it has led already to 13 publications (of today).

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Max WOLF
mwolf@mpib-berlin.mpg.de

Adaptive individual differences:
The evolution of animal personality

The promotion took place in the Theoretical Biology Group, University of Groningen

Advisor: Franz J. Weissing (Groningen)

Laudatio:
In his thesis, Wolf presents a brilliant essay on the evolution of animal personalities with lots of new important ideas and papers which appeared e.g. in Nature and PNAS.

The investigations concerning *'Adaptive Individual Differences'* made by Max Wolf are really innovative and represent a beautiful and creative application of many disciplines (evolutionary biology, personality psychology, behaviour economics). The new findings received already a lot of attention by the experts in the respective research fields. Wolf represents a new type of scientist whose work is primarily devoted to a specific topic and not constrained by the limits imposed by the use of different disciplines. Not only an excellent researcher is decorated with the Reinhard Heinrich Award but also a sign is given that will encourage others to overcome the limits and contribute to the integration of different scientific fields. Surely, Reinhard Heinrich would have been very impressed by Max Wolf if he would have met him personally, since this award is given to this specially creative and at the same time very solid scientist.

Extended Summaries of Theses

Stefan LEGEWIE

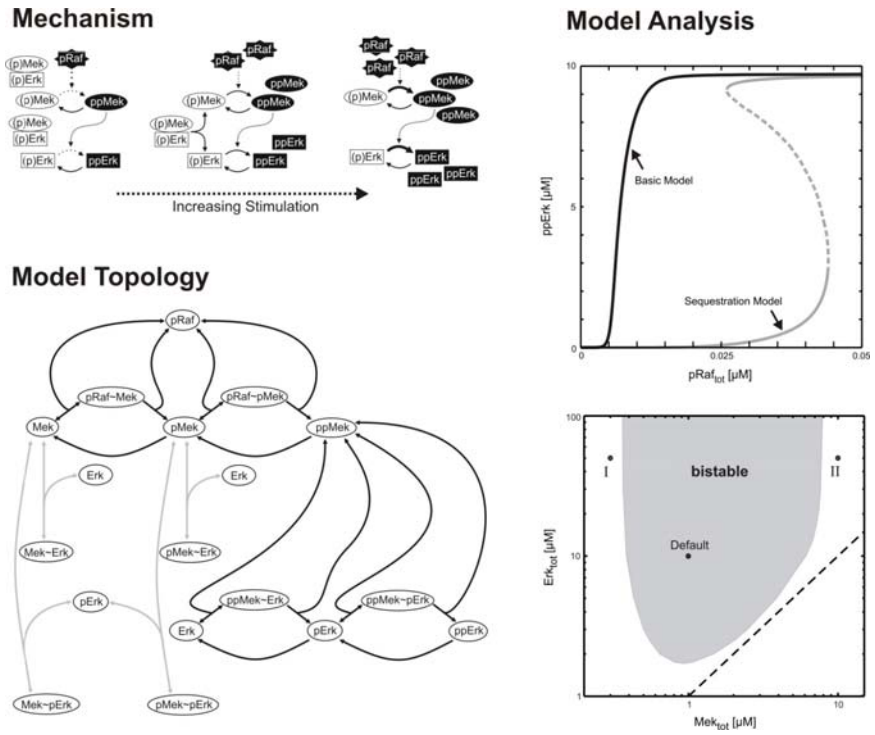
Systems biological analyses of intracellular signal transduction

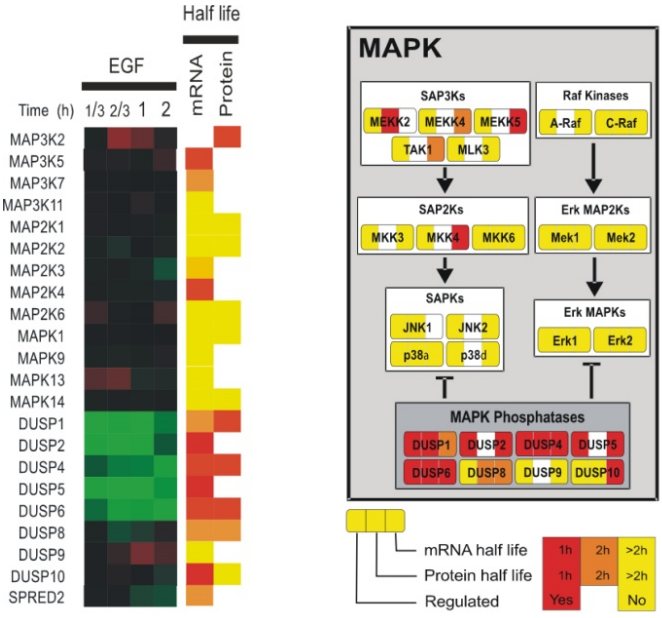
Intracellular regulatory networks involved in the sensing of extracellular cues are crucial to all living organisms. Signal transduction networks allow unicellular organisms sensing nutrient availability, finding mating partners and responding to stress. Moreover, intercellular communication is the fundamental basis for the functioning and homeostasis of multicellular organisms. Accordingly, many diseases including cancer are caused by deregulation of signal transduction networks. Extracellular signals are typically transmitted rapidly from the cell membrane to the nucleus by activation of multi-level enzymatic cascades which ultimately elicit slow changes in gene expression, and thereby affect the cell fate. These signalling cascades are highly interconnected, thus giving rise to complex networks that are hard to understand intuitively. In this thesis, a combination of kinetic modeling and analysis of quantitative experiments is applied to get insights into the principles of intracellular signalling.

In the first part (chapter 2-4), the dynamics of enzymatic signalling cascades involved in transducing signals from the cell membrane to the nucleus are investigated. Chapters 3 and 4 focus on switch-like ('all-or-none') behavior in biochemical regulatory networks. The central importance of positive feedback loops for initiating irreversible cellular responses in the presence of transient external inputs is discussed. The results reveal how cells can distinguish relevant extracellular signals from random biological noise, and how they robustly switch from fate to another. In Chapter 3, previously unknown hidden positive feedback loop that arises from enzyme competition effects in the well-known mitogen-activated protein kinase (MAPK) cascade is described (see Fig.1). The proposed mechanism could explain why MAPK activation and downstream proliferative response are often switch-like when measured at the single-cell level. Programmed cell death ('apoptosis') is a classical example for a digital and irreversible response. Chapter 4 describes the derivation of a mathematical model of the proteolytic caspase activation cascade in the mitochondrial apoptosis pathway. The simulations suggest an unanticipated role for inhibitors of apoptosis proteins (IAPs): Simultaneous inhibition of multiple caspases by IAPs can result in strong positive feedback regulation, and may thus be essential to establish all-or-none and irreversible initiation of cell death. The results help to explain how terminally differentiated cells such as neurons or cardiomyocytes efficiently escape cell death under healthy conditions.

Cellular commitment to a new fate typically requires ongoing extracellular stimulation and/or intracellular signalling for several hours. Thus, the long-term dynamics of signalling cascades and feedback regulation by downstream gene expression responses are important for celllar responses. The second part of the thesis (Chapters 5 and 6) is therefore focused on the modulation of intracellular signal transduction by slow transcriptional feedback loops. In Chapter 5, the design principles underlying transcriptional feedback regulation of mammalian signalling pathways are identified. Gene expression profiles in the first few hours after stimulation are systematically analyzed for induction or repression of signalling proteins. It turns out that all major mammalian signalling pathways (MAPK, PI3K, JAK/STAT, cAMP, Smad) exhibit transcriptional negative feedback regulation, while positive feedback does not appear to be relevant at least at the intracellular level. Furthermore, the analysis reveals a separation of the signalling network into flexible and static parts: feedback occurs by induction of few metabolically unstable inhibitors ('flexible'), while the remaining signalling proteins are not induced and metabolically stable ('static'), see Fig.2. It is likely that transcriptional negative feedback loops enhance

Figure 1: Bistability in the mitogen-activated protein kinase (MAPK) cascade due to a hidden positive feedback loop arising from enzyme sequestration effects. Activation of the Mek kinase by Raf kinase is competitively inhibited by complex formation between Mek and Erk kinases, but the Mek-Erk complex dissociates once Erk is phosphorylated, thus giving rise to a hidden positive feedback (top left). Implementation of a mechanistic ODE model (bottom left) revealed that sequestration brings about bistability for physiologically relevant kinetic parameter values (right).





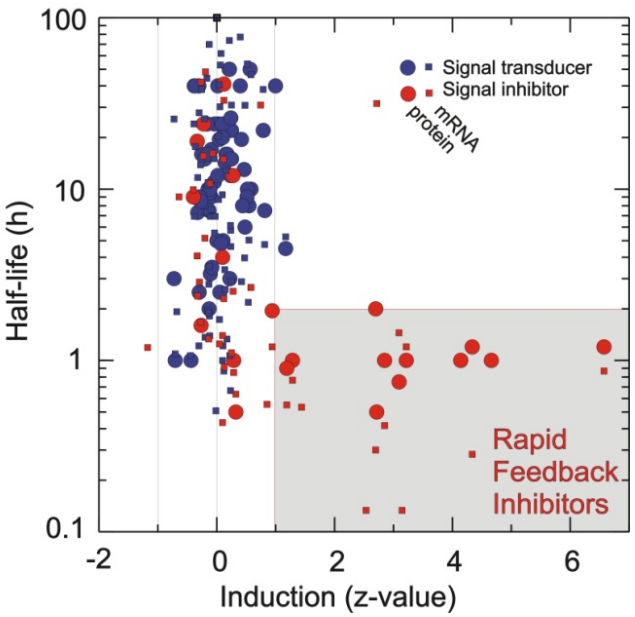


Figure 2: Rapid transcriptional feedback regulation of intracellular signalling pathways predominantly occurs by induction of unstable signal inhibitors. Published microarray studies in response to extracellular stimulation were systematically analyzed for induction of intracellular proteins involved in signal transduction (left). Transcriptional induction was related to metabolic stability of signalling proteins, and to their functional properties (e.g., signal transducer and signal inhibitor). The analysis revealed a separation of the signalling network into static and flexible parts, as most transcriptionally induced feedback regulators are metabolically unstable, while the remaining proteins are uninduced and metabolically stable (right).

the robustness of biochemical signalling pathways, but on the other hand decrease their sensitivity to therapeutic intervention. In Chapter 6, transcriptional negative feedback regulation of the TGFβ/Smad signalling pathway is analyzed by a combination of quantitative experiments in primary hepatocytes (U. Klingmüller et al, DKFZ Heidelberg) and dynamic mathematical modeling. Genome-wide microarray analyses and protein measurements in response to TGFβ stimulation suggest that the SnoN oncoprotein is the central transcriptional feedback regulator in primary mouse hepatocytes (see Fig.3). A mathematical model including TGFβ-induced Smad signalling and SnoN-mediated feedback is fitted to experimental data obtained under various stimulation conditions. The modelling results in Chapter 6 explain how a small pool of SnoN proteins can efficiently regulate a much larger pool of Smad proteins, and therefore provide novel mechanistic insights into Smad signalling. The interplay between TGFβ and SnoN might be relevant during liver regeneration *in vivo*, as SnoN is upregulated during the proliferative regeneration phase when hepatocytes become insensitive to growth inhibition by TGFβ.

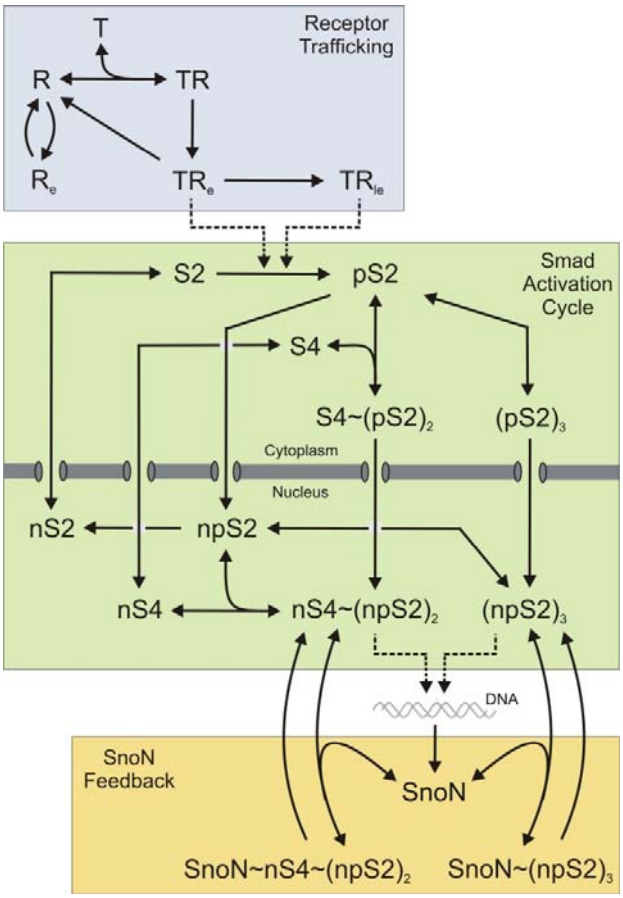


Figure 3: A mechanistic and data-based mathematical model of TGFβ signalling was used to investigate the impact of transcriptional feedback regulation via SnoN, which acts as a signal inhibitor at the level of Smad transcription factors.

