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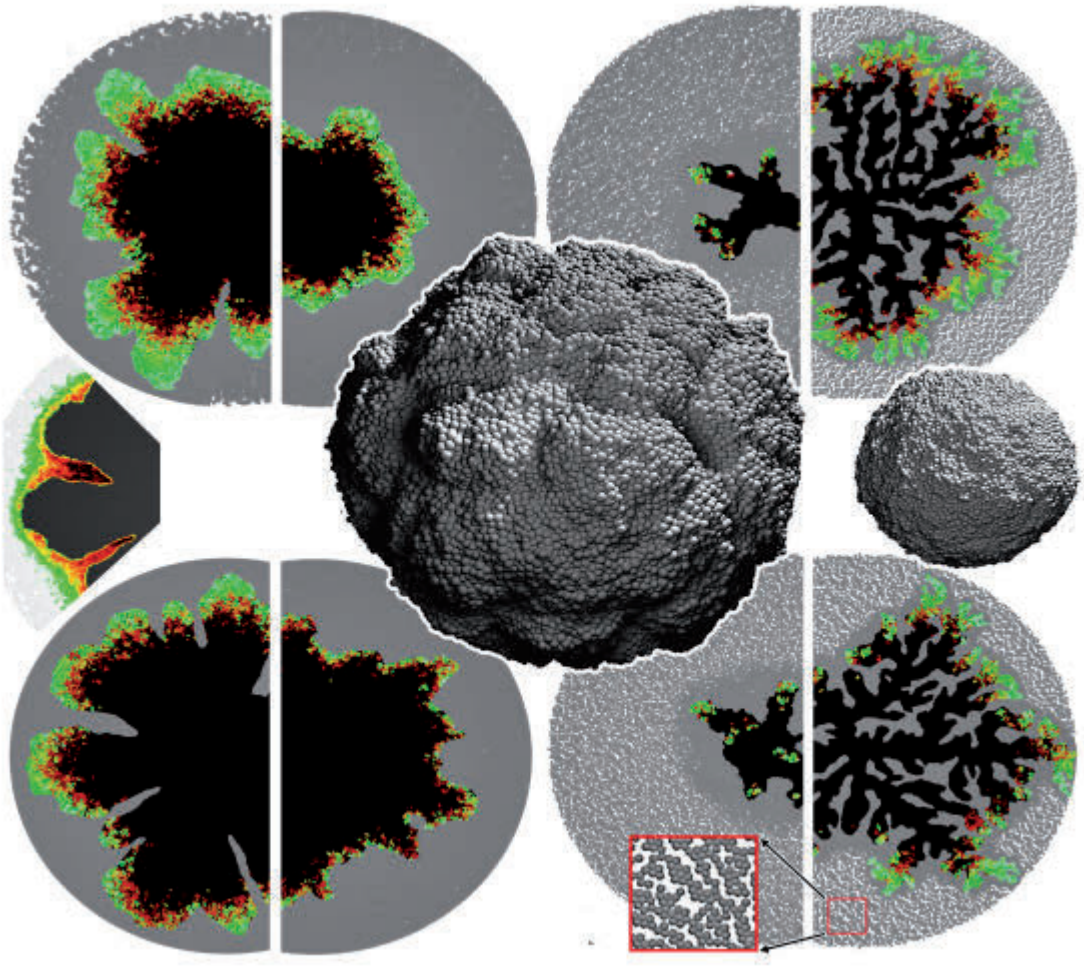
E MTB Communications



European Society for Mathematical and Theoretical Biology

A European Forum for Information, Presentation and Exchange
Official Communication Bulletin of ESMTB

EDITORIAL

Dear Society members, dear Colleagues,

The last year, since the publication of the previous communications, was rich on events. The most important among them was the **8th European Conference on Mathematical and Theoretical Biology** in **Krakow.** With about a thousand of participants from 48 countries it was a magnificent manifestation of the current state and trends in this rapidly developing field. You will find below a short report about the conference. The next conference will take place in Gothenburg, on June 15-19, 2014. The preparation has already started, and it will certainly be an interesting and important scientific meeting accompanied by an exciting cultural program.

The ***General Assembly of ESMTB*** held during the conference in Krakow. It nominated candidates for the ESMTB Board. The electronic vote in the autumn 2011 determined five new Board members. Together with five other Board members who continue their functions for other three years, the new Board had the first meeting in February 2012 in Trento. It elected the new President, Andrea Pugliese, Vice-president, Roeland Merks, Secretary, Barbara Boldin, and Treasurer, Andreas Deutsch.

For the 2011 ***Reinhart-Heinrich Doctoral Thesis Prize,*** the awarding committee obtained six applications. The European Society for Mathematical and Theoretical Biology designated the best thesis award to Dr. Stefan Höhme (Leipzig, Germany). Extended abstract of his thesis followed by the summaries of three other selected dissertations are presented in these Communications.

As usual, we count on your support and on your contribution to the activities of the Society.

The Editorial Board
September 2012

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Please send by e-mail any information, reports or other material for the next issue of the Communications *(ECMTB # 16)* as soon as available, best before **March 31th, 2013,** to Vitaly Volpert, volpert@math.univ-lyon1.fr

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

CALL FOR MEMBERSHIP FEES 2012

http://www.esmtb.org

ESMTB membership includes free electronic subscription of the official journal of the Society
Journal of Mathematical Biology.

Please register at www.esmtb.org and send your payment of the required annual dues for 2012 by bank draft transfer or electronically (PayPal).

Membership Fees per year**:**

a. **Individual Annual Membership Fee**:
- 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. **Institutional Annual Membership Fee**:
- 200 Euro (includes up to 5 full memberships)

c. **Life Membership Fee**:
- 750 Euro (age 40 or above)
- 500 Euro (age 50 or above)
- 250 Euro (age 60 or above)

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.Külz-Ring 10
D-01067 Dresden, Germany

Further information:
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Letter by the President

Andrea Pugliese

Dear Colleagues and Members,

I am really honoured to have the opportunity of writing to you all as the new President of the Society that represents the area of all my scientific work. I thank the members of the Society and of the Board that have trusted me for this role, and all (former presidents, members of the Board, and members that contributed in different ways) that have helped building the Society. I hope that, together with the other members of the Board and the help of you all, we will be up to the challenges and the expectations that the Society will meet, given the growing relevance of mathematical modelling and theory in biological research.

Last year the joint Conference of ESMTB together with SMB and JSMB in Krakow, was the largest ever in attendance (978 participants, many of whom young researchers, from 48 countries) and extremely interesting and diverse from the scientific point of view; personally, I was particularly intrigued by the many presentations that were evidence of the joint work between biologists and mathematicians.

This year is less intense for the Society, the main activity directly organized being the joint ESMTB-EMS Summer School Theory of Speciation, part of the Helsinki Summer School on Mathematical Ecology and Evolution, taking place in Turku, 19 – 26 August 2012.

The local organizers led by Torbjorn Lundh have already been spending quite some time and effort in the preparation for the 2014 ESMTB Conference in Gothenburg. By the autumn, the Conference will have its Scientific Committee and a selection of the main speakers and of the main topics for the sessions. All members are invited to send their suggestions about these to the Board of the Society or the local organizers. Remember to save the date (15-19 June 2014, just before Midsummer festivities in Sweden) and look at the web site **(www.ecmtb2014.org)**; it will certainly be a memorable conference.

In a few months we should already start thinking about the following Conference. In fact, as already announced in Krakow, it has been agreed that, in order to have it again as a joint Meeting with SMB, and to accommodate SMB schedule, the next ESMTB Conference will be held in 2016, instead of keeping our normal triennial cycle. By the spring of next year, we should find a location, and especially the local organizers, for that Conference. Suggestions and candidatures will be highly appreciated.

Certainly the conferences are a high point of the activities of the Society, but we should not forget the other activities, such as the Reinhart Heinrich prize (the award given annually for the best Ph.D. thesis on Mathematical and Theoretical Biology), the Summer Schools, the travel grants for young researchers, or the Perspectives section on the Journal of Mathematical Biology, the official journal of the Society.

All these activities go on only thanks to the patient work of many colleagues and friends; I would like to thank especially Wolfgang Alt, who has been for years the editor of the Communications, and Vitaly Volpert, who is starting his turn as editor with this volume; Helen Byrne, who has been the editor of the Perspectives in Mathematical Biology, and Roeland Merks, who will collaborate with her in the job; Eva Kisdi, who was secretary of the Society for six years, keeping track of all necessary paperwork, Barbara Boldin, who has

replaced her this year, Carlos Braumann, the former president, who has given an effective coordination of activities, and Andreas Deutsch, who, with his many years as treasurer, and in charge of memberships and web site, is keeping the society together.

Overall, I dare to say that the Society of Mathematical Biology is in good shape and has an important role. What is not quite satisfying, in my opinion, is the number of members, who are much fewer than the number of potentially interested people, as seen in the Conferences. Thus I invite you to renew the membership, if you forgot to do so (you can check your payments at the web site www.esmtb.org), and to invite your colleagues to join the Society. At the Board meetings we discussed several times of what could be done to make the membership more rewarding, and what could be the role of a Society in a world where technology has made connections and exchanges of results very easy. Beyond the practical advantages to members (free access to JMB, discounts on Springer books, limited travel support for young researchers), we would like that the Society could have a role in forging collaborations at all levels, and perhaps in shaping the agenda of European research and education policy in the area.

We would thus like that, through the Perspectives and the Communications, as well as through the web site or the involvement in social networks, and together with the sister societies (Society for Mathematical Biology, Japanese Scoiety for Mathematical Biology and similar societies from many countries), we could promote exchanges of ideas about future research directions, about curricula in mathematical biology as well as projects for teaching effectively mathematical modelling to students of Mathematics or of Biology, about bringing the research in mathematical and theoretical biology to the forefront in Horizon 2020, the EU framework for research and innovation.

These are, however, difficult challenges for the Society; we will try to move in that direction, perhaps starting by implementing a database of the current initiatives in education and the European projects involving mathematical and theoretical, but we definitely need suggestions and cooperation. For the moment I invite you to look at the current activities, as documented in this volume of Perspectives, which constitutes the annual tie among all members of the Society.

Best regards

Andrea Pugliese
ESMTB President

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Minutes of the ESMTB Board Meeting

Trento, Italy, 11th February 2012

Meeting starts at 9:45.

Present: Barbara Boldin (BB; minutes), Carlos Braumann (CB), Reinhard Bürger (RB), Andreas Deutsch (AD), Roeland Merks (RM), Andrea Pugliese (AP; chair), Ryszard Rudnicki (RR), Vitaly Volpert (VV)

Absent with apology: Miguel Herrero, Daphne Manoussaki, Peter Jagers

Guest: Torbjörn Lundh (TL; organizer of ECMTB 2014).

Round of welcome.

1. Board elections and constitution of the ESMTB Board for 2012-2014.

A brief summary of Board elections. At the end of 2011, five members of the Board of ESMTB (Carlos Braumann, Christine Jacob, Éva Kisdi, Jean-Christophe Poggiale and Hans Westerhoff) ended their six year term on the Board. The other Board members (Andrea Pugliese, Andreas Deutsch, Daphne Manoussaki, Miguel Herrero and Peter Jagers) continue for the next three years.
During the 8th ECMTB in Krakow in July 2011, the General Assebly of ESMTB nominated nine candidates to replace the outgoing members of the Board for the 2012-2017 mandate. The election candidates were Barbara Boldin, Reinhard Bürger, András Czirók, Radek Erban, Torbjörn Lundh, Pierre Magal, Roeland Merks, Ryszard Rudnicki and Vitaly Volpert. In September 2011, all paying members of ESMTB were invited to cast their votes in an electronic ballot. The candidates were ranked based on the number of votes they received, and the first five became the new members of the ESMTB Board. The results of the elections were as follows:

Candidate:	Number of votes:
Barbara Boldin	59
Vitaly Volpert	42
Reinhard Bürger	41
Ryszard Rudnicki	38
Roeland Merks	36
Radek Erban	33
Pierre Magal	32
Torbjörn Lundh	31
András Czirók	25

The five new members of the Board are thus Barbara Boldin, Vitaly Volpert, Reinhard Bürger, Ryszard Rudnicki and Roeland Merks.
The constitution of the new ESMTB Board. Seven Board members present at the meeting (BB, RB, AD, RM, AP, RR and VV) cast their votes to elect the President, Vice president, Treasurer and the Secretary of ESMTB for the 2012-2014 mandate. The outcome of the voting is: Andrea Pugliese is elected as the new president, Roeland Merks as vice president, Andreas Deutsch continues as Society's treasurer and Barbara Boldin is elected new ESMTB Secretary.

The ESMTB Board for the 2012-2014 mandate is thus the following:
Andrea Pugliese (President)
Roeland Merks (Vice President)
Barbara Boldin (Secretary)
Andreas Deutsch (Treasurer)
Reinhard Bürger
Miguel Herrero
Peter Jagers
Daphne Manoussaki
Ryszard Rudnicki
Vitaly Volpert

2. Reports by the past President and the Treasurer

Report by the past President:

- CB briefly summarizes the 8th ECMTB in Krakow. The next ECMTB will take place in Gothenburg, 15th -19th June 2014 (see below). CB nominates the main organizer of ECMTB, Torbjörn Lundh, as advisor to the Board. All present Board members support the suggestion.
- CB highlights the Society's support to students and meetings. ESMTB has an agreement with EMS to organize joint summer schools. The next joint ESMTB – EMS summer school is the *The Helsinki Summer School on Mathematical Ecology and Evolution 2012: Theory of Speciation*, that will take place in Linnasmäki Conference Centre in Turku, 19th - 26th August 2012.

- The contract with Springer was renegotiated 3 years ago (see below).
- CB and AP report that the database of European MSc programs, which was to be developed by Jean-Christophe Poggiale, has not been developed yet. No further plans are made, RM remarks that inclusion of MSc programs in Systems biology would benefit both sides.

Report by the Treasurer:

AD hands out printed reports and describes his work as the Society's Treasurer. The administrative and IT work related to Treasurer's tasks and to maintaining Society's website amounts to half a job. The support is currently provided by the Technical University of Dresden. The end of AD's term as the Treasurer is the time to modernise the Treasurer position and a more permanent solution should be found in the next three years.

- *Membership development*: AD presents figures describing ESMTB membership development in the period 2003 – 2011. The memberships peaked in 2005 (in the year of ECMTB in Dresden). Despite the ECMTB 2011 in Krakow, the number of members dropped in 2011. In 2011, ESMTB had 206 members from various countries. Figures show that there is great potential for new memberships in several countries.
- *Balance*: Revenues are exclusively from membership fees. On 31.12.2011, the balance was +14.671,08 euro.
- *Travel grants:* There were no requests for ESMTB support of summer schools in 2011. 30 applications for travel support were granted for ECMTB 2011; money from ECMTB 2005 in Dresden is still available for this purpose.
- *Audits:* Audits are needed to check the Society's financial data for 2010 and 2011. AD and AP suggest two auditors.

Board members' comments on membership development, fees and benefits:

RM suggests that payment reminders are sent as personalized emails to ESMTB members. RB expresses concern that ESMTB membership fee is too high and doesn't offer enough benefits. AD adds that not all benefits are direct but often come in the form of support to younger members. Students enjoy reduced membership fees and joint SMB, ISTMB, JSMB, NVTB or SFBT membership offers some benefits. It is decided that no changes of membership fees will be made in 2012. VV adds that credit card payment would be welcomed. AD replies that such method of payment would bring further costs to the Society. Bank transfer is strongly recommended as a method of payment. The possibility of an age-dependent life membership is discussed.

3. Report by Ryszard Rudnicki on ECMTB 2011

RR summarizes ECMTB 2011 by presenting the number of lectures, sessions, mini-symposia, mini-symposia talks and posters. ECMTB 2011 in Krakow had 978 participants, including 54 students who helped with the organization. The participants came from 48 countries. AD asks for the budget of the conference. RR informs the Board that all profit made by ECMTB 2011 remains with Jagiellonian University.

4. ECMTB 2014

T. Lundh introduces plans for ECMTB 2014. The conference will take place in Gothenburg, 15th - 19th June 2014. The website of the conference (www.ecmtb2014.org) is already in preparation. Immediately after the conference, Midsummer festivities will take place in Sweden, thus giving the participants a chance of a unique experience. TL presents preliminary plans for the program and introduces preliminary locations for the lectures. The local organizing committee is named. Board members agree that a scientific committee of 12-15 people should be proposed as soon as possible. Basic topics should be suggested and the expertise of the members of the scientific committee should cover all the proposed topics. By fall 2012, a list of speakers should be prepared. 8 to 10 plenary talks should be as diverse as possible. TL adds that some time should be spent on introducing emerging areas. BB suggests that talks on emerging areas should be used to promote JMB Perspectives.

5. JMB, Perspectives and Springer

- *JMB:* AD presents the numbers related to the Journal of Mathematical Biology. The number of submissions steadily increases, the rejection rate remains fairly constant and is about 74%. The impact factor has increased sharply and stands at 3.021 in 2010. JMB is ranked by ISI as 5/37 in the category of Mathematical and computational biology. AD reiterates Mats Gyllenbergs's comments regarding plagiarism. More special issues should be encouraged. A list of topics should be sent to Mats Gyllenberg.
- *Perspectives:* JMB publishes short views on topical issues in mathematical and theoretical biology in Perspectives series. Perspectives articles are handled by Helen Byrne and reviewed by ESMTB Board members. Helen Byrne continues to be the editor of the series, but she needs help, especially in soliciting articles. RM offers to help Helen Byrne in finding authors for Perspectives. It is agreed that all Board members should think of prospective authors. AD suggests that printed Perspectives articles are handed out at the next ECMTB in Gothenburg.
- *Springer:* A contract with Springer was renegotiated 3 years ago. CB and AD describe the new contract. All paying ESMTB members now get a free online access to the Journal of Mathematical Biology and reduced fees for printed issues of JMB. In addition, ESMTB members are entitled to discounts for Springer Books and Springer Briefs. AD informs the Board that Catriona Byrne will replace Olga Chiarcos.

6. ESMTB Communications and ESMTB Infoletter

- ESMTB Communications are published once a year. Wolfgang Alt (WA), who took care of the Communications, has stepped down and a new editor is needed. VV volunteers as the new main editor of the Communications and all present Board members agree to help with the preparations. WA, AD and AP remain on the editorial board. RB suggests that open positions and information about summer schools and conferences should only be put in the Infoletter and no longer in the Communications.
- AD remains in charge of the Society's Infoletter.

7. The Reinhart Heinrich Award

ESMTB annually gives out the Reinhart Heinrich award to honour the best PhD thesis in mathematical and theoretical biology. The current award committee consists of 5 members: Carlos Braumann, Andreas Deutsch, Philip Maini, David Rand and Stefan Schuster. The question is raised whether self-nomination should be allowed. It is decided that no changes will be made at the moment; if self-nominations do appear, they will be dealt with on a case by case basis by the award committee. AD reports the number of nominated PhD theses in the recent years. The quality of nominated theses remains high but the numbers have gone down. AD suggests that more should be done to increase the visibility of Reinhart Heinrich award.

8. Conferences and Summer Schools

- ESMTB has an agreement with EMS to organize joint summer schools. In 2012 the joint EMS summer school is *The Helsinki Summer School on Mathematical Ecology and Evolution 2012: Theory of Speciation*, that will take place in Linnasmäki Conference Centre in Turku, 19th - 26th August 2012. Possibilities for the joint summer school in 2013 are discussed: one possibility is a summer school on cancer modelling, organized by A. Pugliese, V. Capasso and L. Preciosi. Another possibility would be joining a part of a trimester in math biology in Lyon in February – April 2013. Details are to be finalized via email and during the next Board meeting.

- The next joint ESMTB-SMB conference will be organized in 2016. Having an ECMTB in 2016 means only a two year gap from the ECMTB in Gothenburg. It is discussed whether 2016 will be an exception or whether ECMTB should establish a biennial cycle: AD adds that a biennial cycle would be very difficult in view of organization, CB adds that Conferences on Computational and Mathematical Population Dynamics (CMPD) also have a triennial cycle. It is agreed that ECMTB 2016 remains an exception for the time being. Spain and Portugal are named as possible organizers of ECMTB 2016.

9. Cooperation with other societies

The Japanese Society was invited to the joint ESMTB-SMB conference in Krakow. Cooperation with sister societies is good but further connections should be built. RM adds that a closer collaboration with the International Society for Systems Biology **(**ISSB) would be welcome.

10. Registration of new Board members

The French representative on the Board (VV) will prepare the registration documents and officially register new members of the Board in Grenoble, France.

11. Next Board meeting

The next Board meeting will be organized by Roeland Merks in November 2012 in Amsterdam. The preliminary plan is to discuss the agenda for ECMTB 2014 in Gotenburg and to finalize the joint EMS summer school in 2013. The Board members agree to remain in contact via email. Mats Gyllenberg and Catriona Byrne from Springer will be invited to join the next Board meeting to discuss JMB.

12. Diverse

AD remarks that ESMTB Statutes need to be updated to include information about electronic ballot and to define in more detail the tasks of ESMTB Board members.

AP is thanked for organizing the Board meeting. The meeting ends at 18.40.

Barbara Boldin
Secretary

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)

Kraków, June 28 - July 2, 2011

European Society for Mathematical and Theoretical Biology

ECMTB 2011

8th European Conference on Mathematical and Theoretical Biology, and Annual Meeting of The Society for Mathematical Biology,

In the period of June 28- July 2 the 8th ECMTB brought together scientists and students from all over the world to Kraków to discuss recent advances in mathematical and theoretical biology. It was a joint conference of the European Society for Mathematical and Theoretical Biology and Annual Meeting of The Society for Mathematical Biology. The conference was organized by the Katowice Branch of the Institute of Mathematics Polish Academy of Sciences and by the Faculty of Mathematics and Informatics of the Jagiellonian University. It took place in a modern conference building of the Jagiellonian University called Auditorium Maximum in a walking distance from the main attractions of the city the Main Market Square with St. Mary's Basilica and the Sukiennice Cloth Hall and the Wawel Castle.

The conference was designed for researchers who are active in or interested in this fast growing field where experimental biology and medicine, biochemistry, computational biology, mathematics and computer science merge. The key topics of the conference was immunology and epidemiology, cancer, cellular systems biology, neurosciences, medical physiology, regulatory networks, bioengineering, ecosystems dynamics, genetics and bioinformatics. Modeling of biological and medical phenomena involves a broad spectrum of mathematical methods: all types of differential equations, probability theory, dynamical systems and discrete mathematics.

This meeting brought almost thousand mathematician and scientists together from 48 countries to discuss a wide range of current topics in mathematical biology. There were thirteen eight plenary lectures (including five lectures given by winners of prizes of both societies). In 94 mini symposia and in 63 regular session participants presented 758 talks and in addition more than a hundred postdocs and students presented their posters.

The plenary lectures presented topical subjects of mathematical biology included Uri Alon (Weizmann Institute of Science) *Design principles of biological circuits*, Marek Kimmel (Rice University), *Heterogeneity of proliferating cell populations: Models and data*, Sylvie Méléard (École Polytechnique, Paris) *A rigorous model for adaptive dynamics of Mendelian diploids*, Rob

Phillips (California Institute of Technology) *Random Walks in Physical Biology*, Michael C. Reed (Duke University) *Serotonin Metabolism in Health and Disease*, Peter Swain (University of Edinburgh) *Stochasticity in biochemical networks*, Julie Theriot (Stanford University Medical School) *Quantitative analysis and modeling of cell shape during rapid movement*, Hiroki Ueda (RIKEN Center for Developmental Biology, Japan) *System-level Understanding of Biological Timings.* There were also five plenary talks given by the winners of prizes: Art Winfree Prize: John Tyson (Virginia Tech) *Temporal Organization of the Cell Cycle*, Reinhart Heinrich Awards: Thomas Maiwald *Mathematical modeling and in silico labeling with PottersWheel* and Tina Toni *Approximate Bayesian Computation for parameter inference and model selection in systems biology,* Lee Segel Prizes: W. Brent Lindquist and Ivan D. Chase *Analysis of Winner-Loser Models of Hierarchy Formation in Animals* and Barbara Boldin *Persistence and Spread of Gastro-Intestinal Infections: the Case of Enterotoxigenic Escherichia coli in Piglets.*

The conference had a mentoring program addresses to students and PhD students. The aim of it was to introduce junior and senior scientists with similar research interests and help young scientists in many different ways: by discussing research, career paths, research in different countries or industries and introducing them to other researchers in the area. Five introductory lectures dedicated to students was held a day before the conference. The lectures cover topics from age-structured models, branching processes, cancer invasion, ecology, and epidemiology.

The social program included the welcome party, lunches and coffee breaks, the conference dinner, a party at the poster session and a conference trip. The conference dinner was organized in Folwark Zalesie a nice restaurant in the rustic style placed in a beautiful rural area. The participants could choose one of three different trips: The Royal Route - Krakow's main promenade in the olden days used by Kings, Memorial and Museum Auschwitz-Birkenau, a symbol of terror, genocide, and the Holocaust and the historic Salt Mine in Wieliczka, the only mining site in the world functioning continuously since the Middle Ages. The conference proved that Kraków is the best place for hosting conferences in the Eastern Europe.

More information concerning the conference could be found in the article by Hannah Callender published in SMB Newsletter Vol. 24 (3) and on our website http://www.impan.pl/~ecmtb11.
I would like to thank the members of Scientific Committee for their work in selecting the talks and preparing the program of the conference. I would also thank my collaborators doctors Antoni Leon Dawidowicz, Katarzyna Pichór, and Radosław Wieczorek and the Jagiellonian University Events Office for their help in organization of the conference.

Ryszard Rudnicki
The president of the Scientific and Organizing Committees
of the 8th ECMTB

Cancer Modeling at ECMTB 2011 in Kraków, Poland: from multiscale understanding to clinical practice

Roeland Merks

Cancer modeling is becoming an ever more prominent topic at the ECMTB conferences. In Kraków there were seven sessions with contributed talks on cancer modeling, six multisession minisymposia on modeling of aspects of cancer, and a further five minisymposia with contributions related to cancer modeling, giving a total of almost one hundred talks. These talks covered both the molecular biology of cancer and the biology of the whole tumor. Molecular-level and single cell models described the genetic regulatory networks, metabolism and signaling pathways of tumor cells, with talks covering the Hes1 and p53 pathways, the dynamics of signaling networks, the cell cycle, and the dynamics of heatshock proteins. Tumor-level models included cell population dynamics models, models to study tumor growth, tumor invasion, models of tumor angiogenesis, and models of tumor evolution and plasticity.