Gene expression responses induced by intracellular signalling cascades are central to cellular responses to extracellular stimulation. Many target genes of signalling pathways in turn function as transcription factors or as small regulatory RNAs, thus giving rise to complex transcriptional networks that are analyzed in the third part of this thesis (Chapter 7 and 8). Two major questions are addressed: (i) How can gene expression networks show specificity although different extracellular stimuli frequently activate the same signalling pathways? (ii) Can systems biological approaches help to 'reverse engineer' the topology of gene regulatory networks from high-throughput perturbation data? In Chapter 7, a data-based mathematical model of a cyanobacterial iron stress response and its modulation by a small RNA (IsrR) is introduced. Theoretical and experimental analysis revealed that small RNA-mediated inhibition of gene expression introduces delays and therefore controls the temporal order of stress responses (see Fig.4). Modelling further suggests that genes modulated by small RNAs require sufficiently strong and sustained stimulation, thus potentially explaining why transient and sustained intracellular signals frequently evoke qualitatively different gene expression responses. The final Chapter 8 is focused on gene regulatory networks downstream of oncogenic Ras. The regulatory interactions between seven central transcription factors were deduced from RNAi perturbation data using an ODE-based reverse engineering approach. The calculations revealed a hierarchical transcription factor organization that is supported by independent follow-up experiments (not included in the thesis).

In conclusion, this thesis shows how systems biological analyses can integrate various types of experimental data to enhance our understanding of intracellular signalling networks at multiple

time scales, ranging from rapid post-translational modification to slow gene expression responses.

The findings are based on close collaborations with my PhD supervisor Hanspeter Herzel, Nils Blüthgen (Humboldt University Berlin), Peter Nickel, Ursula Klingmüller (German Cancer Research Center, Heidelberg), Thomas Maiwald, Jens Timmer (University of Freiburg), Iwona Stelniec, Christine Sers, Reinhold Schäfer (Charité Berlin), Dennis Dienst, and Ilka Axmann (Humboldt University Berlin).

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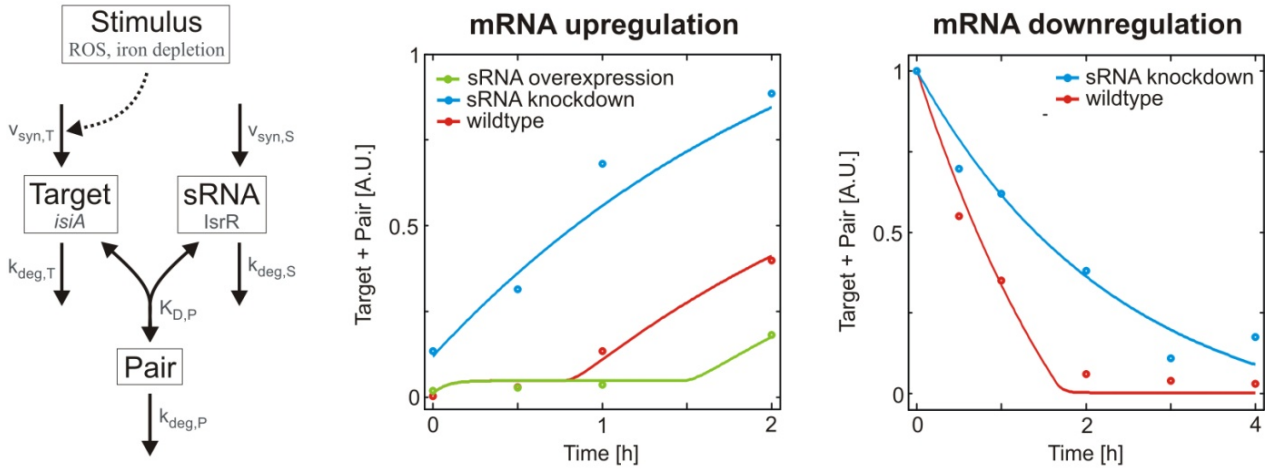

Figure 4: Small RNAs establish sign-sensitive delays in gene expression. A mathematical model describing the regulation of the cyanobacterial iron stress protein isiA by a small regulatory RNA (IsrR) was implemented to investigate the impact of sRNA-mediated inhibition on gene expression (left). Modelling and experimental analysis in cyanobacteria reveals that small RNAs delay mRNA upregulation by transcriptional induction and accelerate mRNA downregulation by transcriptional repression, respectively. Small RNAs may therefore control the temporal order of gene expression responses.

Max WOLF

Adaptive individual differences: The evolution of animal personality

No two individuals are alike. Take two individuals of the same sex, age and social background and you will typically find consistent differences in their motivation, cognition and behaviour. In humans, such differences are referred to as personalities.

Personality or individuality, however, appears not to be restricted to humans. In recent years, consistent differences in suites of correlated behavioural traits have been described in a diverse range of animal species (Sih *et al.*, 2004). Male three-spined sticklebacks (*Gasterosteus aculeatus*), for example, differ consistently in their aggressiveness towards conspecifics and more aggressive individuals are also bolder in response to predators and more active in unfamiliar environments than less aggressive individuals. Such differences have been termed animal personalities (also: coping styles, behavioural syndromes). The emerging notion that *individual differences may be expressions of different behavioural types* – rather than the result of stochastic noise – provoked a large number of empirical research during the last years, most of which aimed at understanding the structure (e.g., what traits are correlated with each other? How stable are these correlations over time?) and the proximate causes of animal personalities (e.g., what are the physiological correlates of personalities? How does experience affect personalities?).

My thesis presented theoretical modelling work that aimed to investigate *how natural selection can give rise to animal personalities*, that is, behavioural differences among individuals that are correlated across situations and contexts and stable for some period of time. The main part of the thesis begins with the conceptual Chapter 2 in which we review the main mechanisms that can contribute to an adaptive explanation of personalities. In particular we discuss how natural selection can give rise to the three key behavioural aspects of personalities: behavioural differences among individuals, consistency of behaviour over time and behavioural correlations across situations and contexts (Wolf et al., in press).

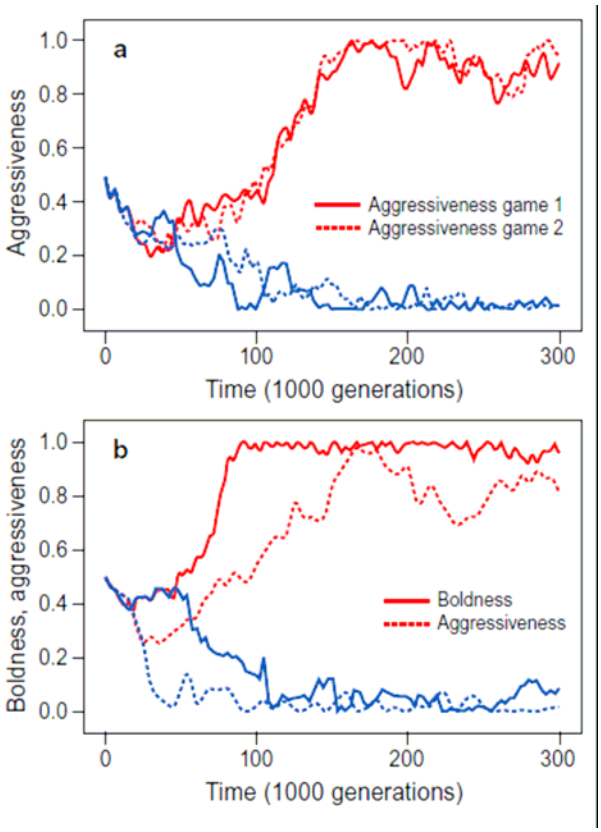

Figure 1:
Evolution of risk-prone and risk-averse personalities.
Two individual-based simulations illustrating the evolution of consistent individual differences between individuals with low (red) and high (blue) future fitness expectations. (a) When individuals face two hawk-dove games individuals with low expectations evolve high levels of aggressiveness in both games whereas individuals with high expectations are consistently non-aggressive. (b) Confronted with both an anti-predator and a hawk-dove game a behavioural syndrome evolves: individuals with low expectations are bold and aggressive whereas those with high expectations are shy and non-aggressive.

The remainder of the thesis presents a series of conceptual evolutionary models. Methodologically, these models are based on analytical methods from evolutionary game theory and adaptive dynamics in combination with individual-based computer simulations. The

models presented are conceptual in nature; their purpose is not to give a complete and realistic description of natural situations but rather to investigate isolated features of those situations that may be important in shaping adaptive animal personalities.

We aimed to address behavioural aspects of animal personalities that appear to have some universality, in that they occur in a range of animal species. As discussed in the General Introduction of my thesis (Chapter 1), at present there seem to be at least two candidates that meet this condition; these two candidates form the focus of the remainder of my thesis. Chapters 3 and 4 deal largely with the boldness-aggression syndrome and Chapters 5 and 6 with individual differences in responsiveness.

The boldness-aggression syndrome is one of most reported findings in the animal personality literature, occurring in a variety of taxa including birds, rodents and fish. In a nutshell, individuals differ consistently in their aggressiveness towards conspecifics and aggressive individuals are also bolder in response to predators and more active in unfamiliar environments than less aggressive individuals. In Chapters 3 and 4 we developed a theory that shows that *the mortality risk associated with behavioural actions may be the organizing factor underlying the boldness-aggression syndrome* (Wolf et al., 2007a). From life-history theory it is known that individuals should adjust their willingness to take risks to their residual reproductive value (i.e., future fitness expectations): individuals with high expectations should be more risk-averse than individuals with low expectations, since they have more to lose. Our evolutionary models showed that this basic principle predicts (under well-defined ecological conditions) the emergence of domain-general risk-prone and risk-averse behavioural types (Fig.1). Some individuals within a population are consistently more risk-prone than others, in all kinds of risky contexts (e.g., aggression, antipredator, and exploration contexts).

Two short essays (Intermezzo) accompany these chapters. The model developed in Chapter 3 gives rise to a stable polymorphism. In the first essay we show two qualitatively different routes through which this polymorphism can be attained in the course of evolution (Wolf et al., 2008a). The second essay (Wolf et al., 2007b) provides a first discussion of feedback mechanisms involved in asset protection, an issue that is investigated in more detail in Chapter 4.

Chapters 5 and 6 turn to individual differences in responsiveness. Empirical studies in a range of animal species suggest that individuals within populations often differ consistently along a responsiveness (plasticity, flexibility, awareness) axis. Many researchers believe that such differences are one of the fundamental factors structuring behavioural types. In Chapter 5 we developed an evolutionary model that predicts that *spatial and temporal variation in the environment gives rise to individual differences in responsiveness* (Wolf et al., 2008b). In brief, responsive individuals can exploit environmental opportunities (e.g., underexploited habitats). The benefits that are associated with these opportunities, however, will typically decrease with the number of other individuals that exploit them. Consequently, the benefits to responsiveness are negatively frequency-dependent, which, in turn, favours the coexistence of responsive and unresponsive behavioural types (Fig.2).

Chapter 6 focuses on the *interaction between social responsiveness and behavioural consistency*. In social interactions, consistency can be favoured since it makes individuals predictable. Predictability can be advantageous in a variety of ecological scenarios; however, it can only be advantageous if at least some individuals in the population are socially responsive. We developed a model to investigate this coevolutionary feedback between consistency and responsiveness. Analyzing this model we found that this feedback can (under well-defined ecological conditions) indeed result in populations in which responsive individuals coexist with unresponsive individuals who show high levels of behavioural consistency (Fig.3). Next to providing a testable explanation for consistency, our results thus also provide a link between two key features associated with animal

personalities, individual differences in responsiveness and behavioural consistency.

The general discussion in Chapter 7 provides a summary of the thesis and puts the main results into a broader context.