Most of these models aim at describing, analyzing and understanding aspects of cancer biology, but some approaches attempt to use mathematical modeling for designing new control mechanisms to kill tumors or to reduce their growth. For example, the minisymposia *Analysis of mathematical models for cancer growth and treatment,* organized by Urszula Ledzewicz and Alberto d'Onofrio and *Bridging the Divide: Cancer Models in Clinical Practice* by Marisa Eisenberg and Harsh Jain were entirely devoted to this topic. Within this minisymposium, Jean Clairambault, INRIA Paris-Rocquencourt described his numerical optimization approach to designing anti-cancer therapeutics delivery schedules: a partial-differential equation system describes the cell cycle phase transitions of healthy cells and tumor cells, both of which are controlled by circadian rhythms and pharmacological agents. This can be turned into an optimization problem, with as objective function a minimal growth rate of the tumor cells and as a constraint the minimal killing of healthy cells. Clairambault sketched the future use of such numerical optimization approaches to design personalized, optimal drug delivery schemes. A computational approach to attain better distribution of drugs in tumors was presented by Holger Perfahl in Eisenberg's and Jain's *Cancer Models in Clininical Practice* minisymposium. Perfahl presented an agent-based, multiscale model of drug delivery to a tumor, with at the largest scale the therapeutics' transport through the blood vessels towards the tumor, and the resulting remodellng of the vascular networks, at the lowest scale an agent-based model of the individual molecules random motion from through the blood vessel walls towards the tumor cell receptors. The model simulations show how heterogeneous structure of tumors affects drug transport; Perfahl argues that such frameworks may eventually help predict the efficacy of alternative, localized drug delivery methods.

Perfahl's work was just one example of the increasing number of agent-based and cell-based multiscale modeling approaches to cancer modeling featured at the Kraków conference. Katarzyna Rejniak of the Moffitt Research Institute presented a biomechanical model of metastasis, focusing on the interactions between circulating tumor cells and the endothelial cells in the vessel wall. Tumor cell intravasation through the vessel wall was also featured in one of the talks of Dirk Drasdo's, also of INRIA Paris-Rocquencourt and of Leipzig University. They combined a biomechanical, cell-based model of tumor-endothelial cell interactions, with a differential equation model describing the expression of cellular adhesion molecules in response to contact between endothelial cells and tumor cells. These and many other talks demonstrated the explanatory power of multi-scale approaches, as they allow us to link events at the molecular level to behavior at the collective cell level. That's one reason why agent-based and cell-based approaches are becoming ever more prominent in the modeling of tumor angiogenesis, as showcased in the minisymposium that Xiaoming Zheng, Trachette Jackson and myself had organized. Beautiful examples of multiscale models in angiogenesis were presented by Florian Milde of ETH Zürich

and Amina Qutub of Rice University, both of whom combine models of the subcellular dynamics of endothelial cells with phenomenological models of tip cell behavior and vessel formation. The promise of such models is that they will help identify the molecular, pharmaceutical targets for controlling tissue level events, e.g., the efficacy of angiogenic sprouting or the functionality of tumor vasculature.

An upcoming topic in which agent-based and cell-based modeling are particularly prominent is tumor evolution, as for example showcased in the minisymposium *The emergence of resistance in cancer using mathematical modeling* organized by David Basanta of the Moffitt Cancer Center in Tampa, Florida. Using a variety of agent-based approaches the speakers in this minisymposium modeled the competition between tumor cell lines and stromal tissues. Their results suggest that chemotherapy in some cases may select aggressive cell lines and result in a post-treatment relapse of the tumor. In the future, this type of mathematical modeling may inspire new strategies for cancer treatment to control tumor progression. The 2011 participants of Basanta's minisymposium may then join hands with the participants of Eisenberg's and Jain's minisymposium *Cancer Models in Clininical Practice*.

Ecology & Evolution during the 8th European Conference on Mathematical and Theoretical Biology in Krakow

Barbara Boldin

European conferences on mathematical and theoretical biology are always an event I look forward to: offering a myriad of interesting presentations, they are guaranteed to be a source of stimulating discussions and to spark new ideas that keep one busy long after the conference has finished.

From June 28th to July 2nd 2011, the beautiful Polish town Krakow hosted the 8th European Conference on Mathematical and Theoretical Biology and the Annual Meeting of the Society for Mathematical Biology. The event brought together almost one thousand scientists from all over the world and the superbly organized conference covered a wide variety of topics. Among them were the very active fields of *Ecology* and *Evolution*. Several parallel sessions on *Evolutionary Ecology* were organized and chaired by R. Bowers, É. Kisdi, K. Parvinen, T. Kostova Vassilevska and A. Yamauchi. An interesting session on *Speciation* was organized by T. Priklopil. M. Broom and K. Argasinski organized two sessions on *Game theoretical modeling and optimization in evolution and ecology.* A number of mini-symposia were devoted to the evolutionary dynamics of infectious diseases: the session *Mathematical models of evolutionary dynamics of infectious agents* was organized by A. Pugliese and V. Andreasen while B. Boldin and É. Kisdi hosted a session on *Ecology and evolution of infectious diseases.* Two sessions on *Mathematical models in eco-epidemiology* were organized by H. Malchow, S. V. Petrovskii and E. Venturino while *Epidemiology, eco-epidemiology and evolution* was hosted by E. Venturino and N. Stollenwerk. Several mini-symposia were organized on *Population dynamics*, hosted by C. Braumann, N.F. Britton, A. Bohn, C. Cobbold, P. Jagers, M. Kimmel, É. Kisdi, M. Lachowicz, P. Pang and D. Wallace. *Ecosystem dynamics* was discussed in a number of parallel sessions organized by H. Kettle, J. Miękisz and J. Müller. C.-S. Chou and R. Gejji organized a session on *Modeling Dynamics of Complex Biological System* while *Models in Spatial Ecology* were discussed in a session hosted by R. Kraenkel. The final day of the conference introduced us to some *Recent developments in the study of Lotka-Volterra and Kolmogorov systems* in a session organized by S. Baigent.

As with every ECMTB, the schedule in Krakow was incredibly busy (but the vast quantities of Polish delights served during coffee breaks ensured we had enough energy to keep us going) and one often finds oneself wishing for bilocation. Several presentations were very interesting, but two talks sparked my attention in particular. Alex Best talked about *Host resistance and coevolution in spatially structured populations.* Within-population spatial and social structure is known to affect the

evolution of parasites. However, very little attention has been paid to how spatial structure affects the evolution of host resistance. One of the conclusions of the work of A. Best and colleagues is that more population mixing may lead to the evolution of both fast-transmitting highly virulent parasites and reduced resistance in the host. Another interesting presentation was given by Samuel Alizon on *Within-host parasite cooperation and the evolution of virulence.* It has been argued that co-infections select for lower levels of virulence in parasites whose virulence is determined by the production of public goods. In his presentation, S. Alizon demonstrated that this prediction is flawed because it neglects epidemiological feedbacks: a nested model that ties together within-host and epidemiological processes in the context of an SI model reveals that co-infections select for less virulent strains for public goods producing parasites only in very special cases.

Bridging the within- and between-host dynamics to study the epidemiology and evolution of communicable diseases has become a hot topic in the recent years with many questions still unanswered. I for one am already looking forward to the 9th European conference on mathematical and theoretical biology in Gothenburg for new developments on this as well as many other fascinating topics in Ecology & Evolution.

Behavioural epidemiology of transmissible infections: two Minisymposia at ECMTB 2011

Alberto d'Onofrio, Piero Manfredi, Piero Poletti

In the last years as epidemiological modellers, we have become increasingly aware that there was an important "missing element" in our otherwise sophisticated models. This missing element was man. Many examples, from the dramatic decline in travels to Far-East during the SARS outbreak, to the changes in contact patterns during the H1N1 pandemic, to the "rational" opposition to MMR vaccine, have demonstrated that the traditional idea of humans as a static component - passive actors on the infection scene – was at best an approximation. The current increase in scientific knowledge about diseases, the fast-than-ever spread of information, and, the increasing value of human life in modern low mortality-low fertility societies, are nowadays giving humans a fully new role in the transmission and control of infections. Agents can change their social behaviour spontaneously in response to the threat of an outbreak, can vaccinate adaptively in response to a sequence of seasonal influenza epidemics, can decide not to vaccinate their children as a consequence of a comparison between the costs and benefits of a routine vaccination program. As a consequence, in the last few years we have assisted, thanks to some pioneering works, to the outbreak of a new branch of mathematical epidemiology, focusing on the complex interplay between the spread of infectious diseases, and individual human behaviour. We have termed this new discipline "Behavioural Epidemiology" of infectious diseases. Behavioural Epidemiology integrates traditional mathematical modelling of infections with tools from a variety of behavioural sciences, ranging from economics and sociology to psychology, in order to predict the extent of the impact of human behaviour on epidemiological outcomes. Many hot topics of Behavioural Epidemiology have been discussed at ECMTB 2011 in the beautiful Krakow's environment, during a Mini-symposium divided in two blocks organised by Piero Manfredi (University of Pisa, Italy) and Alberto d'Onofrio (European Institute of Oncology, Italy). Actually the debate between participants started the day before during a friendly meeting in front of polish beers and pirogyis which lasted very late in the evening).

The first block (4 speakers) was opened by Tim Reluga (Pennsylvania State University, USA) who presented the general approach he developed to describe the complex interplay between infection dynamics at the population scale and agents' decision. The approach combines elegantly, in a single

unified framework, Markov decision processes, game theoretic decisions, and population models of infection transmission. This approach sounds to be a critical avenue for further advances of the discipline. Piero Manfredi (University of Pisa, Italy) reported historical data showing that medical progress in mortality control, and herd immunity due to vaccines, acted as major "killers" of vaccination payoffs in industrialised countries, therefore emerging as the ultimate responsible of the onset of rational opposition to vaccines. He also proposes a model where public interventions can mitigate the negative effects of individual decisions. Sebastian Funk (Zoological Society of London) has used a model based on two inter-connected networks, one for the spread of information, the other for spread of an infection, to show how the spread of awareness of the presence of the disease (in the information network) might be important, through behavior change, to mitigate the impact of a serious threatening epidemics, such as a pandemics. In the last talk Bruno Buonomo (University of Naples, Italy) presented several global results, demonstrated by means of the modern geometric approach to stability developed by Li and Muldowney, about the stability of equilibria in the prevalence-dependent SIR infection models with lagged behavioural reactions (about eg vaccination or contacts). The second mini-symposium has been opened by Sara Del Valle (Los Alamos National Laboratory,US). Sara has presented results from models where individuals can change their behavior (i.e. lower their daily contact rates or adopt protection such as wear masks to reduce the probability of transmission) in reaction to epidemics spread, showing that even mild behavioral changes can dramatically reduce the final attack rate. The subsequent two talks have been devoted to the inductive vaccination games for influenza vaccination decisions. In the case of seasonal influenza indeed, individuals may take their vaccination decisions regarding the new flu season "inductively", i.e by adapting on their memories and past experiences about infection and vaccination. Raffaele Vardavas (Rand Corporation, USA) uses an individual-level model of adaptive-decision making coupled with a population-level model of influenza, to show that severe influenza epidemics might be triggered by the behavioral dynamics in vaccine uptake. He also shows some counter-intuitive consequences of incentives to vaccinate, which in some cases might increase outbreaks' severity. Romulus Breban (Institut Pasteur, France) expands the inductive reasoning games model to include richer information set of individuals compared to the basic model presented by Vardavas. He shows that better epidemiological information may stabilize vaccination coverage and suppress severe influenza epidemics. Istvan Kiss (University of Sussex, UK) reported results about pairwise and individual-based models of infection with multiple sources and routes of information transmission about the disease aimed to better capture the local population contact structure. He shows that these more refined approaches can yield quite different results compared to standard simple transmission models. In the last talk Piero Poletti (Bruno Kessler Foundation, Italy) reported some interesting results on the effects of risk perception on the spread of 2009 H1N1 pandemic influenza in Italy. He shows that the risk of infection was overestimated during the early stage of the epidemic, therefore possibly affecting contact patterns in a dramatic way, and slowing down the initial phase, and eventually the whole course of the epidemics. We all concluded with the hope that this this meeting was the first in an increasing list of events…

Photo gallery from ECMTB 2011 in Kraków

Welcome to the conference

Main lecture room

Conference dinner

Krakow at night

Salt mine

More photos at the conference web site
http://www.impan.pl/~ecmtb11/

Reinhart-Heinrich Doctoral Thesis Award 2011

For 2011 the awarding committee obtained applications by six young scientists, who had recently finished their PhD thesis. Again, as in previous years, the theses represent a broad and interesting range of actual research topics in our growing field of Mathematical and Theoretical Biology: Biological fluid dynamics (Igor Chernavsky, Joanna Stachowska-Pietka),cell and tissue dynamics (Stefan Höhme, András Szabó, Christian Yates), and immunology (Carsten Magnus).

Thanks for all the applications!

Out of these the committee pre-selected four candidates, whose full theses were probed. They obtained their promotion at various institutes at European universities:

Stefan Höhme, University of Leipzig, Germany
Carsten Magnus, ETH Zurich, Switzerland
András Szabó, Eotvos University Budapest, Hungary
Christian Yates, Center for Mathematical Biology, Oxford, Great Britain

A ranking concluded the final decision: The awarding committee nominated as winner of the Reinhart-Heinrich Doctoral Thesis Award 2011

Sebastian Höhme (University of Leipzig, Germany).

In memory and honour of our colleague Reinhart Heinrich the European Society for Mathematical and Theoretical Biology (ESMTB) awarded Dr. Stefan Höhme (Leipzig, Germany) with the first prize for his dissertation on “Agent-based modeling of growing cell populations and the regenerating liver based on image processing” as best annual thesis from any area of Mathematical and Theoretical Biology.

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Agent-based modeling of growing cell populations and the regenerating liver based on image processing

In the presented thesis we developed an agent based model for multicellular populations. We used this model to shed light on processes that determine the growth of avascular tumor spheroids and studied the key mechanisms of liver regeneration.

In order to make such analyses possible, we developed a comprehensive software tool that allowed us to effectively simulate, visualize and analyze the constructed computational models [1]. We started with a minimal model for two-dimensional monolayers which are a common experimental technique for in-vitro cell cultures [2], [3]. We successively advanced our model in order to reflect an in-vivo situation more closely for example by simulating complex three-dimensional tumor spheroids embedded in granular medium and host tissue [4].

We proposed a biomechanical form of contact inhibition that was able to explain the experimentally observed linear growth of the diameter in monolayer cultures and their specific proliferation pattern where cells mainly proliferate at the monolayer border as experimentally observed in [5] and [6]. Furthermore, our model could mimic the growth dynamics of monolayer cultures very precisely.

Subsequently, we considered three-dimensional cell aggregates by studying substrate detachment whereby normally two-dimensional monolayers due to the failure of certain control mechanisms expand perpendicular to the monolayer plane. Failure of growth control mechanisms is known to play an important role in the development of cancer [7]. By additionally introducing nutrient diffusion and consumption, we established a further extended model for three-dimensional tumor spheroids which are a common experimental model in therapeutically oriented cancer research [4], [8]. Surprisingly, we found that the proposed biomechanical form of contact inhibition also explains the growth of these tumor spheroids. Thereby, our model suggests in agreement with experimental data [9], [10] that the nutrient concentration in the environment of a growing tumor, which is widely believed to control its growth, only determines the size of its necrotic core. Moreover, also in this three-dimensional situation the model precisely mimicked the growth dynamics and proliferation pattern of tumor spheroids in vitro where the

necrotic core is enclosed by an intermediate layer of quiescent cells and an outer layer of proliferating cells [11].

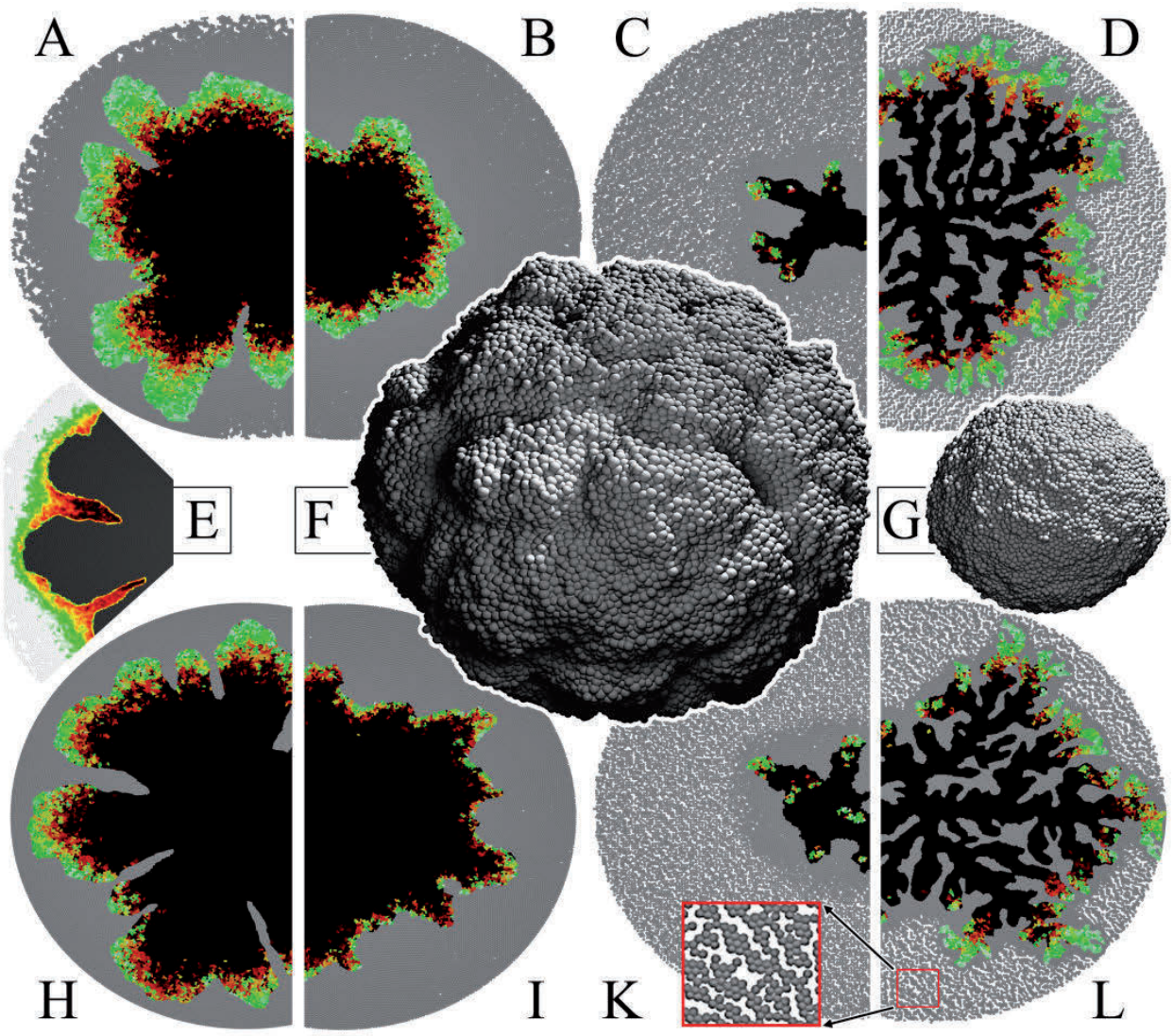

Fig.1 Impact of initial cell density and elasticity of tumor host tissue.

A: Tumor monolayer growing embedded in tissue (colored grey) of decreased initial cell density (~3500 cells per mm²), B: Tissue of increased density (~7000 cells per mm²), C: Same setting as (B) only with additionally lowered motility of the embedding cells ($D_T = 0.05D_0$), D: Same as (A) but with lowered host tissue motility ($D_T = 0.05D_0$), E: Alternative coloring of a section of (H) where tumor cells were colored black and embedding cells were colored according to the pressure exerted on them (black/red=high, yellow=medium, green=low), F: Tumor growing into host tissue (not shown here) in 3D (~$5*10^5$ cells). Host tissue of decreased density. G: Same as (F) only with increased host tissue density. H: Tumor monolayer (E=450 Pa) growing into host tissue of lowered elasticity (E_T=300 Pa), I: Same as (H) only with increased tissue elasticity (E_T=1000 Pa), K: Same setting as (I) only with additionally lowered tissue motility ($D_T = 0.05D_0$). Red framed inset: magnification of embedding tissue. L: Same setting as (H) only with additionally lowered tissue motility ($D_T = 0.05D_0$). The coloring of tumor cells (A-D, H-L) shows their proliferation activity (green = high, black = low).

We further advanced the model for the growth of three-dimensional cell populations closer towards in-vivo tumors by including aspects from the surrounding tissue [12]. We showed that the biomechanical

properties of an embedding tissue have a major impact on the growth dynamics and morphology of growing cell populations by systematically varying the biophysical properties of the embedding tissue. Our model predicts Saffman-Taylor-like instabilities leading to fractal interfaces and an increased ability of cells to invade harsh environments if the motility of the embedding cells is small. We additionally

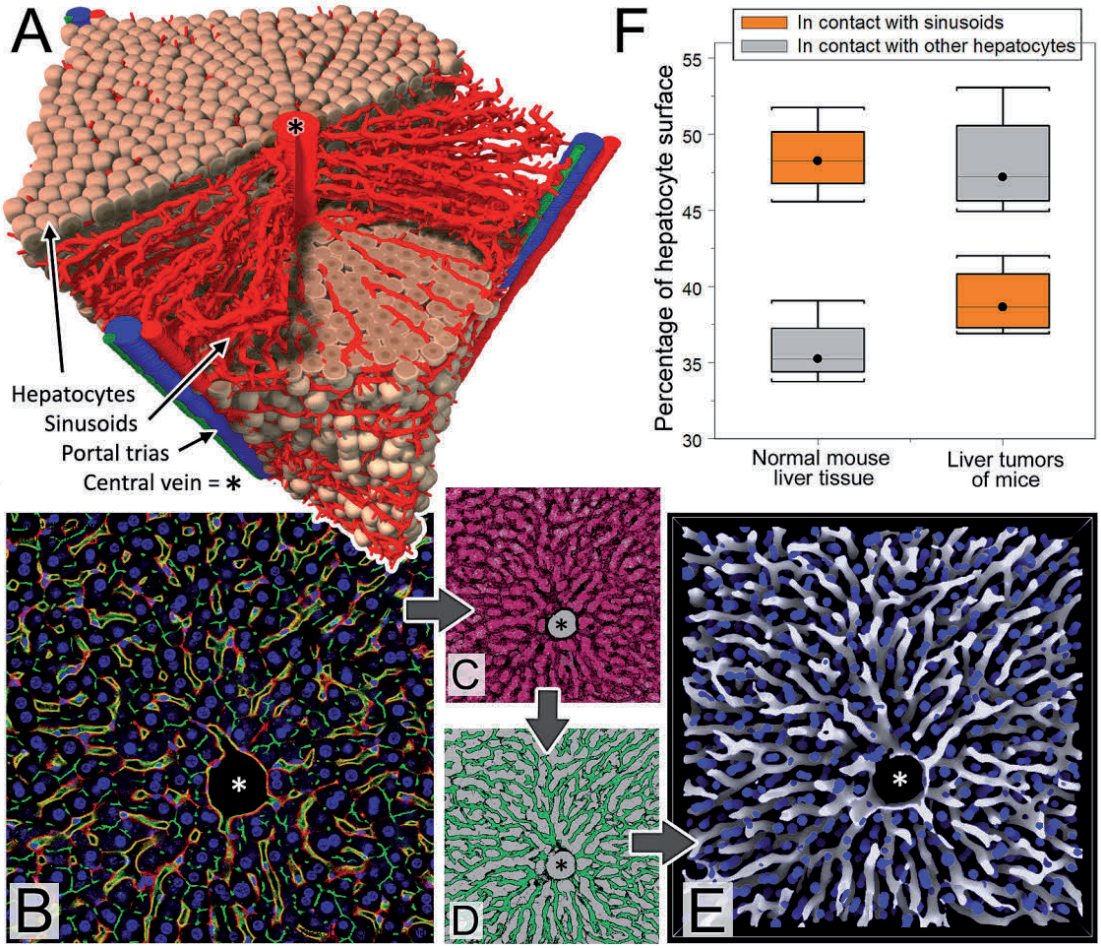

Fig.2 Three-dimensional model of the liver lobule.

A: Concrete liver lobule inferred from experimental data by the image processing chain shown in B–E and successive image analysis. Reconstructed lobules served as an initial state for the mathematical model. B: A typical image obtained by confocal microscopy after adaptive histogram equalization filtering. Blue: DAPI (hepatocyte nuclei); yellow: ICAM + DPPIV (sinusoids); red: ICAM; green: DPPIV. C: Effect of generalized erosion filtering (all red pixels will be removed). D: Effect of generalized dilatation filtering (all green pixels are added). E: Result of image processing chain in three dimensions. Blue: Hepatocyte nuclei; white: sinusoids. Note the complex architecture that links the periportal zone with the central vein in the middle of the lobule. F: Fraction of the surface area of hepatocytes in contact with sinusoids (orange) and other hepatocytes (gray) in normal liver tissue and liver carcinomas.

observed large wavelength instabilities as a consequence of decreased density, increased elasticity, strong adhesion or increased cell size of the embedding tissue or granular medium (Fig.1). Interestingly, we found a nearly complete inhibition of tumor growth for specific properties of the embedding tissue which, if experimentally validated, could have direct therapeutical implications.

Furthermore, we achieved a remarkable agreement with experimental data on tumor growth dynamics in [13] and [14]. However, the large variety of complex influences predicted by our model strongly

indicates that the widespread experimental technique of embedding growing tumor spheroids in agarose gels [13] may not be sufficient to realistically capture all the biomechanical effects of an embedding tissue. Effects due to the granularity of the surrounding tissue, for example, are missing in experiments like those performed in [13].
We established a procedure to use three-dimensional confocal laser scans to reconstruct in vivo tissues by image processing and image analysis. We then combined this very detailed and quantitative information

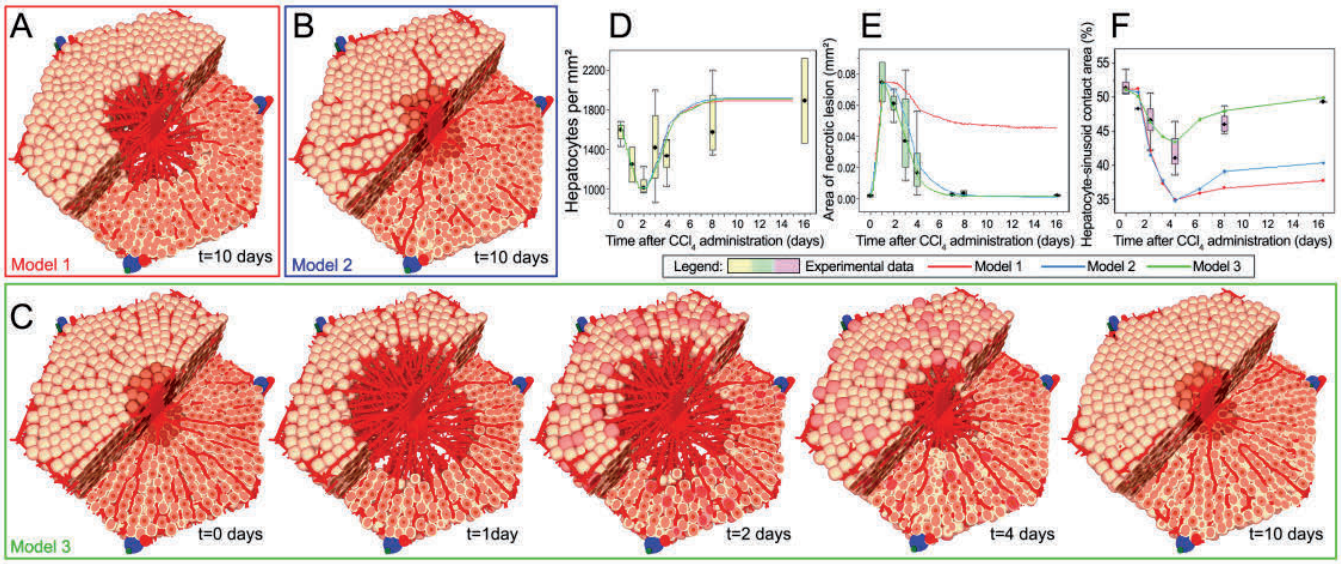

Fig. 3. Regeneration in the simulation model.