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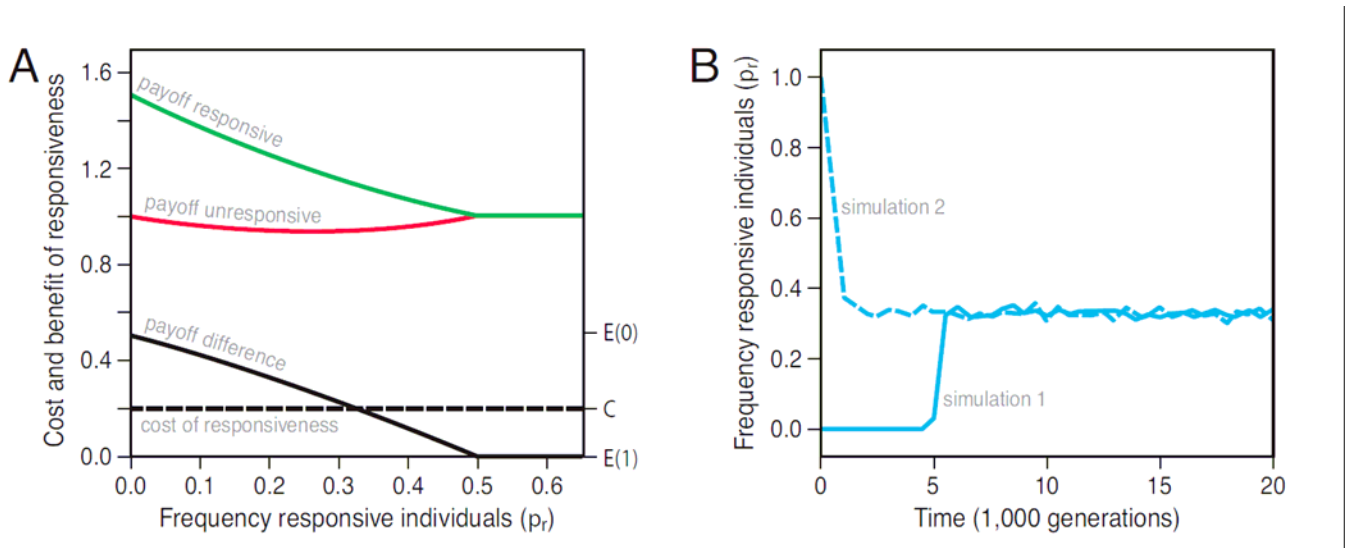

Figure 2. Coexistence of responsive and unresponsive individuals due to frequency-dependent selection.
(A) Dependence of payoffs on the proportion of responsive individuals in the population. Responsive individuals (green line) always obtain a payoff that is at least as high as the payoff to unresponsive individuals (red line). The benefits of responsiveness (i.e., the excess payoff of responsive individuals, black line) decreases from a value $E(0)$ in a population of unresponsive individuals to $E(1)$ in populations with a high proportion of responsive individuals. For the example considered, the benefits of responsiveness exactly balance the cost of responsiveness at $p_r = 0.32$. (B) Two individual-based simulations illustrating that, independent of the initial conditions, natural selection gives rise to the stable mixture of responsive and unresponsive individuals predicted by (A).

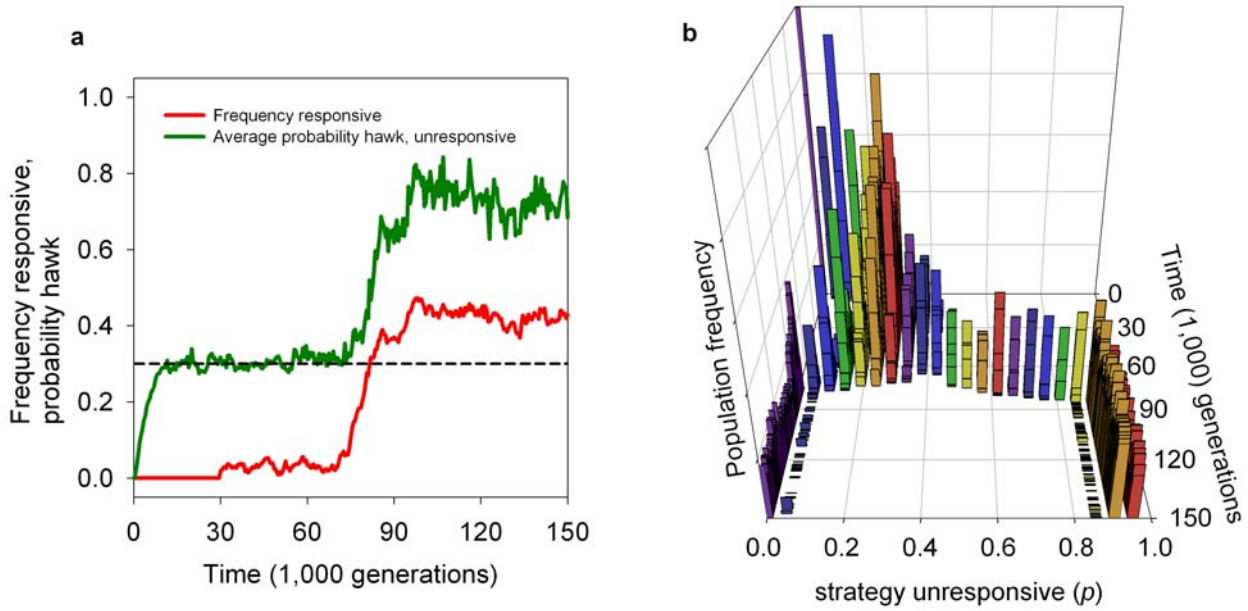

Figure 3. Coevolution of responsiveness and behavioural consistency in a hawk-dove game. Individual-based simulations where, after 30.000 generations, we allow rare mutations that give rise to responsive individuals. (a) Responsive individuals increase in frequency over time (red line) and select for an increased frequency of hawks among unresponsive individuals (green line). (b) The presence of responsive individuals gives rise to benefits of consistency which, in turn, select for high levels of consistency among unresponsive individuals, that is, unresponsive strategies with maximal behavioural consistency ($p = 0$ or $p = 1$) are favoured over less consistent one.

Haralambos HATZIKIROU

Lattice-gas cellular automata models for the analysis of cancer invasion

The biological problem

Cancer describes a group of genetic and epigenetic diseases, characterized by uncontrolled growth of cells, leading to a variety of pathological consequences and frequently death. Cancer
progression can be depicted as a sequence of traits or phenotypes that cells have to acquire if a neoplasm (benign tumor) is to become an invasive and malignant cancer. A phenotype refers to any kind of observed morphology, function or behavior of a living cell. Hanahan and Weinberg [4] have identified six cancer cell phenotypes: unlimited proliferative potential, environmental independence for growth, evasion of apoptosis, angiogenesis, invasion and metastasis.

In this thesis, we concentrate on the *invasive phase* of tumor growth. The progression of a benign tumor with limited growth to a tumor that is invasive and potentially metastatic is the major cause of poor clinical outcome in cancer patients, in terms of therapy and prognosis. A substantial understanding of tumor invasion could potentially lead to the design of novel therapeutical strategies. However, despite the immense amounts of funds invested in cancer research, the dynamics that govern tumor invasiveness *in vivo* remain poorly understood. Biomedically, invasion involves the following tumor cell *processes* [9]:

- tumor cell proliferation,
- cell migration, which is a result of down-regulation of cadherins (Important class of transmembrane proteins. They play a

significant role in cell-cell adhesion, ensuring that cells within tissues are bound together.) and the corresponding loss of cell-cell adhesion, and

- tumor cell-extracellular matrix (ECM: Components that are extracellular and composed of secreted fibrous proteins (e.g. collagen) and gel-like polysacharides (e.g. glycosaminoglycans) binding cells and tissues together. interactions, such as cell-ECM adhesion, and ECM degradation/ remodeling, by means of proteolysis. These processes allow for the penetration of the migrating tumor cells into host tissue barriers, such as basement and interstitial stroma [3].

Tumor invasion facilitates the emergence of metastases, i.e. the spread of cancer cells to another part of the body and the formation of secondary tumors. It is obvious that tumor invasion comprises a central aspect in cancer progression. However, invasive phenomena occur not only in pathological cases of malignant tumors but also during normal morphogenesis and wound healing.

Solution strategy

Our aim is to shed light on important aspects of tumor invasion, under the magnifying glass of mathematical modeling and analysis. Our approach relies on the mathematical abstraction of the tumor invasion problem. We reduce the tumor invasion problem to the *interplay* of the two main tumor cell processes, i.e. proliferation and migration. Our strategy is to describe the relevant phenomena that influence tumor cell migration and proliferation (e.g. ECM cues) at the cellular scale and analyze the emergent collective behavior of the invasive tumor cells. Mathematics provide tools that allow for a consistent transition from a cellular scale description to a macroscopic one. A convenient mathematical tool, are considered the cellular automata (CA). Here, we use a special type of CA models, the so-called lattice-gas cellular automata (LGCA) [1] which facilitate analytical investigations allowing for deeper insight into the modeled phenomena.

Tumor invasion is recognized as a complex phenomenon. The philosophy of our approach is based on the analysis (from the Greek word ανά+λύειν which means to break down into little pieces) of tumor invasion into basic biological processes (see Sec. 1). Each process comprises a subproblem - here we call it module. The goal is to develop simple models of the different tumor invasion processes that are mathematically tractable and analyzable. Therefore, we split the tumor invasion problem into modules (questions) that correspond to the impact of the basic invasion processes on tumor behavior:

Q1. What is the impact of the environment on tumor cell migration?
Q2. How do tumor proliferation and migration influence a tumor's invasive behavior?
Q3. Which are the mechanisms of tumor invasion emergence?
Q4. How can we compute \emph{in vivo} tumor invasion?

The synthesis of these modules, accompanied with the insight gained from the mathematical analysis of the corresponding models, may provide a deeper understanding of the full problem, i.e. the tumor invasion.

Main Results/Contents

This thesis is divided in two parts. In the first part (Chapters 2-4), we present the tools for the mathematical analysis of LGCA in basic biological concepts, such as random cell motion and growth. The second part of the thesis (Chapters 5-8) deals with tumor invasion and it provides answers to the questions (Q1)-(Q4). In particular, this thesis consists of the following chapters:

Chapter 2: Here we introduce the nomenclature of lattice-gas cellular automata and basic elements of the discrete kinetic theory, in particular the derivation of the lattice Boltzmann equation (LBE).

Chapter 3: here, we focused on the investigation of the most elementary cell migration mechanism, i.e. random cell motion. We defined a LGCA model of random walk dynamics and

we derived the motility rate for (i) a single cell and for (ii) the whole cell population. In the first case, we calculated the Green-Kubo formula and the corresponding single cell diffusion coefficient. In the cell population case, we derived a macroscopic description from the definition of the LGCA. In particular, we distinguished two different scalings, the parabolic and the hyperbolic, and we derived to limit macroscopic equations, the diffusion and the telegraph equation, respectively.

Chapter 4: In this chapter, we investigated a LGCA cell growth process. Here we focused on the application of a mean-field approximation under the assumptions of (i) a well-stirred system and (ii) a spatially distributed system. In the first case, we derived an ODE that describes the temporal evolution of the total cell population. In the case of the spatially distributed system, we
provided the macroscopic dynamics by means of three different scaling methods, the Chapman-Enskog, the Coupled Map Lattice and the spectral methods. All three methods provide different
macroscopic equations and they are valid for different regimes of the LGCA's parameters. Finally, we compare the well-stirred and spatially distributed system assumptions in terms of important macroscopic observables, such as per capita growth rate [6].

Chapter 5: In the definition of tumor invasion (Sec. 1) the environmental cues play a significant role. The tumor microenvironment is a highly heterogeneous medium for cell motion including the extracellular matrix composed of fibrillar structures, collagen matrices, diffusible chemical signals as well as other mobile and immobile cells. Of great interest is the influence of ECM on the migrating behavior of tumor cells [3] (cp. Q1). A LGCA model, of cell migration together with a mathematical characterization of different biological environments can contribute to understand the interplay of moving cells with their heterogeneous environment [8]. In particular, the mathematical analysis of the LGCA model can yield an estimate for the cell dispersion speed within a given environment.

Chapter 6: In this chapter, we investigate the influence of tumor cell proliferation and migration on the tumor's invasive behavior (cp. Q2). Uncontrolled proliferation is the essential requirement for tumor development. Combined with tumor cell migration - no ECM effects are considered -
provides the minimal prerequisites for tumor invasion. The main question that rises is how fast the tumor expands or, in other words, what is the invasion speed of a tumor. Therefore, we develop LGCA model of tumor cell proliferation, necrosis and tumor cell migration. Our analysis aims at predicting the velocity of the traveling invasion front, which depends upon fluctuations that arise from the motion of the discrete cells at the front. We find an excellent agreement between the velocities measured in simulations of the LGCA and an analytical estimate derived in the *cut-off mean field approximation* via the discrete Lattice Boltzmann equation and its linearization. In particular, our method allows for the inclusion of single-cell fluctuations effects in a mean-field description. Finally, we predict the front velocity to scale with the square root of the product of probabilities for mitosis and the migration coefficient [7].

Chapter 7: Here, we attempt to answer the question what are the mechanisms that trigger the progression from benign neoplasms (high proliferation) to malignant invasive tumors (high migration) (cp. Q3). In particular, we challenge the currently prevailing view that the emergence of invasiveness is mainly the consequence of acquired random cancer cell mutations. To study this, we mainly focus on the *Glioblastoma Multiforme* (GBM) tumor which is a particularly aggressive and invasive tumor. In particular, with the help of a simple growth model, we demonstrate that the short time required for the recurrence of a GBM tumor after a gross total resection cannot be deduced solely from a mutation-based theory. We propose that the transition to invasive tumor phenotypes can be explained on the basis of the microscopic ``Go or Grow'' mechanism (migration/proliferation dichotomy) and the oxygen shortage, i.e. hypoxia, in the environment of a growing tumor [5]. We test this hypothesis with the help of a

lattice-gas cellular automaton. Finally, we suggest possible therapies that could prevent the progression towards malignancy and invasiveness of benign tumors.

Chapter 8: In order to predict the spatio-temporal *in vivo* tumor invasion, we need to design appropriate computational algorithms (cp. Q4). In particular, in Chapter 8, we design such an algorithm to study the development of GBM invasion. The main ingredients are:

Biomedical data: It is known that glioma cells tend to spread faster along fiber tracks. Diffusion Tensor Imaging (DTI) data provide the local anisotropy information in terms of diffusion tensors. High anisotropy points correspond to brain's white matter, which consists of fiber tracks. Additionally, a time-series of Magnetic Resonance Images (MRI) provides information concerning the *in vivo* spatiotemporal tumor growth.
Tumor invasion model: The model is a combination of the LGCA models introduced in previous chapters. In particular, the model developed in Chapter 5 allows for the modeling of cell migration taking into account the information provided from DTI data. The Chapter 6 model accounts for the description of tumor cell mitosis and necrosis.
Parameter calibration method: We propose an evolutionary algorithm that estimates the parameters of a tumor growth LGCA model based on time-series of patient medical data.