A: Result of a representative simulation of an initial naive model without HSA after 10 days, B: Simulation result of the best model without HSA after 10 d, and C: Illustration of the regeneration process (after t = 0, 1, 2, 4, and 10 d) using a model with HSA. A–C show cross sections of 3D model simulations. D–F: Quantitative comparison of experimental data with each model: D: Average hepatocyte density, E: Area of central necrosis, and F: Hepatocyte-sinusoid contact area.

with a further advanced version of our repeatedly experimentally validated model. We started with a minimal two-dimensional model for the regenerating liver lobule that nevertheless led to first impressions of the specific impact of the various factors that influence liver regeneration [15] [16]. On that basis we extended our model and created the first three-dimensional agent-based model of the regenerating liver lobule [17] (Fig.2).
By capturing a 16 day regeneration process, our model underlined the importance of the complex columnar microarchitecture within the liver lobules, which is formed by hepatocytes and sinusoids. This microarchitecture ensures optimal exchange of metabolites between blood and hepatocytes. The model predicted a so far unrecognized mechanism, the alignment of daughter hepatocytes along the orientation of the closest sinusoid, which we named hepatocyte-sinusoid alignment (HSA), as essential for liver regeneration. Only if HSA was included into the model the simulated tissue architecture was in agreement with the experimentally obtained data and no other likely mechanism could replace it (Fig.3). In order to experimentally validate the model prediction of HSA, we analyzed the orientation of daughter hepatocytes in relation to the sinusoids in three-dimensions. The results of this analysis confirmed the model prediction and thus verified HSA as a yet unknown key mechanism of liver regeneration.

During this analysis we introduced novel techniques that made currently experimentally not accessible information available by image processing and analysis of volumetric datasets obtained by confocal laser scanning microscopy. In addition to the three-dimensional analysis of HSA, we used a similar approach

to obtain further currently not experimentally available information on the average contact area between hepatocytes and sinusoids. Surprisingly, we found this parameter to possibly allow for an automatic differentiation between normal liver tissue and hepatocellular carcinoma.

In summary, in this thesis we present an interdisciplinary approach to combine microscopic imaging, image processing and analysis and computational modeling - all in three dimensions. The integration of methods and results from different scientific fields like cell biology, physics and computer science enabled us to obtain new insights cancer research and hepatology. We therefore consider the presented interdisciplinary approach and the corresponding procedures widely applicable in the systems biology of tissues in general.

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Empirical and computational study of vasculogenesis

Vasculogenesis is the formation of the primordial blood vessel network during embryogenesis. In later stages of development this network is remodeled through sprouting, pruning and fusing of the branches, to give rise to a functional vasculature. It is believed, that vasculogenesis is a self-organized process of endothelial cells, that remain the inner lining of the blood vessels after creating the network.

My thesis focuses on the emergence of the primordial network from three main aspects: (i) formation of multicellular linear segments, that eventually connect and give rise to the network; (ii) active, persistent motion of cells; (iii) sprouting.

I. Network formation

The formation of multicellular linear segments is not an exclusive property of the vascular endothelial cells: it is observed in cultures of C6, C2C12 and 3T3 cell lines as well. This indicates that a general cellular mechanism might be responsible for this behavior. Several hypotheses have been suggested for vasculogenesis. One such hypothesized mechanism is autocrine chemotaxis, in which cells secrete a diffusing compound that acts as an attractant. Another group of models suggests a more mechanical explanation: as cells pull on the elastic substrate, they create stretched filaments between clusters that guide cell motion.

Our experiments showed, however, that linear segments do form on rigid surfaces, excluding the mechano-chemical hypothesis, and with significant convection of the medium above the cell culture. This convection would introduce a bias in the concentration fields of any chemoattactants present, or secreted by the cells. According to the chemotaxis hypothesis, this bias should be apparent in the cell configurations, but such a bias was not observed.

Our suggested mechanism is a preferential attachment of cells to their elongated neighbors. The biological mechanism behind this behavior is not yet clear. Cells in elongated structures are possibly under mechanical tension, therefore the micro-mechanical properties of their cytoskeleton are altered. Cells are able to detect mechanical differences in their surroundings, as has been shown with the variations in extracellular matrix stiffness. A similar mechanosensing is feasible between cells: for example, VE-cadherin, a major cell-cell adhesion receptor of vascular endothelial cells, was shown to be incorporated in cell surface mechanosensing complexes.

To support our hypothesis experimentally, we analyzed individual cell trajectories and local morphology, revealing a correlation between close contact with elongated structures and cell motility (Fig. 1). Local anisotropy was calculated with the help of a diffusion process.

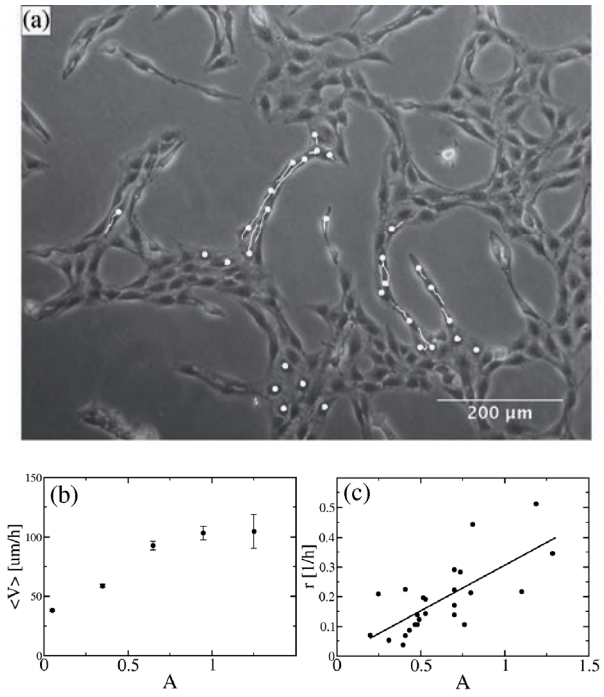

Figure 1: The dynamics of sprout formation in a cell culture on a rigid substrate is visualized by time-lapse microscopy. (a): Cell trajectories demonstrate intense motility within elongated structures. Current cell positions are marked with white dots, trajectories covered are drawn with white lines. (b): Mean cell velocity is almost three times greater in highly anisotropic sprouts (A=1.5) than in isotropic topologies (A=0). Error bars represent SEM. (c): Manually determined rate of branch widening is also positively correlated with the average anisotropy of the branch. Increase in widening reflects increased migration into the branches. [Szabo et al. 2008]

To test the validity of the preferential attachment hypothesis, a cell-based model is proposed in which cells (i) are adhesive, (ii) maintain a fixed size and (iii) have a preference to adhere to elongated neighbors Simulations with a particle model and a cellular Potts model (CPM) both predict a quasi-stationary state in which network-like patterns similar to the experimentally observed ones are produced (Fig. 2). Characteristic pattern size in the models depend only slightly on the cell density above the percolation threshold, which is in good agreement with experimental findings.

Cells in the particle model are represented by their center of mass, behaving as interacting particles that follow a stochastic dynamics. An important assumption we have to make in this model is that cell elongation is determined by the local configuration of the neighbors. The effect of the neighborhood on cell motion is the sum of local, isotropic pair-interactions between Voronoi neighbors. The pair-interaction consist of a soft-core repulsion term and a medium-range attraction. The attraction towards a cell is proportional to its "elongation" derived from its neighborhood.

In the CPM cell shape is explicitly represented and therefore can be measured more directly. Here, cells are represented as compact domains on a two-dimensional lattice, and are required to stay connected throughout the simulations. The dynamics is regulated by a Monte Carlo algorithm: at each step of the simulation, a lattice site and one of its neighbors is selected at random. An attempt is made to overwrite one of the lattice sites with the value from the other. The copy attempt is accepted if a global goal function, the Potts-energy, or Hamiltonian, decreases. If the value of the Hamiltonian is increasing, the attempt is accepted with a Boltzmann probability, relating the change in energy to an abstract temperature. Cell behavior can be controlled through additive terms in the energy. In the standard CPM, cells maintain a constant size through a "volume term" that penalizes the deviation of cell volume from a target volume with the square of the deviation, and adhesion through an "adhesion term" that penalizes cell-cell and cell-medium borders.

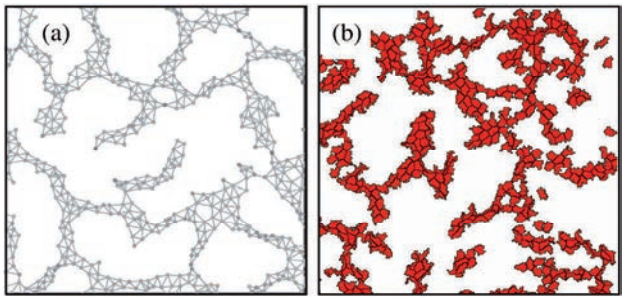

Fig2: Simulations of network formation through preferential attachment to elongated cells in the particle model (a) and the cellular Potts model (b). In the particle model (a), cells are represented by their center of mass, the gray-scale value indicates the calculated anisotropy of the cells, and Voronoi neighbors are connected with lines. In the cellular Potts model (b), cells are represented as domains in red. Simulations were started with randomly dispersed cells, which connect and form linear multicellular segments and networks. The networks are quasi-stationary: new branches form, existing branches break up, but the characteristic pattern size is approximately constant. [Szabo et al. 2007, 2008].

The unit of time in the model is the Monte Carlo Step (MCS), which is equivalent to N overwrite attempts, where N is the number of lattice sites. This definition ensures that the time-unit is independent of the system size.

To implement the preferential adhesion hypothesis, a novel term is added to the energy, which increases the probability of a spin-copy if it results in extending the cell's border with an elongated neighbor. Cell elongation is measured in the CPM by fitting an ellipsoid to the cell domain.

One intriguing feature of the proposed mechanism is its asymmetry: if cell "A" is more elongated than cell "B", then the attraction of "A" towards "B" is less than the attraction of "B" towards "A". This

asymmetry prevents the system to reach an equilibrium state, however, a quasi-steady state of the emerging cellular structures is obtained.

In both models, the quasi-stationary nature of the networks is observed in the balance between formation of new branches through spontaneous sprouting and breaking of existing branches. Sprouting is driven by random fluctuations in cell movement, and the sprouts are relatively short and irregular, when compared to in vivo or in vitro sprouts. To correct the sprouting behavior, we analyzed the phenomenon further.

II. Persistent active cell motion

A basic feature of cells forming networks is their ability to move persistently, leading to the active outgrowth of new sprouts from an existing cluster of cells. In the above models, simulated cells perform a random walk and therefore the growth speed of spontaneously forming sprouts is decreasing in time. We suggested a mechanism for active cell motion by introducing planar cell polarity of the cytoskeleton that promotes directional motility and, in turn, polarity is updated in the direction of the movement. The polarity vector magnitude relaxes to zero with a characteristic decay time that defines persistence time and consequently the persistence length of the motion. The resulting cell motion is a persistent diffusion process, used to describe cells in previous experimental studies.

In the CPM formalism, a new Potts energy term was introduced that enhances the probability of accepting a copy attempt, if it shifts the cell's center of mass in the previous direction of the polarity vector. If the copy is accepted, the polarity vector is incremented by the copy-vector, keeping the polarity vector from relaxing to zero. Here the copy-vector is defined as the vector pointing from the center of the source lattice site to the center of the target lattice site that participate in the copy.

An excellent test for this mechanism was the reproduction of collective cell motions in monolayers (Fig 3a,b). In high density endothelial cell cultures, cells form 3-5 cells wide streams, with neighboring streams often moving in the opposite direction, creating shear lines and vortices. To capture the stream geometry, we calculate the spatial, two-dimensional autocorrelation function of the cell velocities, describing the average flow field around cells.

The patterns reveal correlations at distances of 200-300 um along the streams and 100 um perpendicular to the stream directions. At lower densities streams disappear, indicating an important role for the steric repulsion of cells. Simulations of confluent, actively moving cells reproduce the observed streaming motion (Fig3c). Furthermore, the autocorrelation functions reveal streams remarkably similar to the experimental ones.

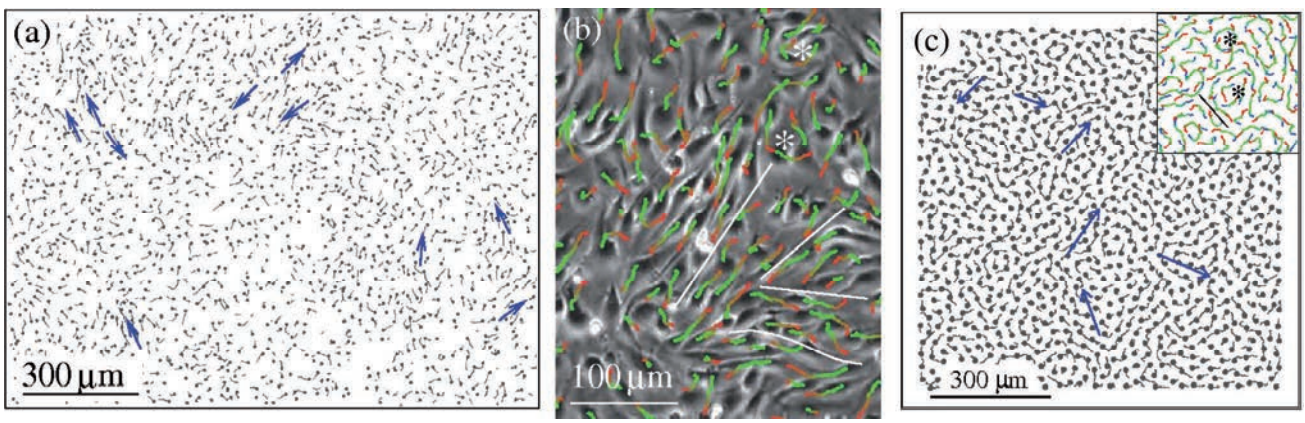

Figure 3: Collective cell streaming within an endothelial monolayer (a,b) and computer simulation (c) is visualized through trajectories. (a): A velocity field snapshot is indicated by short trajectories, obtained during 30 minutes. Cell centers are marked with black dots. Blue arrows show groups of cells moving together in streams. (b): A phase-contrast image detail with superimposed cell trajectories depicting movements during one hour. Red-to-green colors indicate progressively later trajectory segments. Adjacent streams moving in opposite directions are separated by white lines, vortices are denoted by asterisks. (c): Model cell trajectories from a 40 min long time interval reveal streams formed by several cells (blue arrows). The inset shows trajectories from a 90 min long interval.

III. Sprouting

Early vasculogenesis involves sprout formation in quail embryos in vivo, but is also observed in cell cultures. The speed of reported sprout expansions is constant throughout the process. Studies focusing on sprout development distinguish a leader cell in the tip of the sprout. We hypothesized that the main functional difference between leader cells and followers is the long motion persistence of leader cells.

Experimental studies depict sprout extension as the leader cell pulling the passive bulk of follower cells forward through cell-cell adhesions. Cadherin-mediated cell-cell adhesion has been shown to be analogous to surface tension, and has been modeled accordingly in theoretical studies. However, surface tension-stabilized structures are prone to the Plateau-Rayleigh instability: a column of liquid with a circular cross-section should break up into drops if its length exceeds its circumference. Due to this instability a sprout pulled by a leader cell should also break up. Therefore, multicellular sprouting cannot be fully accounted for by the presence of leader cells and cell-cell adhesion alone. While stalk cells may be detached from the matrix, their motion should not be entirely passive: an active cell-guided motility might be present, which invalidates the tissue-fluid analogy and the arguments for the Plateau-Rayleigh instability do not apply.

Our simulations demonstrate that passive follower cells are indeed unable to provide the sufficient supply of cells and thus the sprouts break. However, if follower cells actively adhere to elongated neighbors, the steadily growing sprouts can be stabilized.

***

The mechanisms described in this thesis provide a new model of vasculogenesis: the emerging model successfully reproduces network formation under circumstances that exclude other well-known hypotheses. The formulation of active cell motility describes the experimental observations well in several cell types, on different substrates and varying densities, providing a new, essential feature for future cell-based models. Based on these mechanisms, we provide a model for sprout formation and show that active cell behavior is essential for sustained sprout growth.

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The mathematics of HIV entry and antibody neutralization

In contrast to bacteria, viruses are not able to replicate by themselves. They need a host cell which they manipulate to produce offspring according to the genetic code the virus particles, or virions, provide. But the first step in infecting a cell is entry into the cell. Different viruses evolved different strategies for entry. The Human Immunodeficiency Virus, HIV, has spikes on its surface that consist of three identical envelope proteins. These spikes bind to target cell receptors. Once bound, the spikes undergo a structural change and the viral and cellular membrane fuse. The genetic code can now be inserted into the cell.

The viral spikes bind to specific host cell receptors and are therefore relatively well conserved over different viral strains. Conserved regions are the best targets for neutralizing antibodies. Indeed, the main antibody responses in HIV infected individuals are directed against the viral spikes. However, it is not known how many antibodies have to bind to a specific virion such that it is neutralized. The main part of my thesis deals with inferring this number by studying stoichiometrical parameters. Borrowed from chemistry, the term stoichiometry describes how many molecules or viral subunits are involved in a certain process. Studying the number of antibodies required to neutralize a whole virion can be subdivided into studying (i) how many trimers have to establish contact to target cell receptors for mediating cell entry and (ii) how many envelope proteins of one trimer have to bind to antibodies for loosing functionality. Knowing the number of trimers on the surface of one virion, the number of antibodies neutralizing one single trimer and the number of antibodies neutralizing a whole virion can then be calculated. In my thesis I define and study the following stoichiometries (see also Figure 1):

- *stoichiometry of entry, T:* number of trimers needed to mediate cell entry
- *stoichiometry of (trimer) neutralization, N:* number of envelope proteins that have to bind to antibodies such that the trimer loses its functionality
- *stoichiometry of virion neutralization:* number of antibodies that have to bind to one virion for virion neutralization
- *stoichiometry of population neutralization:* number of antibodies needed to bind to all virions of a virus population for complete neutralization

In the first part of my thesis I study the stoichiometry of entry. To this end, I derive a stochastic model that can be used to analyze *in vitro* infectivity experiments with pseudo-typed virions. HIV virions

express varying trimer numbers on their surfaces. It is experimentally not possible to sort virions according to their trimer numbers.

Therefore, experimentalist generate virions expressing genetically engineered trimers. These trimers consist of wild-type and mutated envelope proteins. One mutated envelope protein makes the whole trimer non-functional. By varying the overall fraction of mutated envelope proteins, one can generate different viral stocks with different amounts of functional trimers. In addition, these viral stocks are genetically manipulated such that they do not produce offspring upon infection of a cell. Instead, virions that successfully entered the cell express a fluorescent reporter gene. The emitted light is a measure for the number of infected cells.

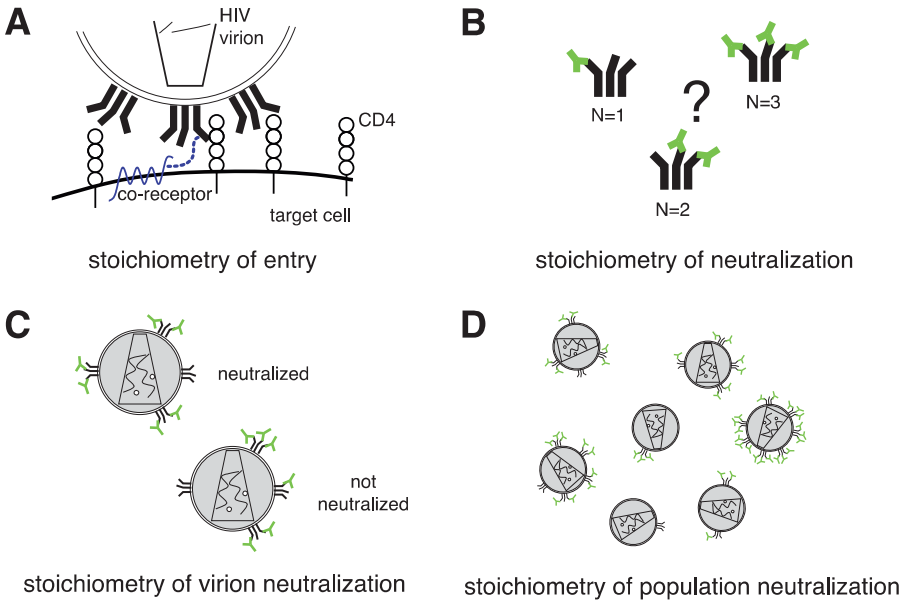

Fig 1. Illustration of the different stoichiometry parameters studied in this thesis. (A) Stoichiometry of entry, T, or how many trimers are needed to mediate call entry. (B) Stoichiometry of neutralization, N, or how many antibodies render a trimer non-functional. For the following, we assume T=2 and N=2. (C) Stoichiometry of virion neutralization, or how many antibodies must bind to a virion, such that it is neutralized. The sketch shows, that the location of antibody binding is important for neutralization (see also Figure 2) (D) Stoichiometry of population neutralization, or how many antibodies must bind to a population such that the whole population is neutralized. The scheme illustrates, that the virions differ in their trimer numbers and the required number of neutralizing antibodies also differs from virion to virion.

Wild-type and mutant envelope proteins form trimers randomly. Therefore, one needs a stochastic model to predict the infectivity of a virus stock as a function of the fraction of mutant envelope proteins. Our model incorporates the random aspect of trimer formation as well as the random number of trimers expressed on the virion surface. In four model extensions, we relax different assumptions on the biological system made on trimer formation, transfecting the cell, spatial requirements and requirements for entry. We re-analyze an existing data set with our models. We find that the estimates for the stoichiometry of entry range from 2 to 19 depending on these biological parameters. Because most of the biological assumptions are not experimentally clarified yet, it is impossible to determine the stoichiometry of entry to date. However, we identify which biological parameters have to be determined before one can reliably estimate the stoichiometry of entry and list experiments that help us to study these assumptions.

In the second part of my thesis I study the stoichiometry of (trimer) neutralization, N. Because the binding location and the binding mechanism of different monoclonal antibodies might differ, one has to determine the stoichiometry of neutralization for every monoclonal antibody separately. The experimental system employed to estimate this parameter is similar to the one used for the study of the stoichiometry of entry. The infectivity of different viral stocks expressing mixtures of wild-type and mutant envelope proteins are tested in infectivity assays. The mutated envelope protein in the assays for estimating the stoichiometry of neutralization, however, does not render a whole trimer non-functional but is resistant to binding of the tested antibody. Before these virions infect cells they are saturated with the monoclonal antibody such that all open binding sites (that are the ones on wild-type envelope proteins) are bound by an antibody. A trimer is only functional when less than N antibodies are bound. I adapt the mathematical models for estimating the stoichiometry of entry to the antibody binding scenario. Besides the stoichiometry of entry, we can now estimate the stoichiometry of (trimer) neutralization out of infectivity data. These two parameters can be estimated simultaneously. However, the uncertainty of the estimate for the stoichiometry of neutralization is smaller when first estimating the stoichiometry of entry according to the estimates in the first part of my thesis and then using these parameters for estimating the stoichiometry of neutralization. We re-analyze an existing data set in which different monoclonal antibodies were tested. While the majority of these antibodies appear to follow a (N=1)-stoichiometry, it is currently not possible to rule out that stoichiometric differences between monoclonal antibodies exist.

The number of spikes needed for cell entry in combination with the number of antibodies rendering one spike non-functional can be used to estimate the number of antibodies needed for virion neutralization. In the third part of my thesis, I describe the difficulties arising due to the stochasticity of antibody binding. With the above defined stoichiometry of entry, T, and the stoichiometry of trimer neutralization, N, a virion with s trimers is neutralized if s-T+1 trimers are each bound to N antibodies. However, the product of antibodies neutralizing one trimer and the number of trimers needed to be neutralized, N(s-T+1), is only a lower bound for the number of antibodies neutralizing the whole virion. If the N(s-T+1) antibodies do not bind to the right epitopes, the virion might still be infectious. Figure 2 shows an example for unproductive antibody binding for the specific case of T=2 and N=2. We model virion neutralization as a restricted occupancy problem. This framework can also be used to calculate the number of antibodies needed to neutralize one virus population and to predict the fraction of neutralized virions by adding a certain amount of antibodies. We show that more antibodies are needed for virion neutralization than suggested by multiplying the number of trimers needed to be neutralized and the number of antibodies neutralizing one trimer. The neutralization of a whole population also requires more antibodies than the product of the number of antibodies neutralizing a virion and the population size. However, I show, that there is an almost linear relation between the stoichiometries of virion and population neutralization.

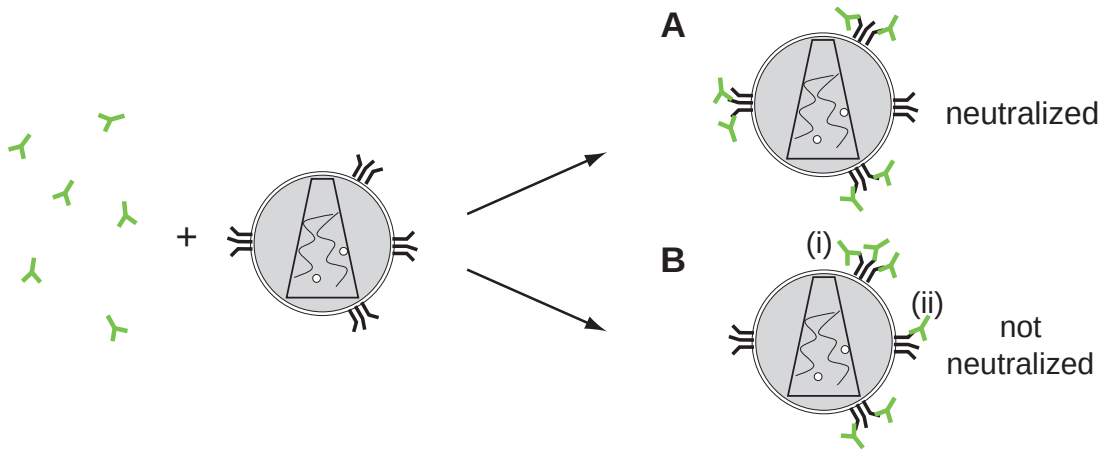

Fig 2. An example of random effects during antibody binding. Six antibodies bind in two different ways to a virion with four trimers. The stoichiometries of entry and neutralization are assumed to be T=2 and N=2 in this example. At least three trimers must be bound by at least two antibodies each. In (A), three different trimers are each bound to two antibodies and the virion is neutralized. In (B), only two trimers are neutralized, because trimer (i) is bound by more than the required number of antibodies and trimer (ii) with less.