These parameters may allow reproducing clinically relevant tumor growth scenarios for a specific patient, providing a prediction of the tumor growth at a future time stage

To summarize, we believe that this thesis contributes in the understanding of tumor invasion dynamics. Our aim was not only to shed light on aspects of tumor invasion but also to identify appropriate mathematical tools for the analysis of tumor invasion behavior. Additionally, we hope that we could motivate new research ideas that may help in the profound comprehension of the mechanisms of tumor growth and the design of novel therapeutic strategies.

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Alexander Skupin

How Does Calcium Oscillate? – An Interdisciplinary Approach

Calcium is an important and versatile second messenger in eukaryotic cells serving as a critical link between a variety of extracellular stimuli and their intra- and intercellular responses. The external signals are translated most often into repeated increases of the cytosolic Ca^{2+} concentration. Due to their importance and frequent appearance, Ca^{2+} oscillations have been extensively studied in experiments and most of the involved physiological elements are identified. Despite this knowledge, the link between these microscopic elements and the cellular dynamics was still only vaguely understood.

An important mechanism to generate cytosolic Ca^{2+} transients is Ca^{2+} release by channels from internal storage compartments, mainly from the endoplasmic reticulum (ER) and the sacroplasmic reticulum. A common channel type present in many cells is the inositol 1,4,5-trisphosphate receptor (IP_3R) which opens and closes randomly in dependence on binding and dissociation of IP_3 and Ca^{2+}. The open probability of IP_3 exhibits a nonlinear dependence on the cytosolic Ca^{2+} concentration leading to Ca^{2+} induced Ca^{2+} release (CICR), the key element of Ca^{2+} signaling. An initial opening of a single channel increases the open probability of adjacent channels, and Ca^{2+} release spreads throughout the whole cell until channel inhibition caused by high Ca^{2+} concentrations terminates the release.

The traditional point of view regarding these oscillations is that diffusion blurs intracellular signal structures leading to globally coupled channels. Subsequently, this leads to the assumption that the large number of channels allows for averaging out single channel fluctuations. This picture is contradicted by experimental observations of large gradients of the Ca^{2+} concentration close to open channels that can have functional consequences for the oscillations.

The thesis uses an interdisciplinary approach combining experimental techniques from biology, analytical tools from theoretical physics and computer simulations to clarify the question of the oscillation mechanism and how cells can generate globally coordinated Ca^{2+} signals originated from local stochastic channel dynamics. In this context, the spatially inhomogeneous distribution of IP_3Rs, forming channel clusters which are separated by 1-7 µm, plays a key role. Together with Ca^{2+} pumps and buffers, this induces the huge concentration gradients close to open clusters, leading to a hierarchical organization of Ca^{2+} signals. In combination with the random behavior of single IP_3Rs, this might generate a stochastic medium, which is known in pattern formation.

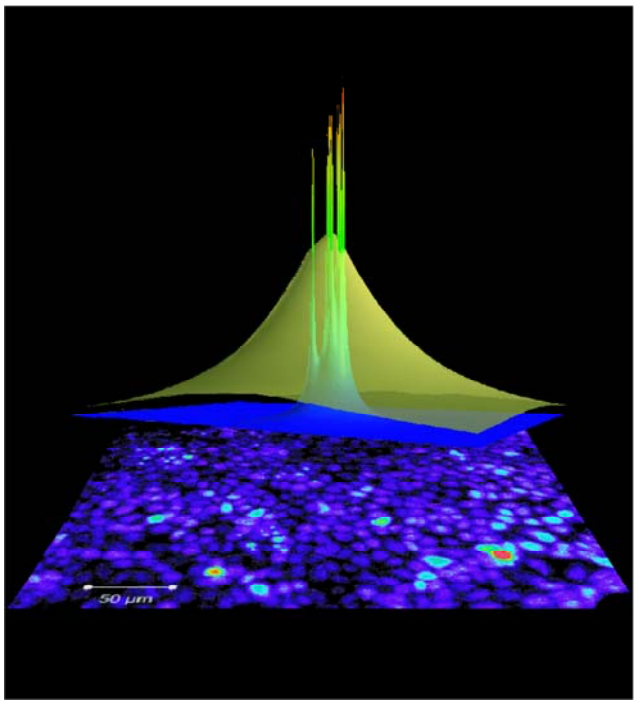

Figure 1: Lower layer shows a fluorescent image of a calcium measurement in a processed lipoaspirate cell culture where red corresponds to high cytosolic calcium concentrations and dark blue to low concentrations. The upper surfaces exhibits simulations of the calcium dynamics close to a channel cluster with 25 channels. The color coded surface describes free cytosolic calcium and the brown surface corresponds to a calcium bound fluorescent dye demonstrating that dyes cannot resolve the dynamics of individual channels separated within a cluster by 25 nm.

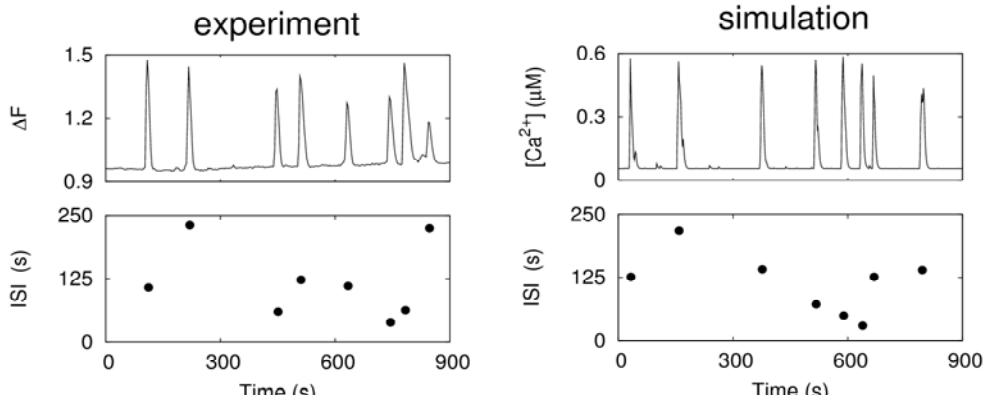

Figure 2: Single cell calcium signals in experiment (left) and in simulation (right). Upper panels show the cytosolic fluorescent signal and the spatially averaged free Calcium concentration respectively. Lower panels depict the individual interspike interval (ISI) defined by the time between two maxima in the signals. The variation in ISI points to the stochasticity of spiking.

Starting from this knowledge, Ca^{2+} oscillations are predicted to be stochastic as well as to consist of repetitive wave nucleation and hence to have a spatial character. This hypothesis is justified experimentally in the first part of the thesis by analyzing Ca^{2+} oscillations of four different cell types in terms of their mean periods and standard deviations exhibiting a linear dependence. Hence, Ca^{2+} signaling constructively uses thermal noise to build global signals. Thereby, the molecular fluctuations are carried on the level of the cell by the hierarchical signaling structure rendering Ca^{2+} oscillations stochastic. This contradicts the current opinion of the last decades of Ca^{2+} being a representative cellular oscillator. Moreover, this makes Ca^{2+} a first natural example of array enhanced coherent resonance, a phenomenon theoretically predicted by statistical physics. The knowledge of the oscillation mechanism allows as well for determination of intrinsic cell properties by global observations. To illuminate the structure of the signaling mechanism, the data were also analyzed with respect to information processing.

Furthermore, the temperature dependence of Ca^{2+} signaling in astrocytes was analyzed experimentally. The findings show that the reported difference between cultured astrocytes and astrocytes in acute brain slices are mainly caused by the different temperatures at which cells are used to be measured. This leads again to a more general interrogation as to how temperature is recognized. Are the decreased Ca^{2+} signals at higher temperature caused by an increased pump activity and hence spatially controlled or does temperature mainly change local properties like the channel dynamics?

In the modeling part of the work, a physiological model for intracellular Ca^{2+} dynamics in three spatial dimensions is developed that takes the spatial arrangement of cells seriously. In contrast to most models of Ca^{2+} dynamics using ordinary differential equations, it uses a detailed channel model for the discrete release sites and takes into account diffusion and buffer interaction of Ca^{2+}. The model is based on separation of the two involved length scales. The Ca^{2+} concentration is determined on its part by the channel states acting as source terms of the corresponding reaction diffusion system (RDS) describing the macroscopic scale. The two model segments are coupled by a hybrid version of a Gillespie algorithm.

On the microscopic scale, the IP_3R are described by Markov chains, the dynamics of which depend on the local Ca^{2+} concentration.

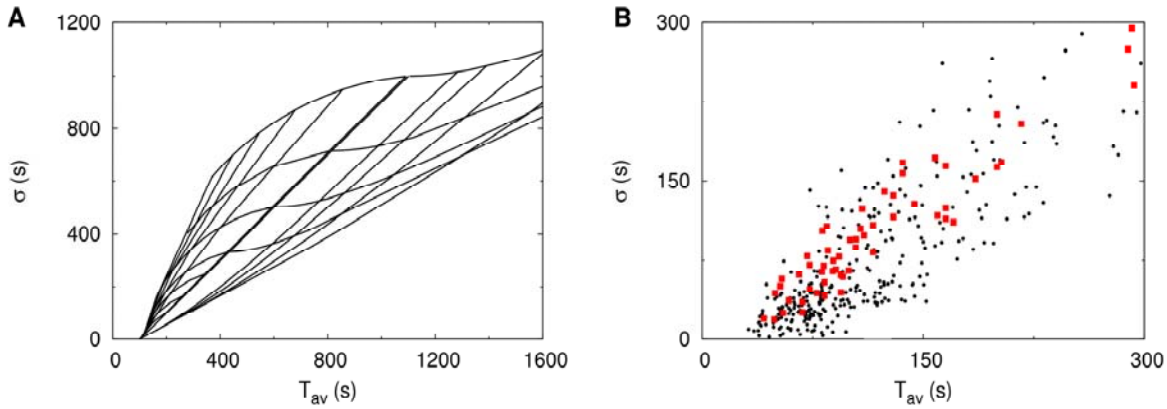

Figure 3: **A**: Theoretical predicted dependence of the standard deviation of the mean ISI $T_{av.}$ **B**: Experimental determined dependence (black dots) and obtained from simulated time series (red squares) exhibit a good agreement.

For an efficient simulation tool, the RDS is linearized and solved analytically by a three component Green's functions describing cytosolic free Ca^{2+}, mobile and immobile Ca^{2+} buffers, respectively. The linear RDS allows for an elegant parallel algorithm enabling detailed physiological simulation of intracellular Ca^{2+} dynamics. In dependence on physiological motivated parameters, the developed *Green's cell algorithm* (GCA) generates in a natural way the whole spectrum of experimentally known Ca^{2+} signals and fits the experimental data of the first part in a almost perfect manner.

Thus, the temperature dependence of astrocytic Ca^{2+} signals are in line with an increased pump activity and highlights once more the spatial character of Ca^{2+} signaling. In simulations that go beyond the experimental possibilities, the role of IP_3R clustering in Ca^{2+} signaling is studied and the influence of intrinsic channel properties on Ca^{2+} signals is analyzed. We have shown that clustering leads to more stable spiking than diffusive arranged channels and can be achieved by a surprisingly small number of channels what was recently confirmed in experiments. We could demonstrate with the GCA that the experimentally found halved open time of clustered IP_3R compared to isolated channels leads to an eight fold increase of global Ca^{2+} spike intervals. This demonstrates how changes

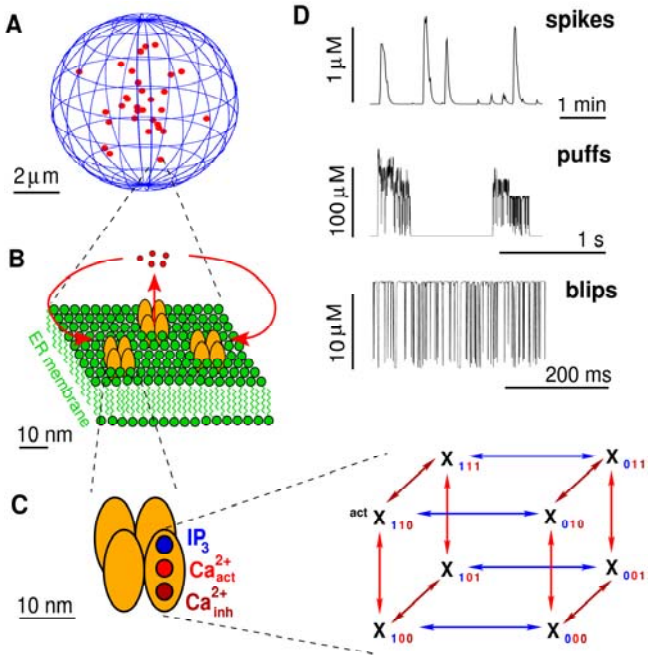

Figure 4: IP_3R properties and clustering generate a hierarchical system. A: IP_3R form channel clusters (red dots) that are randomly scattered and separated by 1 to 7 µm in the cell. B: Compared with inter-cluster distances, channels (orange) within a cluster are tightly packed in the ER membrane and are strongly coupled by calcium (red). C: Single IP_3R consists of four subunits the dynamics of which is described by the DeYoung-Keizer model. The 8 subunit states form a cube and subunit state transitions correspond to jumps along the edges. D: Combined with the spatial clustering, the resulting hierarchical structure transforms fast fluctuating single channel dynamics (blips) firstly into locally amplified cluster signals (puffs) and finally into cellular release spikes.

of molecular properties on a fast time scale influence cellular behavior on the slower time scale of cell signaling.