Antibodies are only one of several different weapons of the immune system to fight pathogenic invaders. The first barrier is the so-called innate immune system. The cells of this arm begin to attack pathogens as soon as they enter the body. The cells of the innate immune system have to fight a lot of different pathogens and this is the reason why their mechanisms are quite unspecific. If a pathogen has survived the first attack, a more specific answer comes into play, the adaptive immune system: B-cells produce antibodies and cytotoxic T-lymphocytes induce a suicide program in infected cells. But the production of these specific weapons takes some days. Individuals are often confronted more than once with the same pathogen. The immune system has developed a mechanism to react faster in such cases: some specific cells are stored and can be re-activated very quickly. This phenomenon is called immune memory. Indeed, most prophylactic vaccines simulate a natural infection and lead to B-cell memory.
In the fourth part of my thesis, I focus on the evolution of immune memory. The immune system and the immune memory have been developing as a response to a constant exposure to pathogens. We study how memory traits evolve as a response to different pathogen environments to provide the optimal immune system based protection. In an individual-based simulation model, we follow all individuals and challenge each of them with pathogens from a certain pathogen pool. We simulate the evolution of immune memory traits under the selective pressure induced by different pathogen environments, characterized by the virulence and prevalence of the pathogens. We find that even without a cost related to the maintenance of a memory pool, the positive effect of bigger memory pool sizes saturates.
The optimal diversity of a limited memory pool is determined by the probability of re-infection, rather than by the prevalence of a pathogen in the environment, or the frequency of exposure. Relating immune memory traits to the pathogen environment of the hosts, our population biological framework sheds light on the evolutionary determinants of immune memory.

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Comparing stochastic discrete and deterministic continuum models of cell migration

In humans, cell migration is an integral feature of many developmental and homeostatic mechanisms, including embryo formation, wound healing and immune response. In addition, cell migration is critical for the development and progression of pathogeneses such as cancer, vascular disease (e.g. atherosclerosis) and chronic inflammatory diseases (e.g. arthritis). Mathematical modelling is one of the major driving forces behind the systems biology revolution. The inherently interdisciplinary nature of its study and the multiple spatial and temporal scales which characterise its dynamics make cell migration an ideal candidate for a systems biology approach. Due to its ease of analysis and compatibility with the type of data available, phenomenological continuum modelling has long been the default framework adopted by the cell migration modelling community. However, in recent years, with increased computational power, complex, discrete, cell-level models, able to represent increasingly detailed data describing the dynamics of experimental systems, have become more prevalent. These two modelling paradigms have complementary advantages and disadvantages. The challenge now is to combine these two seemingly disparate modelling regimes in order to exploit the benefits offered by each in a comprehensive, multiscale equivalence framework for modelling cell migration.

The main aim of this thesis is, starting with an on-lattice, individual-based model, to derive a continuum, population-based model which is equivalent to it in certain limits. For simple models this is relatively easy to achieve: beginning with a one-dimensional, discrete model of cell migration on a regular lattice we derive a partial differential equation for the evolution of cell density on the same domain. We are also able to simply incorporate various signal sensing dynamics into our fledgling equivalence framework. However, as we begin to incorporate more complex model attributes such as cell proliferation/death, signalling dynamics and domain growth we find that deriving an equivalent continuum model requires some innovative mathematics. The same is true when considering a non-uniform domain discretisation in the one-dimensional model and when determining appropriate domain discretisations in higher dimensions.

Moreover higher-dimensional simulations of individual-based models bring with them their own computational challenges. Increased numbers of lattice sites in order to maintain spatial resolution and increased cell numbers in order to maintain consistent densities lead to dramatic reductions in simulation speeds. We consider a variety of algorithms to increase the efficiency of our simulations and derive novel acceleration techniques which can be applied to general reaction systems but are especially useful for our spatially extended cell migration algorithms.

The incorporation of domain growth in higher dimensions is the final hurdle we clear on our way to constructing a complex discrete-continuum modelling framework capable of representing signal-mediated cell migration on growing (possibly non-standard) domains in multiple dimensions.

Background and Summary

Although great strides have been made in furthering our understanding of the detailed mechanisms of cell migration there are areas which remain impenetrable to experimentalists. As such, in recent years, in part due to the advent of systems biology, increasing emphasis has been placed on a partnership between mathematical modelling and experimental exploration. An early mathematical model of cell migration in response to a signal profile which has been extensively studied over the last 40 years was presented by [1]. This approach leads to a continuous reaction-diffusion model.

Keller-Segel-type models are particularly successful when cell populations are large and can be approximated as a continuum. Inevitably, by making this assumption, the discrete nature of individual cells is lost and, as a result, explicitly linking the model parameters and processes to the behaviour of individual cells is difficult.

Individual-based models, however, treat each cell as a discrete entity which can be endowed with its own rules for movement and response to external signals taken directly from experimental observation. As such, individual-based models present a natural environment in which to incorporate the available experimental data. Individual-level models have also been used successfully, although less ubiquitously than population-level models, to represent cell migration.

Depending on the biological questions of relevance and available experimental data, either the deterministic-continuum or stochastic-discrete models (or both) may be appropriate. The two modelling frameworks have complementary strengths and weaknesses: discrete models are generally intuitive to formulate and, as such, can be more easily related to experimental data, whereas the formulation of continuum models often necessitates phenomenological assumptions. Continuum models for large cell populations can generally be solved quickly and their solutions may be expressed directly in terms of the model parameters, whereas individual-level simulations typically require multiple, slow, computationally intensive (especially so for large numbers of cells) repeats in order to gain insight into the population-level behaviour. Ideally we would combine an individual-level, discrete model and a population-level, continuum model and exploit their complementary advantages. We must be careful, however, when we choose models from the two regimes to describe the same phenomenon, that they agree with each other. Indeed, in some cases it is possible to take individual-based models and derive, from them, continuum models for cell density that accurately capture cell-level detail.

The broad remit of this thesis is to create a comprehensive discrete-continuum modelling framework for cell migration, incorporating a variety of biologically motivated features. In particular we choose the on-lattice position-jump model as our discrete representation of cell migration.

Chapter by chapter outline

Chapter 1 is given over to outlining the background and challenges of building discrete-continuum equivalence frameworks and introducing the thesis content.

In Chapter 2 we begin by replicating and generalising some of the results of [2] for cells moving in response to a fixed signalling profile sensed via a variety of different mechanisms. Into this basic, discrete-continuum equivalence framework we are able to incorporate time-varying signal profiles, cell proliferation and death, and density-dependent cell migration. In the second part of Chapter 2 we extend this framework by introducing a simple method for domain growth in a discrete setting. We are able to demonstrate the equivalence of this discrete model of cell migration on a growing domain and a continuum counterpart. The `interval-splitting' domain growth method we incorporate is sufficiently versatile for us to induce linear, logistic or even density-dependent domain growth in the discrete model and still find a continuum equivalent [3]. When an interval is chosen to grow it instantaneously doubles in size and divides into two daughter intervals. The cells that were initially positioned in the parent interval are divided up evenly (on average) between the daughter intervals. All intervals (and associated cells) to the right of the dividing interval are moved one interval length to the right. Our findings are corroborated with numerical simulations and comparisons of the discrete and continuum models (See Fig. 1).

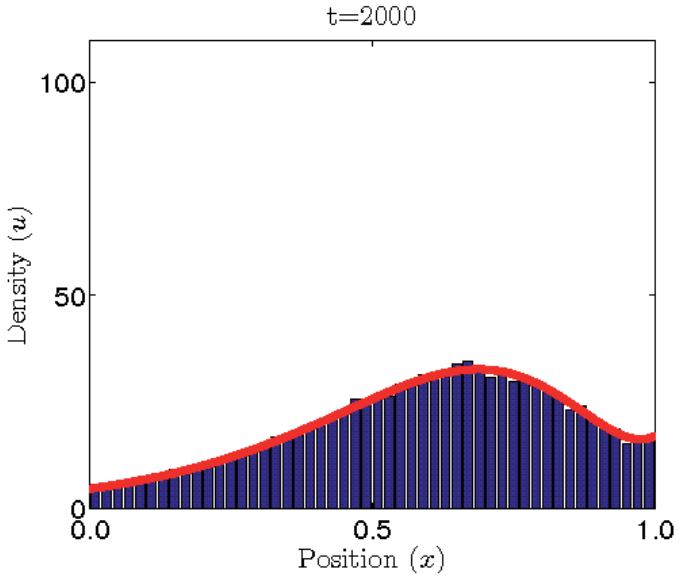

Figure 1. Snapshot of cells moving in response to a locally sensed signal profile. The histograms represent an average of 40 realisations of the stochastic system. The red curves represent the solution of corresponding PDE.

Although this initial method for incorporating domain growth is versatile and robust we struggle to justify it biologically due to its overtly discrete nature. In Chapter 3 we establish a method of domain growth which can, by tuning a parameter, be made arbitrarily similar to a continuum approach, whilst maintaining its discrete nature. Domain intervals are allowed to grow incrementally and independently. As a result, the lattice upon which the cells move is allowed to become non-uniform. This causes us to consider more carefully the appropriate transition rates between intervals of different sizes and precisely what we mean by `cell density' in the discrete version of the model. We do this initially for the non-growing domain, considering the incorporation of domain growth only when the correct transition rates have been determined. The non-uniform domain partition also engenders two different domain division

paradigms, both of which we investigate when we reincorporate domain growth. Through a novel consideration of the probability master equation we are able to demonstrate the equivalence of our revised, discrete domain growth model and a continuum counterpart [4]. We again corroborate our findings using numerical simulations and appropriate qualitative and quantitative comparisons (See Fig. 2).

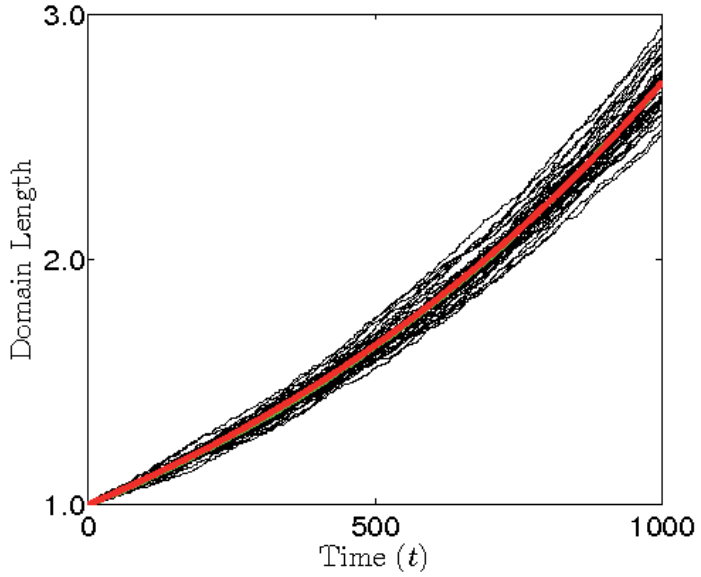

Figure 2. Evolution of the average stochastic domain length plotted in green (along with the evolution of the domain length of each individual realisation in balck) with the deterministic PDE domain length overlaid in red. Due to the close correspondence between the individual-based model and the PDE, the green curve lies almost exactly underneath the red curve and can hardly be seen.

As we add functionality to our discrete models and consider venturing into higher dimensions, the computational complexity of simulating these models increases. With this in mind, in Chapter 4, we review several methods of increasing the efficiency (and hence the speed) of the stochastic simulations of the individual-based models. However, the increased complexity of higher dimensional simulations may necessitate the sacrifice of statistical accuracy in order to restore reasonable simulation times. One way to achieve this goal is to use accelerated stochastic simulation algorithms. We review the current state-of-the-art method which produces accelerated simulations whilst avoiding negative species populations [5]. We note, however, that the method of avoiding negative species populations is of less than optimal efficiency. We therefore introduce a confidence-based method which serves (as we demonstrate through numerical comparisons) to accelerate the majority of simulations (i.e. for general reaction systems) in comparison to the previous method, whilst continuing to avoid negative species populations [6]. The acceleration is especially evident in our discrete simulations of cell migration.

Moving into higher dimensions our equivalence framework is presented with a number of additional hurdles to clear. In Chapter 5 we demonstrate that the continuum model we derive is independent of the method used to discretise a two-dimensional domain. We also demonstrate that it is possible to compare the discrete and continuum models on non-square domain geometries. The majority of the chapter, however, is dedicated to implementing domain growth in two dimensions. By considering cluster aggregation theory we review a series of models with the potential for producing a radially growing domain through interval division. After rigorous investigation we eventually determine that no such model exists in the literature and are forced to invent our own. We demonstrate that our model produces isotropically growing domains via cell division and is therefore suitable as an underlying representation

of domain growth. We complete this chapter by demonstrating excellent agreement between the densities of our discrete and continuum models on a radially growing domain (See Figs. 3, 4.).