Although this work is inspired by Ca^{2+} dynamics, the general concept how cells can generate predictable behavior from noisy molecular properties may also hold for other signaling pathways, especially for those exhibiting spatial concentration gradients as well, such as cyclic adenosine monophosphate. Even the developed new modeling method connecting molecular and cellular dynamics can be easily adapted to other signaling processes and may serve as a prototype of a full cell model.

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Orsolya Kapuy

Mathematical modelling of yeast cell cycle transitions

To understand the characteristic features of cell cycle the complex regulatory network has to be explored. Beside the experimental methods the characterization of the molecular regulatory networks in cells can be performed by mathematical modelling. The models make possible to reveal the relationships between regulatory proteins by equations. I got acquainted with the pillars of biochemical reaction kinetics and the investigation strategies based on mathematics and biological data as a PhD student in Professor Béla Novák's research group. I concentrated on a deep understanding of the complex cell cycle regulatory network and that of various important cell cycle events. These works were done using budding yeast test-organism.

To describe the regulation network of the biological system non-linear ordinary differential equations (ODE) was written for the time dependent rate variation of concentration for the components creating a multi-parameter, non-linear, first order differential equation system. The initial conditions and parameters of the equations were estimated. The analytical solution of the non-linear differential equation system is nearly impossible. The equations can be dealt with simulations or with approximate methods of non-linear dynamics (time series, phase plane analysis and bifurcation diagrams). These mathematical methods make possible the quantitative and qualitative comparisons between theory and experiment.

One of the basic features of the cell cycle is to provide the proper direction of the processes for the cell. How the CDK/cyclin complexes (short

by Cdk) can control the cell cycle transitions and make the processes of one-way type? After mitosis the mitotic Cdk activity drops rapidly from high to low level. This activity drop is due to Cdc20 and Cdh1 promoting ubiquitin dependent degradation of cyclin at mitotic exit. While the protein degradation is thermodynamically irreversible process, the one-way process of the cell cycle transition has been defined by hydrolysis for many years. Professor Novák and his co-workers proposed that the irreversible transitions require systems-level feedbacks during the cell cycle. The one-way process is determined by the mutual antagonism between Cdk and its inhibitors Cdh1 and Sic1 molecules at the M/G1 transition.

Collaborating with Frank Uhlmann's lab a mutant version of Cdh1 was expressed, called Cdh1-m11. Cdh1-m11 can not be phosphorylated by Cdk, which deletes the negative effect on Cdh1-m11 by Cdk, only Cdh1-m11 is able to inhibit Cdk. The cells were synchronized with high mitotic Cdk activity in the metaphase of mitosis. To switch on and off the proteasome activity easily, which is responsible for the protein degradation one APC subunit was changed for its temperature-sensitive mutant. To describe the experimental results with mathematical equations a simple network diagram was created. The cyclin degradation is regulated by APC/Cdh1-m11. Cdk synthesis is promoted by transcription factors, and these factors are activated by a positive feedback. The Cdk is bound and inactivated by Sic1, however, Cdk has also a negative effect on Sic1, creating a double negative feedback between the two molecules. Using this experimental conditions reversible mitotic exit can be implemented. Although the cells enter G1 phase, they are able to return mitosis after a transient period. That was the first time when experimentalists managed to prove that the protein degradation is still working in the cells, but the cells can go back to mitosis.

Reversible mitotic exit could be managed under the following experimental conditions: Cdh1-m11 was induced in metaphase arrested cells for 30 minutes. The APC activity was turned off after 50 minutes (Figure 1a). While the Cdk level disappears rapidly from the system the Sic1 level is increasing when Cdh1-m11 is active. Turning off APC makes it possible the re-activation of Cdk helps itself by its own transcription factor. The stoichiometric inhibitor disappears and after a transient period the cell goes back to mitosis. Although Cdk underwent proteolysis, the mitotic kinase can be re-activated in the system. Irreversible mitotic exit was reached when Cdh1-m11 induction was kept throughout the whole cell cycle, while the APC/Cdh1-m11 activity was turned off after 60 minutes (Figure 1b). The level of the mitotic kinase disappeared from the cell by this time, while Sic1 was stabilized at a high level.

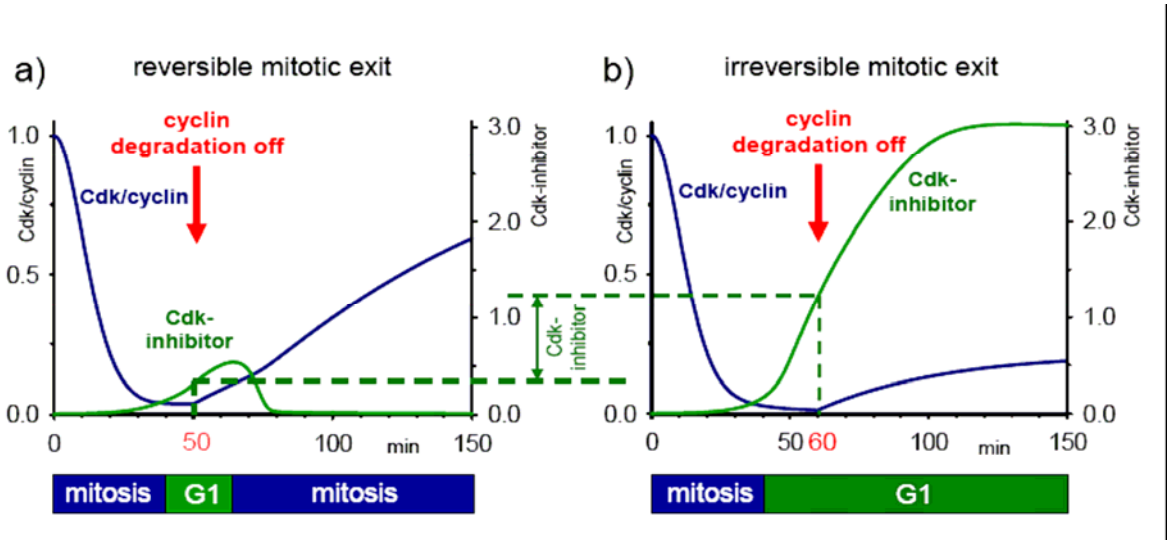

Figure 1. Studying the irreversibility of mitotic exit in budding yeast. a) reversible mitotic exit, Cdh1-m11 was induced for 30 min, APC was turned off after 50 min; b) irreversible mitotic exit, APC was turned off 60 min after the start of Cdh1-m11 induction

The cyclin degradation is not sufficient to render M/G1 transition irreversible. It is not enough to decrease the Cdk level, but its low level has to be maintained. Then the Cdk-inhibitors can be activated and the increasing Cdk-inhibitor activity can reach a certain threshold and the high inhibitor level prevents cyclin re-synthesis. We have shown with other experiments that cyclin degradation even is not essential to render the mitotic exit irreversible [1;2].
A mathematical analysis was done to describe the kinetic behaviour of the double negative feedbacks in the regulatory networks using multiple phosphorylation. The basic assumption implied that the main regulatory targets of Cdk have more than one phosphorylation sites, which sites might have crucial role in the activation/inactivation of the protein. I have set up simple mathematical models, which are able to study the different multiphosphorylation mechanisms. The ordered, distributive and disordered, distributive multiphosphorylation mechanisms were analysed with phase plane analysis and bifurcation diagrams. Both phosphorylation mechanisms were able to describe the bistable states during the cell cycle. This method produces a multistep ultrasensitivity, which gives a more realistic description for the bistability at transitions in the cell cycle regulatory system [3].

New scientific results indicate that the double regulation of proteins both by Cdk and transcription factors (TF) is a very general motif in cell cycle regulation. Using experimental data and bioinformatics databases, we have shown there is a third connection between Cdk and the transcription factors as well. In this network the protein (Pr) is regulated directly and indirectly by Cdk creating feed-forward loop motif (FFL). The indirect way happens through TFs. Eight different FFL motifs can be distinguished, and these motifs are different according to the signs of the interactions between the three components.
FFL networks were tested by computational simulations; how these motifs respond to a Cdk activity change. When Cdk activates Pr through both directly and indirectly then the active protein level follows Cdk activity. In case Cdk inhibits both arms, Pr becomes active only if Cdk is not present. The two most interesting cases are when Cdk has opposite effects on the two arms. When Pr is activated directly by Cdk, but inhibited indirectly, active Pr peaks, when Cdk is rising. In the second case (Pr is inhibited directly but it is activated indirectly by Cdk) Pr has a peak only when Cdk activity is dropping. The behaviour of the FFL regulatory motifs is independent of the order of events on the indirect regulation arm. The feed-forward network is of importance: cells have proteins in each phase of the cell cycle and the essential Cdk activity determines the type of proteins getting activated. The established system is robust and can give quick answers on environmental changes [4].
There is a special example for the FFL motif activated at the end of mitosis. The complex regulatory network of septation initiation (SIN) has the same characteristic feature in fission yeast. The simplified mathematical model shows the essential role of the motif, it can be activated only when Cdk is dropping from high to low level after mitosis. Beside describing wild type behaviour the model is also able to explain different septation defected mutants [5].
In addition to the molecular biological experiments the mathematical modelling has a crucial role in exploring the eukaryotic cell cycle regulatory network. The experiments help researchers to understand the living organisms and improve their models; however, the theoretical methods make possible studying the regulatory network as a complex system. Using this knowledge the missing regulatory elements and interactions might be predicted.

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Yael Artzy-Randrup

Modeling Spatially Structured Biological and Ecological Systems

There are very few systems, if any, that do not embed some form of structure. It is not always clear, however, how significant the role of such structure is. When attempting to describe a system, it is usually very tempting to incorporate as many features as possible. Yet, to get a clearer understanding of the dynamics of a system, the opposite is usually true. There is a need to focus only on the most dominant components, keeping the description of a system as simple as possible. As John Maynard Smith, the renowned mathematical ecologist, wrote in his book, *Models in Ecology* (1974):

"A theory of ecology must make statements about ecosystems as a whole, as well as about particular species at particular times, and it must make statements that are true for many species and not just for one… For the discovery of general ideas in ecology, therefore, different kinds of mathematical description, which may be called models, are called for. ***Whereas a good simulation should include as much detail as possible, a good model should include as little as possible****."*

And so, when attempting to model a system, it is not always clear where to draw the line; what is the level of simplicity that we can afford so that a model is still sufficiently descriptive and how reliable are the approximations we make? Indeed, in many cases, different existing forms of structure can be ignored, and the system's main features can still successfully be encapsulated. However, this is not always true.

This is the main question of this thesis. Four separate cases are studies, in which additional incorporation of structure is crucial. For each of these cases we discuss earlier results in which structure was not accounted for, and then proceed to studying each case with an additional level of structural complexity. For each of the cases we demonstrate the importance of this addition, and highlight new insights that are revealed. Hence, these studies open the way for new directions of study, interpretation and thought, as well as questioning past conclusions.

In the **first chapter** we extend a family of population models making them size-structured models by means of continuous transport equations (see Figure 1). We focus on coral reefs as a case study, but the results of the analysis are relevant for a diverse range of populations. We find that when size is incorporated into the models, regimes of instability, which were believed to exist and to depend on the level of recruitment into the system, are eradicated with density dependence growth, giving new insights to an unresolved question. Based on earlier modeling attempts it was predicted that areas of low recruitment levels should be highly stable. This however, contradicted observations that showed that many areas with low recruitment are actually fragile and endangered, such as the coral reefs in the Gulf of Eilat. The incorporation of size-structure gives an answer to this paradox and opens the door to future work, which might include more realistic scenarios such as seasonal forcing and pulses in recruitment. For further reading see Ref. [1].

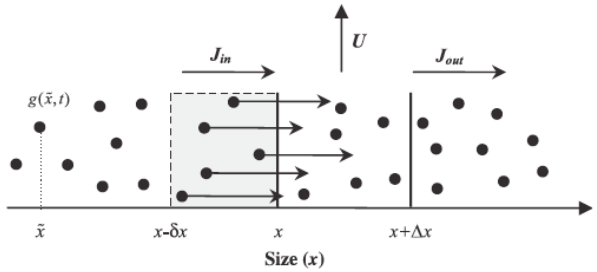

Figure 1: A schematic description for the construction of a continuous transport equation for size-structured populations.

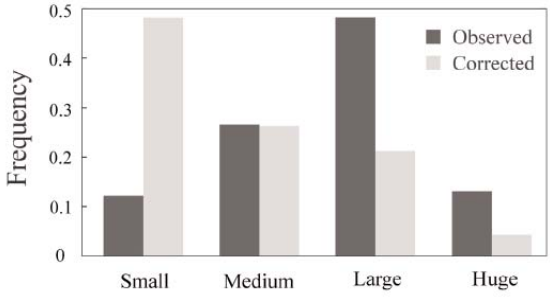

Figure 2: A histogram showing the observed and corrected estimated size frequency distribution (SFD) of corals in Katza (Eilat, Red Sea) using the line-intercept method (LIM). The observed data shows a SFD skewed to the left, with a higher frequency of larger colonies, and the corrected data gives the opposite conclusion, with the SFD strongly skewed to the right.

In the **second chapter** we study the complexities introduced by size-structure when attempting to assess *count-based measures* such as size-frequency distributions, diversity indices and mean size and population density. When sampling natural populations, the probability of selecting different individual is not always equal, and can directly depend on the size of the individual being sampled. This leads to biased estimates of the statistical properties of populations. Here we develop a correction for this bias, which is applicable not only for the improvement of future sampling, but also for the correction of past results. We demonstrate the importance of this correction with empirical data that was collected in the coral reefs of Eilat. In addition, we implement this correction on previously sampled data published by the Israeli Monitoring Project of the Gulf of Eilat, and show how this correction can potentially impact ecological policy decisions (see Figure 2). In this chapter we specifically focus on correcting estimates of size frequency distributions, a measure that is important for determining the status of ecosystems such as coral reefs. However, based on the same principles described here, this correction can be extended for the correction of a family of *coun- based measures*. For further reading see Ref. [2].

In the **third chapter** we focus on the role of structure in null hypothesis testing in systems that can be represented by 0-1 matrices (see two examples in Figures 3 and 4). We define three main assumptions that need to be fulfilled for the results of these tests to be reliable, and study the role of structure in each. The first and second assumptions deal with posing a correct null model according to realistically imposed constraints and defining appropriate statistical features. Here we demonstrate that when structure is not accounted for, it can lead to incorrect results and conclusions. This suggests that the development of new methods for generating null models that account for structure should be an important future research direction. The third assumption deals with generating uniformly distributed random samples. As discussed in chapter 2, to find an unbiased estimate of a population (in this case these are 0-1 matrices), each individual or object must be sampled with equal probability. However, because each matrix is structurally different, the probability of sampling varies. Here we offer a correction for this problem, which generates uniformly distributed random matrices. For further reading see Ref. [3] and [4].

Figure 3: Representation of presence and absence of species over different sites as a 0-1 binary matrix. On the left five different islands are sketched, indexed as I_1 through I_5. The four species present in each site are marked in orange with the letters A, B, C and D. On the right is the corresponding 'presence absence matrix'. Here each of the four rows represents a single species and each of the five columns represents a single site. Species C, for example, is present in site I_2, and so cell (3,2) of the matrix has a value of 1. Alternatively, because species B is absent from site I_3, cell (2,3) of the matrix has a value of 0.

In the **fourth chapter** we extend statistical measures of network topologies in the presence of local clustering. To do so we define a new concept, which we call the "free excess degree distribution", using a generating function framework, and we find accurate predictions of the threshold point at which the giant component emerges. Analytically analyzing networks with some form of structure, in contrast to the random network scenario, is not trivial. To date, the threshold point at which a giant component is formed has only been solved for the most random cases. The results here are useful for more realistic networks, such as those describing social groups and the spread of an epidemic where clustering is commonly observed. For further reading see Ref. [5] and [6].

As an extension to the **first**, **third** and **forth chapters** of this thesis, we study the effects of network architecture on metapopulation persistence of age structured communities. We present a model formulation for determining those factors that control the stability and persistence of complex biological systems, and as a case study, we focus on ecological metapopulations, which may be viewed as a set of distinct subpopulations (/sites) that are connected via a dispersal network of arbitrary complexity (see Figure 4). Metapopulation persistence is found to depend critically on the topology of cycles, and cyclical components in the connectivity network (see Figure 5), because they allow the offspring of the population to eventually "return home" to the sites from which they originated. The methodology identifies critical migration routes, whose presence are vital to overall stability, and are thus of high conservation priority – information that may be of value when designing networks of marine protected areas. In contrast, links that do not participate in a cyclical component have no impact on persistence and thus have low conservation priority (see Figure 5). The key results are easily extended to other biological contexts (e.g., disease networks), particularly in situations whereby the network controls the dynamics of a complex system. For further reading see Ref. [7].

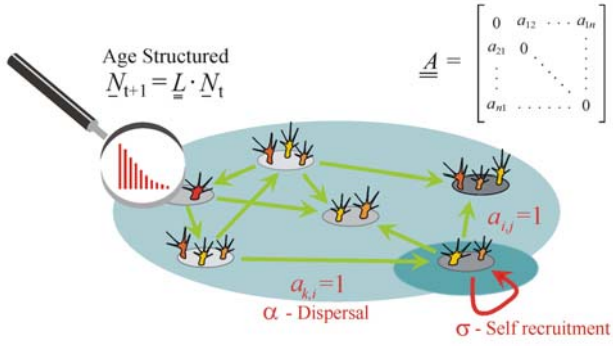

Figure 4: On the top right a 0-1 binary matrix is used to represent the topology of dispersal pathways between a set of local patches in a metapopulation (bottom). In this matrix each cell represents a directed dispersal pathway; cell (i,j) has a value of 1 if a directed pathway exists from patch i to j, and a value of 0 otherwise. The sum of row i in the matrix equals the number of dispersal pathways originating from patch i (the "out going degree" of this node in network terminology), and the sum of column i equals the number of dispersal pathways entering patch i (the "in going degree" of this node). The parameter α represents the intensity of dispersal between patches while σ represents the amount of self-recruitment in each patch. The population dynamics within a patch follow the Leslie matrix growth equations $N(t+1) = LN(t)$ where $N(t)$ is a vector defining the numbers of the population in each age-class at time t while the matrix L defines survival and fertility rates.

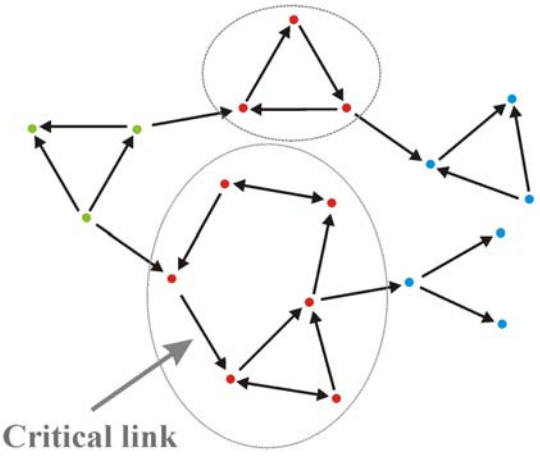

Figure 5: Persistence is controlled by the network's cyclical components, of which there are two in this example (red patches); one simple component (3 patches, 3 links) and one complex component (6 patches, 9 links) formed by intersecting cycles. The other nine patches (blue and green) may be completely neglected since they do not belong to any cycle and therefore play no role in determining persistence. In addition, removal of dispersal routs associated with cyclic components may have a critical effect on persistence of the metapopulation, while removal of any of the other routs has no impact at all.

We are now in an era in which our science is moving from being mainly descriptive to a science that is more mechanistic and therefore predictive. When trying to uncover simple laws, scientists must balance the accuracy and complexity necessary to describe essential mechanisms. In this thesis we have focused of several case studies in which an extra degree of complexity is necessary in order to comprehend more accurately the rules that are in play.

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Some Notes on the History of Branching Processes, from a Personal Perspective

Peter Jagers, University of Gothenburg, Sweden

After dinner lecture at Oberwolfach, January 2009

Few fields within the mathematical sciences, may be none, cherish their past like branching processes. Ted Harris's classical treatise from 1963 opens by a terse but appetising two-page flashback. Three years later, David Kendall's elegant overview was published, and like Charles Mode in his monograph (1971), I could borrow from that for the historical sketch opening my 1975 book, but also add some observations of my own.

At that time we all knew that the French, notably de Candolle and Bienaymé, had considered the nobility and family extinction problem, before Galton publicised it. I also speculated about connections between Bienaymé and the demographer Benoiston de Châteauneuf, who had been studying noble families founded in the tenth to twelfth centuries. This contact was vindicated by Chris Heyde and Eugene Seneta in their *"I. J. Bienaymé: Statistical Theory Anticipated"*, where they also showed that Bienaymé was not only first at formulating the mathematical problem, but indeed knew its solution already in 1845. The original publication has not been found, but as pointed out in the recent monograph by Iosifescu *et al.*, Bernard Bru has discovered a proof in a treatise by A. A.Cournot, published only two years after Bienaymé's communication. Though this is not explicitly stated, it seems plausible that Cournot reproduces Bienaymé's argument. The book by Iosifescu and co-authors also presents an intriguing discussion by Bienaymé arguing that the limited size of mankind (in the mid XIX:th Century!) should show that human mean reproduction must have varied above and below one in historical time.

There are good reasons for branching processes to keep its heritage alive. Not only is the background in the frequent disappearance of family names, even in growing populations, picturesque and easily understood, it is also something that could not have been explained by prevailing – and long dominating – deterministic population theory. Indeed, it provides convincing arguments for a stochastic population theory, and not only for "small" populations. And in spite of its alluring disguise, the family extinction problem concerns an important and basic feature of population development, about frequent extinction and shared ancestry.

It also tells a story of interplay between mathematics, natural science, culture, and society, which we should listen to in times when on one hand side mathematicians tend forget about the social context of their science as well as its roots in physical or biological problems; on the other hand post-modern philosophers proclaim that everything is social, as though there were no mathematical or physical truth.

The many-faceted interplay is beautifully displayed in Galton's classical formulation in Educational Times 1873:

"PROBLEM 4001: A large nation, of whom we will only concern ourselves with adult males, N in number, and who each bear separate surnames colonise a district. Their law of population is such that, in each generation, a_0 per cent of the adult males have no male children who reach adult life; a_1 have one such male child; a_2 have two; and so on up to a_5 who have five.

Find (1) what proportion of their surnames will have become extinct after r generations; and (2) how many instances there will be of the surname being held by m persons."

Rarely does a mathematical problem convey so much of the flavour of its time, colonialism and male supremacy hand in hand, as well as the underlying concern for a diminished fertility of noble families, the crowds from the genetically dubious lower classes thus threatening to take over society.

It also exhibits a mathematical theory initiated not by mathematicians but by a broad *savant,* Francis Galton, a polyhistor well versed in mathematics but primarily, if anything, a biologist. We see an example falsifying both extremist views on science, that of a pure science – and in particular mathematics, devoid of political meaning and implications; and that degrading science and scientific development into a purely social phenomenon. Indeed, in branching processes, they all meet: pure mathematical development, biology, physics, and demography, and the concoction is spiced to perfection by the social and cultural context in which it is formed.

As is well known, Watson determined the extinction probability q as a fixed point of the reproduction generation function, from which he and Galton (1874) intriguingly concluded:
"All the surnames, therefore, tend to extinction in an indefinite time, and this result might have been anticipated generally, for a surname lost can never be recovered, and there is an additional chance of loss in every successive generation. This result must not be confounded with that of the extinction of the male population; for in every binomial case where q is greater than 2 we have $t_1 + 2t_2 + \&c. + qt_q > 1$, *and, therefore an indefinite increase of male population."*

It is strange that so intelligent a couple as Galton and Watson (the latter turned clergyman but had been second Wrangler at Cambridge, carried on mathematics and physics as a Rector and even was awarded an honorary D. Sc. by his *Alma Mater*) could have presented, and even believed in this seductive verbiage, and it is even stranger that it took more than fifty years to rectify it, in particular since Bienaymé had already published a correct statement of the extinction theorem, and according to Heyde and Seneta, "its implications were strongly doubted" already at the time of publication.

The only (almost) contemporary criticism I have read, is by a Swedish historian/political scientist/statistician, Pontus Fahlbeck, a commoner who married a baroness, and became the author of a monumental two-volume treatise on the Swedish gentry (1898, 1902). He gives a correct, verbal description of the relation between growth of the whole versus frequent extinction of separate family lines, and writes – somewhat condescendingly or intimately, it may seem: *"Galton, who with habitual curiosity considered the question, has tried to investigate to what extent families ... must die out, with the help of a competent person."* Fahlbeck then recounts special examples considered by Galton, showing that "the tendency is the extinction of all". (The account is not completely lucid.) This is followed by a sequel of questions, and a reassuring answer:

"If this course of events be based on a mathematical law, then it should be as necessary, or not? And what then about our general conclusions, that no necessity forces extinction? Is there not in this a contradiction, which if both arguments are right, as they undoubtedly are, leads to what philosophers call an antinomy? However, mathematical calculations, as applied to human matters, may seem unrelenting but are actually quite innocuous. The necessity lies buried in them like an electrical current in a closed circuit, it cannot get out and has no power over reality." (pp. 133-135, my translation).

As you know, it was another polyhistor, J. B. S. Haldane, chemist, physiologist, geneticist statistician, and prolific political writer in the New Statesman and Daily Worker, who got things basically right, although the really correct formulation was printed slightly later (Steffensen, 1930).

When telling this history and then stating the correct extinction theorem, I sometimes meet the comment at that this is all very amusing, but how does it explain that frequent extinction of family lines occurs even in quickly growing

populations? The answer is, of course, that the extinction probability q and mean reproduction $m = f'(1)$ can be large simultaneously, for very convex reproduction generating functions f. Indeed, values of 0.75 and 2, respectively, e.g., are obtained for realistic reproductive patterns among human males, or for that sake females, in historic times.

Lecturing in Peking in October 2008, I met with a cute illustration of this, which may well have occurred to some of you. In the *China Daily* I read that Kung Te-chen, who was the 77th great...grandson of Confucius (Kung Fu-tse) had died on Taiwan at the age of 89. Yes, same surname inherited from father to son for more than 75 generations. Since Confucius (500 B.C.), China's population has undergone a tremendous growth, but as we all know, there are few Chinese family names. Indeed, Wikipedia tells us that three surnames (partly different in different parts of the country) are carried by some 30% of the population. In Korea the situation is even more extreme; among half the population has one of the names Kim, Lee, or Park.

Thus, branching processes were born out of a social demographic context. Its first fundamental result, the extinction theorem, has relevance far beyond that, in explaining homogeneity in large populations, as well as (part) of the more than frequent extinction in the course of natural evolution. Indeed, the palaeontologist David Raup claims that 99.99% of all species, ever existing on our earth, are extinct now (1991).
When branching processes reappear in scientific literature, between the great wars, the impetus comes from genetics (Fisher and Haldane) and biology more generally. Haldane deduces his approximation for the survival probability, still very important for the consideration of fresh, slightly fitter mutants in a resident population. In Russia, Kolmogorov coins the term *branching process* itself.

After World War II, nuclear war threatens. In Stalin's Moscow, Kolmogorov and his disciples, people like the Yaglom twin brothers and B. A. Sevastyanov, try to pursue their research as a purely mathematical undertaking. But of no or little avail. Sevastyanov's thesis was classified, while being written, and since he himself was not deemed reliable he was not allowed to keep it. Every morning a KGB officer opened a safe in the library and handed it out to its author, who continued writing on it until five, when he had to give it back.

Kolmogorov and others, including some physicist Academy members protested, and finally the ban was lifted (Sevastyanov, 1999). Things had become easier than in the 30's. In the United States, Ted Harris was employed by the Rand Corporation, an integral part of the military-industrial complex, and his work on electron-photon cascades and Galton-Watson processes with continuous type space (energy) was clearly inspired by nuclear physics. But both he and Sevastyanov saw themselves as mathematicians, though working on a pattern relevant for natural science. Sevastyanov even takes a rather purist stance; I have heard him saying that mathematics is nothing but mathematics, a somewhat unexpected opinion from a discrete mathematician working with branching processes, combinatorics, and cryptography; maybe more natural to one who has devoted his life to mathematics in the overly politicised Soviet Union.

With such leaders, it is not surprising that the 50's and 60's was an era of mathematisation. Time structure was added to the simply reproductive branching process in what Bellman and Harris called *age-dependent* processes, depicting populations where individuals could have variable life spans, but split into a random number of children at death, independently of age. Truly age-dependent branching processes were introduced by Sevastyanov, the reproduction probabilities possibly affected by the mother's age at splitting.

The processes thus arising were not Markovian in real time, but could be analytically treated using renewal properties, and the then remarkable renewal theory, which had recently been established by Feller and others. Another development retained the Markov property, but viewed population evolution as occurring in real

time, thus establishing connection to the elementary birth-and-death processes that were flourishing in semi-applied literature.
These approaches however remained in a sort of physical world, far from animal or even plant population dynamics, in the sense that they all considered child-bearing through *splitting* only, like fission, cell division, or molecular replication. Or, for the classical Galton-Watson process, there was the alternative interpretation of disregarding time, counting generations only. The only exception was the models from the-birth-and-death sphere, where exponentially distributed life spans allowed alternative interpretations. That also lead to the first model of populations where individuals could give birth *during* their lives, Kendall's generalised birth-and-death process (1948).

The first monographs, Harris's from 1963 and Sevastyanov's from 1971, as well as Athreya's and Ney's from 1972, however firmly stayed in the tradition of physical splitting. Branching processes stayed separated from the Lotka-Volterra tradition of population dynamics and mathematical demography. It was the development of a general point process theory that rendered the formulation of general branching processes natural, so as to depict populations where individuals can give birth repeatedly, in streams of events formed by a point process, and possibly even of various types. 1968 time was ripe, and Crump's and Mode's article and mine appeared simultaneously in the winter 68-69. Mine was also part of my Ph.D. thesis, defended in October, fortunately. In those times in Sweden, formal originality was still required, in a somewhat square manner, and in spite of the enormous friendliness of my polite Japanese opponent, Kiyosi Ito himself, I might not have been let through, had the stern local mathematics professors known that some Americans had done the same, sceptical towards probability theory, as they were. The status of probability within mathematics has certainly changed since then!

The advent of general branching processes meant that branching processes now embraced virtually all mathematical population theory. The dominating mathematical population framework since more than a century was the *stable population theory*, dating back to Quetelet and Lotka. Its real father or forerunner was, however, Euler who deduced its main findings, the exponential increase of population size and how the ensuing stable age distribution is determined by survival and reproduction rates, already around 1750. As I pointed out in my 1975 book, Euler even used rapid population growth as an argument against those incredulous who would not believe that the sons of Adam could have filled the earth during the 5000 years since the first couple was ousted from Eden. Nevertheless, his contributions seem long forgotten in the demographic and mathematical biology communities.

Stable population theory is deterministic but based upon a probabilistic formulation of individual life events. All its findings could now be strictly proved in terms of general branching processes, and basic concepts like average age at childbirth given an interpretation. Furthermore, the stabilisation of population composition could be brought one step further: stable population theory had only considered the distribution of age in old populations. Age is what could be called an individual property: it is your age and nobody else's. In a population there are however also important relational properties.

My research into this area started in a quaint manner. In my youth, Gothenburg had a well-known doctor caring for the city's alcoholics. Now that he had retired in the late 70's he took up a research idea that he had toyed with for some time. He had made the observation that an astonishing proportion of his patients were first-born.

Studying the literature, he found that not only Gothenburg alcoholics, but also poets, statesmen, and people suffering from various mental disorders had been found often to be first-born. Galton had even claimed that the first-borns were the motor of history. He realised that this could be an artefact, and performed a primitive but adequate simulation experiment, drawing the family trees of an invented but realistic population on a long paper table cloth,

and then sampling individuals at random. Now he wanted to discuss with me.

I found the probability of being first-born in an old single-type supercritical general branching process. It is $E\{exp(-\alpha\tau)\}$, where α is the Malthusian parameter and τ mother's age at her first bearing. Since the Malthusian parameter equals *ln 2* divided by the doubling time and the latter is usually larger than age at first bearing, we see that the probability of being first-born tends to be larger than 0.5, even in populations with large broods or families (Jagers, 1981).

The important is, however, that being first-born is not a property of your own life and birth-time. It concerns your relation to your sibship. Thus this simple observation led on to an investigation of how the whole pedigree, family structure, and type distribution in multi-type populations stabilise during exponential growth. A framework was formulated in which type distribution and pedigrees, and hence mutational history could be traced backward in a Markov renewal structure. Our group published a whole sequel of papers on these topics during the 80's and 90's, and indeed a final (?) attempt to popularise the admittedly heavy theory by restriction to discrete time quite recently (Jagers and Sagitov, 2008).

In the mean time, deterministic population dynamics had advanced through work by eminent mathematicians like Odo Diekmann and Mats Gyllenberg, inspired by the biologist Hans Metz. They had realised that the differential equations formulations they had been brought up with were becoming a straitjacket, and turned to semigroups of positive operators, yielding a theory corresponding to the Markov renewal theory of expectations of multitype general branching. However, they took a further step, considering the feedback loop individual -> population -> environment -> individual. Through this theory, *structured population dynamics,* they were able to analyse the fascinating new ideas that Metz and his followers had advanced to explain evolution, under the name of *adaptive dynamics*.

This was a new challenge to branching processes, and has been met in a series of path-breaking papers by Sylvie Méléard and her co-workers. We have also tried to formulate models investigating the consistency of adaptive dynamics, and in particular the problem of *sympatric speciation*, i.e. how successive small mutations can lead to new species, and their coexistence – but with less success so far.

The general problem of interaction in population dynamics is elusive. On one hand, the very concept of population builds upon individuals in some sense being the agents, those changing the population by their actions. The branching process idea is to distil this "individual initiative" into the strong requirement of statistical independence between individuals. This is proper as an idealisation, but obviously takes us far from reality. In special cases this can be remedied, as in the models considered by Méléard and Champagnat and Lambert, or in the population size dependence studied by Klebaner and others, and allowing an understanding of the linear growth occurring in the famous polymerase chain reactions, PCR, (cf. Haccou *et al*.).

This overview has been rather centred on my own interests, branching processes as a form of theoretical biology. However, much of the revival the area experienced in the 90's, and which continues to this day has a different character. Mainly it is purely mathematical; partly it is inspired by computer algorithms. The whole area of superprocesses and measure-valued Markov branching processes, seems to belong to the former realm, whereas random trees though certainly a pure mathematical area also has drawn upon both phylogenetics and computer science. But these are areas where others have much more insight than I, and I leave it to you to comment upon the impressive growth of these fields during the past three or so decades.

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PAST ACTIVITIES

The European Congress on Image Analysis and Stereology (ECS10)

22-26 June, 2009, Milan, Italy

ECS10, the 10th European Congress of Stereology and Image Analysis, is part of the quadrennial European Conferences of ISS (the International Society for Stereology), which are intertwined with the series of the quadrennial International Conferences on Stereology.

The aim of ECS10 has been to bring together leading scientists working on recent advances on methods in Stereology, Stochastic geometry, Spatial processes, and related Statistical methods, including Statistical Shape Analysis, Image and Signal Analysis and emerging areas of applications such as Biology and Medicine, Biotechnology, Materials, Micro- and nanostructures, etc.

The Conference attracted more than 160 participants from all over the world; including 34 countries from all five continents, Africa, North and South America, Asia, Australia, Europe (sorry, no penguins!).

The Scientific Programme included an Opening Lecture delivered by *Daryl Daley*, a Special Lecture, dedicated to Ewald Weibel on his 80th anniversary, by *Luis Cruz-Orive*, 9 Invited Lectures delivered by *Arun Gokhale, Ken Kieu, Ville Kolehmainen, Krzysztof Kurzydlowski, Salvatore Lanzavecchia, Claudia Redenbach, Evgeny Spodarev, Alessandro Verri, Rick Vitale*; 15 Minisymposia (around 60 presentations), 53 Contributed Talks, and 20 Posters.

The choice of the Invited Lectures had been made by an International Advisory Board in such a way that the most recent research trends were illustrated. The overall standard of the Conference was unanimously recognized at top levels (we are still receiving letters of congratulations from participants, and in particular from members of the Board of ISS), and it is impossible to highlight particular cases. But we like to mention that the Milan Conference has offered a unique opportunity for young scientists to meet many internationally recognized experts. We are sure that it has been instrumental in furthering interactions for joint research and exchange of information among groups beyond disciplinary silos. We have been witnessing intense discussions between mathematicians, statisticians, engineers, biologists, medical scientists, etc.
It may be of interest to record that all sessions, from the first to the very last day, have been highly attended, notwithstanding various attractions and opportunities of social life in Milano.

The ISS had offered six "Hans Elias" fellowships to young participants (recipients were selected by an ISS committee). At the Closing Ceremony two prizes (including a Diploma, in addition to a "concrete" prize) were offered by the ECS10 Local Committee to authors of Posters, as selected by an ECS10 Special Committee, including members of the ISS Board and of the Local Committee of ECS10.

The Social Programme had been very intense; out of five evenings, it included a very well attended Social Dinner, which seemed to be extremely appreciated by all attendants, but Dominique Jeulin, who spent all of his time jumping from one table to another for taking pictures (you will find them too in the ECS10 web site); Ewald Weibel gave a speech about the history of ISS, and its series of Conferences.

On Wednesday evening a Concert was organized, with a pianist and a violinist playing a delicious European programme, based on a musical itinerary along the Danube.

On Thursday evening the Big Event came to all participants and their accompanying persons: a visit to the Cenacolo (Last Supper) by Leonardo da Vinci; note that it is not trivial to

organize such a visit for more than one hundred people, during the same evening. After that visit everybody was much nicer to each other, and participants felt how special the site of the Conference, Milan, is.
Based on the accurate illustration (by the guide) of the painting, in which laws of geometry had been so magisterially applied, the Cenacolo was unanimously declared, by an International Jury, the BEST POSTER on IMAGE ANALYSIS and STEREOLOGY at ECS10.

The Proceedings of the Conference, are available on a CD; they have been regularly registered as a publication, so that they can be further disseminated after the conference. In addition to contributions by the Invited Speakers, it contains papers related to minisymposia and contributed talks, which have gone through a standard peer review system, by international experts in the field.

Extended versions of selected contributions will appear on the official journal of the ISS, Image Analysis and Stereology.

We wish to thank here all those who, directly or indirectly, have contributed to the organization of the Conference: participants, speakers, the International Scientific Committee, and last but not the least, the Board of ISS for his trust and active support. Thanks are also due to many national and international organizations for their important auspices.

We take the opportunity to convey the wish of the Board of ISS too, that the membership of the Society is enlarged by number, by age, by geography, and of course by scientific interests, in order to keep it as vital as possible.

All information regarding ECS10 can be found at the web site of the conference:
http://ecs10.mat.unimi.it/
where a gallery of pictures will soon appear.

The "flame" of the ISS Conferences has now been passed on to our Chinese colleagues, to whom we wish solidarity and success for ICS-2011.

Giacomo Aletti, Vincenzo Capasso, Alessandra Micheletti (ECS10 Local Committee), Milano

EMBO Conference Series on Morphogenesis and Dynamics of Multicellular Systems

2-6 October 2009, EMBL Heidelberg, Germany

http://www.embl.de/training/courses_conferences/conference/2009/conf_118/

The conference organized by D. Gilmour, D. Brunner and E. Wieschaus took place in the old EMBL Operon Lecture Room as the long awaited EMBL Advanced Training Centre was not finished, yet. The aim of this meeting was to bring together scientists from developmental biology, cell biology, biophysics, mathematics and computer science because the problem how cells organize into three-dimensional tissues can only be solved by intertwining these research fields.
Among the about 130 participants 50 were selected to give presentations on six main topics:

1) Mechanics in Morphogenesis
2) Moving Cell Collectives
3) Cancer as a Morphogenetic Process
4) New Methodologies adressing
Tissue Dynamics and Morphogenesis
5) Shaping Cell Collectives
6) Coupling Domains in Embryos

The presentations were given successively which kept ways short and facilitated discussions among all research fields. A high percentage of these talks were of extraordinary good quality and it became clear that mathematical modeling and quantitative measurements are key features to understand morphogenetic processes. But although modeling and quantification are currently trendy in the field it must not be done for its own sake and it remained unclear what one learned from it in some presentations.

Fabian Rost
Technische Universität Dresden

"***Mathematics closes the Darwin year"***

The mathematics of Darwin's Legacy
23-24 November 2009, Lisbon

This was one of the few events dedicated primarily to the mathematical aspects of the theory of evolution: On November 23rd 2009 (exactly 150 after the publication of *"The Origins of Species"*), a group of leading biomatematicians met for a two days conference.

The conference was opened by Warren Ewens (U. Pennsylvania), and followed by talks by R. Buerger (Vienna), H. Metz (Leiden), S. Méléard (Paris), B. Perthame (Paris), M. Gyllenberg (Helsinki), P. Schuster (Vienna), P. Taylor (Queens), J. Pacheco (Lisbon), F. Weissing (Groningen), V. Jansen (London) and M. Mimura (Tokyo). During the two days, population genetics, adaptive dynamics, evolution of cooperation, pattern formations and evolution of sex, among others, were discussed by leading specialists and an audience of more than 50 students. The slides of the talks are available at the conference webpage http://www.cim.pt/Darwin2009.

As a follow up of the conference, a collective book, including most of the talks of the conference, will be published by Birkhauser in the series "Mathematics and Biosciences in interaction", edited by Wolfgang Alt.

The scientific committee was formed by F. Chalub (Lisbon), J. F. Rodrigues (Lisbon), E. Kisdi (Helsiki) and P. Jagers (Gothenburg). The last two organizers are from the board of the ESMTB. The president of the ESMTB, Carlos Braumann (Evora), participated in the opening session. Braumann and Jagers also participated in the following day in a "Journey of Biomathematics" organized in the same place by the International Center of Mathematics and the Portuguese Mathematical Society.

The conference was co-organized by the International Center of Mathematics (Portugal, http://www.cim.pt) and the European Society for Mathematical and Theoretical Biology (http://www.esmtb.org) and had financial support from the Gulbenkian Foundation (http://www.gulbenkian.pt), Portuguese National Science Fund (http://www.fct.mctes.pt), the Center of Mathematics and Fundamental Applications of the Universidade de Lisboa (http://ptmat.ptmat.fc.ul.pt) and the Center of Mathematics and Applications of the Universidade Nova de Lisboa.
(http://www.dmat.fct.unl.pt/cma)

Fabio Augusto da Costa Carvalho Chalub, Lisboa

Moreover, please, notice the special issue of the journal *Theory in Biosciences* ***129***, Sept. 2010.

Modelling and Biology in Regenerative Medicine

26-27 April 2010, University of Nottingham, United Kingdom
http://www.maths.nottingham.ac.uk/mrm/events/

The workshop organised by Oliver Jensen took place on the University Park Campus in Nottingham, East Midlands, UK. The 18 talks were held by theoreticians and experimentalists without exception in a captivating manner. Invited speakers included PIs from France, Italy, and the UK. The topics ranged from cellular signalling and gene regulatory networks to tissue engineering and embryonic development of vertebrates. Some thirty participants obtained information on current applications of different mathematical frameworks (e.g. Boolean networks, ODEs, PDEs, DDEs) in life sciences.

The work in Nottingham was showcased by eleven of the speakers who currently do research at the University of Nottingham. The intertwining of theoretical and experimental studies became most evident in four talks given by two pairs of biologists and mathematicians working on the same topic (Growth-induced epithelial buckling in a developing colorectal crypt, Gene regulatory networks in early osteogenesis).

Breaks for tea (and coffee) and the joint lunches in the Telford Orangery of the Pope Building turned out to be a suitable setting for deepening discussions. Altogether, the workshop made a point underlining that diverse fields from basic research in molecular biology to applied studies in medicine benefit from a combination of theoretical and experimental investigations.

Arnd Korn
Technische Universität Dresden

2010 OCCAM Conference on Modelling at Different Scales in Biology

21-23 June, 2010, St Anne's College, Oxford

Organisers: Paul Bressloff, Jon Chapman, David Gavaghan and Philip Maini

Biological function arises as the result of processes interacting across a range of spatiotemporal scales. It is now being increasingly recognised that mathematical and computational tools are necessary if we are going to be able to fully understand these complex interactions. This requires modelling at each spatial level, model reduction, and model integration across scales. The aim of this conference was to bring together researchers in these areas with applications in a range of biological systems.

This conference was the first subject specific one organised by the Oxford Centre for Collaborative Applied Mathematics (OCCAM), one of 4 centres funded by the King Abdullah University of Science and Technology (KAUST). The meeting was attended by over 100 participants and there were 13 plenary lectures and over 40 poster presentations. John Ockendon (Director, OCCAM) introduced the conference with a brief summary of the research mission of KAUST and OCCAM. *Jim Murray* (Washington, Oxford, Princeton) then gave the opening address. He emphasised the importance of close interdisciplinary collaboration between mathematicians and experimentalists and illustrated with a number of examples drawn from diverse areas in medicine and biology how in many cases simple mathematical models have significantly contributed to important scientific advances.

The first plenary speaker was *Alain Goriely*, recently appointed to Oxford as Professor of Mathematical Modelling. His talk showed how taking an alternative view of protein folds through a continuous representation rather than the discrete description using position of alpha carbons could lead to important structural insights. He then developed the geometry and mechanics of protein structure to, amongst other things, generalise the classical results of Crick on chirality. *Benoit Perthame* (Paris 6) presented a mathematical framework in which to develop ideas related to adaptive dynamics in evolutionary theory and showed through asymptotic analysis that a new type of Hamilton-Jacobi equation emerges. *Mark Alber* (Notre Dame) used a computational model to show that the regular reversing behaviour of Myxococcus

xanthus is essential for swarming and that the observed frequency of reversal optimises swarming rate of the population. He then briefly described a multiscale model for blood clotting investigating in particular the dynamics of fragmentation. *Michael Mackey* (McGill) addressed two problems. He first considered the effects of extrinsic and intrinsic noise in the distribution of molecules in bacterial operons, and then presented a mathematical modelling study of the mammalian hematopoietic system linked to drug pharmacokinetics which results in personalised treatment protocols for various diseases. In particular, he showed how this has led to a two-fold reduction in treatment costs for certain diseases. The day ended with *John Archer* (KAUST) describing the exciting developments in Saudi Arabia with the formation of this new graduate university, its diverse links with other universities worldwide and the opportunities for collaborative, international, multidisciplinary research that are emerging as the university grows.

The first talk of the second day was given by *Wolfgang Alt* (Bonn) who presented a multiscale mechanochemical model for the ubiquitous phenomenon of crawling cell motility. The model, a two-dimensional hyperbolic-elliptic-parabolic stochastic partial differential equation system with free boundary conditions, was shown to be capable of reproducing various cell behaviours and was also amenable to detailed analysis via different one-dimensional approximations. *John Tyson* (Virginia Tech) focussed on mammalian signal transduction networks with particular application to control of cell growth, division and death. He showed how seemingly impossibly complicated networks could be understood by breaking them down into simpler modules. He described how these models are being used to account for the progressive transformation of breast cancer cells. *Juan Soler* (Granada) tackled the classical problem of establishing morphogen gradients. He showed how detailed experimental results suggested that in certain cases these were inconsistent with the idea of a diffusive front, and then he developed a new model which resulted in a highly nonlinear transport equation which was consistent with the observations.

The afternoon of the second day was devoted to posters and this session was very well attended. The posters mainly showcased the work of graduate students, postdocs and young faculty and were uniformly of very high quality. The day ended with a talk by *Leah Edelstein-Keshet* (UBC) on swarming. She presented a model which showed how the integration of local attraction-repulsion rules could account for global swarming behaviour and used the model as a hypothesis generating tool to suggest new interactions in certain circumstances.

The final day of the conference had three talks. *Helen Byrne* (Nottingham) began with a multiscale model of tumour growth which linked intracellular behaviour (cell cycle, production of signalling factors etc) through to tissue-level behaviour and vascular adaptation and angiogenesis. She used the model to investigate the effects of combination therapies (such as chemotherapy and macrophage-delivered therapies) and how they could work synergistically. *Lisa Fauci* (Tulane) then presented a talk on swimming lamprey and showed how a comparatively simple model of a lamprey considered as a series of springs interacting with the dynamics of the surrounding fluid could result in amazingly life-like swimming motion. This then allowed her to compare the model predictions of swimming in different fluid viscosities with experimental results. The conference ended with *Hans Othmer* (Minnesota) presenting new results on the classical problem of timescale analysis. In virtually all (bio)-chemical reactions there are many different timescales of reaction and the challenge is to write the system in such a way that these can be identified. He showed how this could be done in a systematic manner which can now greatly simplify the analysis of complex reaction networks.

The conference was very lively with a lot of interaction between the participants. The younger participants were inspired by meeting some of the major names in the field while the latter were excited to see that the future of the field is in good hands.

Philip K. Maini, Oxford

Reinhart-Heinrich Doctoral Thesis Award

ESMTB announces the Reinhart Heinrich Doctoral Thesis Award to be presented annually to the best doctoral thesis from any area of Mathematical and Theoretical Biology.

Professor Reinhart Heinrich (1946 – 2006) began his research in theoretical physics, then moved into biochemistry and in 1990 became full professor and head of theoretical biophysics at the Humboldt University, Berlin. He is considered a forefather of the field that is now named Systems Biology, since he investigated various topics such as modeling metabolic networks and metabolic control theory, modeling of signal transduction networks, nonlinear dynamics as applied to biological systems, protein translocation, lipid translocation, vesicular transport, and even DNA repair.
Reinhart Heinrich was always searching for the principles behind observations, looking for different perspectives and connecting abstraction with biological evidence. In this way, he inspired numerous students, gave them insight and direction for future research in modern mathematical and theoretical biology, and organized a large number of memorable conferences.
Gratefully acknowledging his stimulating support of our interdisciplinary field and, in particular, his way of guiding students and young scientists, the Board of ESMTB has decided to annually award a Doctoral Thesis Award in honour of Reinhart Heinrich and his legacy in mathematical and theoretical biology.

After two years of broad response (with more than 10 applicants each) and successful selection of winners, see the documentation in the annual *European Communications (ECMTB No. 10 and 11),* ESMTB continues to ***honour the annually best thesis*** showing most impressing modelling ideas and useful innovative methods with ***an award***. Responsible for the selection will be the

Awarding Committee consisting of:

Wolfgang Alt
Carlos Braumann (president of ESMTB)
Andreas Deutsch
Edda Klipp (former assistant to R. Heinrich)
David Rand

Award

The award comprises

- ***an invitation to present a lecture at the next triennial ESMTB Conference or, alternatively, a travel grant by ESMTB for a scientific visit of the recipient's own choice.***
- ***1 year of free ESMTB membership.***

The extended summary of the thesis receiving the award will be preferentially published in the next issue of ECMTB (*European Communications*) along with a brief laudatio.

Application

To be considered for this award, please send (by e-mail to wolf.alt@uni-bonn.de):

1. an ***extended summary of your thesis*** (about 3-10 pages)
2. a CV containing your current (or future) scientific affiliation.

Deadline for nominations is ***31st October*** of each year, by which time the nominated thesis should have received final acceptance by the doctoral granting institution. Candidates whose thesis is accepted after 31st of October will be considered in the next calendar year. Names of potential applicants may also be suggested by any ESMTB member (by writing to wolf.alt@uni-bonn.de).

Shortlisted applicants will be asked to send their full thesis.

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The scheme on the front cover is taken from a poster inviting you to participate the

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