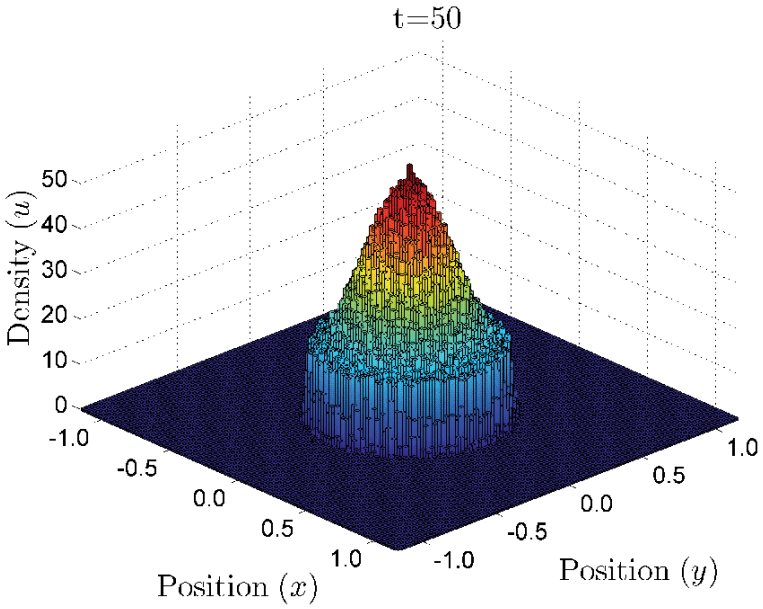

Figure 3. A comparison of the individual-level (with square domain tessellation) and population-level models of diffusion on a growing circular domain. The histograms represent the density of cells in each square of the domain tessellation.

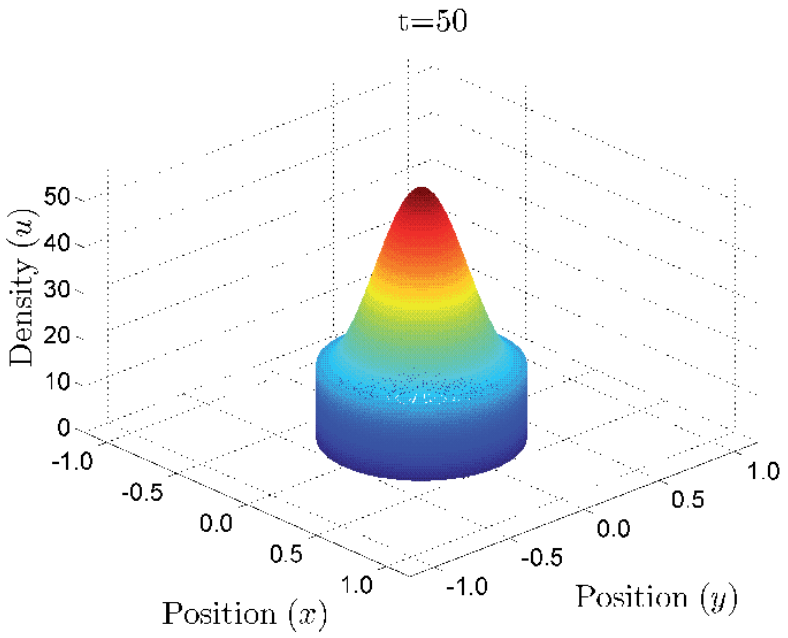

Figure 4. The surface represents the radially symmetric solution of the diffusion equation on a radially growing domain.

Conclusions and outlook

The central theme that runs through this thesis is connecting individual and population-based modelling regimes in what we have called an `equivalence framework'. Beginning with an individual-level description of the specific phenomenon we are trying to model we are able to determine a continuum equivalent which will replicate the population-level characteristic of the model in the appropriate limits. We have been able to incorporate proliferation and death, the response of cells to signalling molecules, density dependent migration and domain growth into our basic equivalence framework. In addition we have refined our method of domain growth by incorporating individual-based models on non-uniform domains and we have been able to establish the equivalence framework in both stationary and growing domains in higher dimensions.

In the future we intend to explore how our modelling framework may be used to investigate the interplay between the microscopic and macroscopic aspects of a variety of biological systems. We are currently parameterising our model in collaboration with experimentalists in order to begin to answer questions which are out of reach of current experimental techniques.

Acknowledgements

This thesis was written under the supervision of Professor Philip Maini, Dr Ruth Baker and Dr Radek Erban and with the assistance of Professor Kevin Burrage all of the University of Oxford.

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Centenary of the birth of Alan Turing

The year 2012 marks the centenary of the birth of Alan M. Turing, one of the fathers of the modern computer, a key figure in the decryption of the secret codes of the Nazis in the second world war, and a contributor of key ideas to many areas of modern science, in particular the mathematical theory of pattern formation.

In addition to the central contributions to so many research fields, Turing became iconic not least due to the tragic events surrounding his suicide; the public apology of prime minister Gordon Brown on 10 September 2009 for the ``utterly unfair treatment'' created a general public interest in Turing as a person that went well beyond those who normally deal with models of computation, encryption algorithms, artificial intelligence, and the mathematical theory of pattern formation in nature.

Events

Pattern Formation: The inspiration of Alan Turing. A satellite workshop of the Isaac Newton Institute for Mathematical Sciences St. John's College, Oxford 14-16 March 2012.

To celebrate the centenary of Alan Turing's birth, the Isaac Newton Institute for Mathematical Sciences in Cambridge, U.K., has a six-month research programme entitled ``Semantics & Syntax'' (SAS) which covers computability theory, complexity theory and cryptography. Since these areas are only part of Turing's research interests, the organizers of SAS decided to hold a satellite workshop on pattern formation in Oxford, organized by Bernold Fiedler (Berlin), Benedikt Lowe (Amsterdam & Hamburg) and Philip Maini (Oxford). The workshop was funded by the Isaacn Newton Institute for Mathematical Sciences.

This workshop aimed to show how mathematical modelling of pattern formation has led to (i) significant advances in the understanding of certain aspects of biology and chemistry, (ii) new mathematical and computational challenges. It brought together researchers ranging from those who do experiments to demonstrate pattern formation, to those who develop mathematical and computational techniques to analyse proposed models. This rapprochement of the empirical and the mathematical formed the recurring theme of the workshop and was reflected in the discussions and talks.

Invited keynote talks were given by Markus Bär (Berlin), Markus Dahlem (Berlin), Patrick De Kepper (Bordeaux), Irv Epstein (Waltham MA), Alan Garfinkel (Los Angeles CA), Frank Jülicher (Dresden), Shigeru Kondo (Nagoya), Masayasu Mimura (Kanazawa), Yasumasa Nishiura, (Tohoku), Hans Othmer (Minneapolis MN), Kevin Painter (Edinburgh), Arnd Scheel (Minneapolis MN), Jonathan Sherratt (Edinburgh), and Angela Stevens (Munster). More information can be found at

http://www.newton.ac.uk/programmes/SAS/sasw08.html

Thematic school:

Present challenges of mathematics in oncology and biology of cancer: modeling and mathematical analysis

19th to the 23rd march of 2012, CIRM, Marseille.
http ://www.latp.univ-mrs.fr/mcc/

The conference took place at the CIRM in Marseilles from march 19th to 23rd, 2012. The scientific committee was composed of D. Barbolosi (Aix-Marseille University, CRO2), J. Clairambault (INRIA Rocquencourt, Paris), T. Colin (INRIA futur, Bordeaux), C. Falcoz (PHARSIGHT), N. Andre (AP-HM, Aix-Marseille University) and N. Bellomo (Polytecnico, Torino) while the organizing committee consisted of Assia Benabdallah (Aix-Marseille University, LATP), Sebastien Benzekry (Aix-Marseille University, LATP), Guillemette Chapuisat (Aix-Marseille University, LATP), Yves Dermenjian (Aix-Marseille University, LATP), Manuel Gonzalez-Burgos (Universidad de Sevilla, Spain) and Florence Hubert (Aix-Marseille University, LATP). This meeting was supported by ANR (Grant ANR-09-BLAN-0217-01 “MEMOREX-PK"), CNRS, CIRM, Canceropole PACA, city of Marseilles, CG13 and Aix-Marseille University.

Scientific program

This thematic school was in the area of mathematical oncology which has shown very promising results in the last decades thanks to modeling and mathematical analysis. This meeting wished to be part of this process. This school was following the previous school “Present challenges of mathematics in oncology and biology of cancer" which happened in February 2009. The idea of these events was to bring together specialists and young researchers coming from different cultures about modeling, numerical simulations andmathematical analysis in oncology, as well as to suggest news topics. This school was attended by more than 80 participants, including more than a third of young researchers, coming from various countries around the world (more that 12 different countries).

Organisation

The school was divided into 8 thematic sessions of half day each. Each session started with a 1h30 lecture from a known expert of the domain and was followed by 3 research talks of 30 minutes each. One afternoon was devoted to "Medical challenges in oncology”. The 8 sessions were:

“Structured population dynamics". Mini-course by B. Perthame (Paris).
“Cancer modeling : Phenomenological aspects". Mini-course by A.d'Onofrio (Milano).
“Cancer modeling : Imaging". Mini-Course by O. Saut (Bordeaux).
“Cancer modeling : Mechanistic aspects". Mini-course by H.M. Byrne (Nottingham).
“Tumour patterns". Mini-course by D. Bennequin (Paris).
“Inverse problems and cancer". Mini-course by J.P. Zubelli (Rio).
“Pharmacokinetics". Mini-course by J. Ciccolini (Marseilles).
“Cancer modeling : Therapies". Mini-course by M. Edgerton (Houston).

A poster session was organized on Monday evening with a competition. The two winners were Alice Erlinger (University de Nice Sophia-Antipolis) and Tommaso Lorenzi (Polytecnico, Torino). They were awarded with scientific books.

Conclusions

The satisfaction survey at the end of the conference showed that the participants werereally satisfied by the atmosphere as well as by the scientific content. We warmly thank the lecturers for the pedagogical effort they made to make their talks accessible to this large audience. The participant appreciated the multidisciplinary of this school and enjoyed particularly the session with medical doctors and the round table that followed. The aim of the round table was to share experiences on multidisciplinarity in mathematical oncology. The main conclusions were the following:
- Importance of the geographical proximity of the different laboratories implicated in the collaboration.
- Importance to start as soon as possible the multidisciplinarity formation.
- Importance to increase the possible academic positions available after a multidisciplinarity formation.

Thematic school:

Numerical Experiments and Hybrid Systems as Efficient Alternatives to Understand Living Sytems

The end of PDE's reign ? With this underlying question, the SFBT (Société Francophone de Biologie Théorique) *i.e.* the French Speaking Society of Theoretical Biology, resumed its teaching activity 14 years after the last school was held in its historical hosting place of Saint Flour in the heart of France.

The theme for this first school of the 21st century concerned "Numerical Experiments and Hybrid Systems as Efficient Alternatives to Understand Living Sytems" (1) based on the increased awareness that computational (*i.e.* discrete (2)) approaches have progressively invaded the landscape of theoretical biology other the past decade.

There is no denying that theoretical biology cannot be restricted anymore to a "pure" mathematical approach (*i.e.* based on continuous equations (3)). The computational approach, although well known for years, with for example Conway's famous game of life, remained restrained due to the limited computing capability of the machines. The increased speed of the processors has since unleashed the potential of computational models. However, the risk to fall into facility is big; it is easier to define rules than to derive and solve complex systems of ODEs or PDEs. There is also the risk of losing control since the ability to predict the behaviour and the outcome of a simulation is lost with the use of automata. This led to the concept of « numerical experimentation » as the only mean to explore the properties of the virtual object. The actual trend is towards hybrid modelling where PDEs and discrete approaches, in other words mathematical and computational approaches are coupled depending on the problem at hand. Hybrid is now a generic and widely used term to designate these new approaches. Hybrid models proved very useful to handle multiscale processes in particular.

The all aim of the school was to present to a young audience (mainly PhD students) such new discrete or hybrid approaches. For one week, from the 4th to the 10th of last June, 19 academics from french research institutions (CNRS, CEA and Universities) but also from Canada (University of Manitoba) and USA (Albuquerque and Yale Universities) were invited to lecture upon this theme by presenting alternative approaches or ideas, that they contributed to develop and promote. This was done in a didactic way with concrete examples which spanned a variety of fields including enzymology, embryology, physiology, cancer, cell migration, cytoskeleton dynamics, animal behaviour and ecosystems.

The school was opened to all with an interest in these new alternative approaches and willing to explore their potential and discuss their limitations. The school was a success with more than 40 registered participants among which 20 students.

Thanks to the support from the CNRS, but also from IXXI (Rhône-Alpes Institute of Complex Systems) and Joseph Fourier University, 6 foreign students from Maghreb countries could be supported to come to participate to the school and 3 more students got support from their host universities. Thanks to the partnership with universities, the courses could be integrated in the student formation scheme to award ECTS.

Beyond the number of participants, we could measure the success of the event by the convivial atmosphere that develop over the days. The peculiarity of the place, an old seminary of the 17th century protected by the ramparts of the medieval city of Saint Flour, certainly helped in building up the proximity between the participants. Perhaps the magma of ideas that emerged from passionate discussions could also be related to the volcanic nature of the place, with the biggest volcano of Europe sleeping right under our feet. Those discussions were for most pursued until very late in "round tables" in the local pub "The Viking"(4). New collaborations are certainly born in this pub and the promise to renew the event was sealed in the vapours of single malts. This added to the unusually cold and damp weather for this month of June, almost made us believed that we were in Scotland ...

With the organization of this school, we opened up more widely the doors of the SFBT to a new community, this of computer scientists. We hope to pursue this effort of bringing together scientists from various horizons. Our main target will be experimental biologists who still feel excluded mostly by the barrier of the mathematical language. The involvement of computing which uses a more accessible language would help to fill the gap between the disciplines.

Stimulated by the success of the event and the demand of the participants to pursue what we just started, we already planned to renew the school on a regular bi-annual basis. We hope to restore the prestige it had for many years before it abruptly stopped. The rendez-vous is given in Saint Flour for the Spring School 2014 on a still unknown but definitely new theme !

Angélique Stéphanou and Nicolas Glade
Organizers of SFBT Spring School 2012

(1) http://sfbt-2012.imag.fr/
(2), (3) These are short cuts for the sake of simplicity. The relationships between computational and mathematical approaches are far more complex and their definitions as well ...
(4) Apparently the unreachable fortress was taken at least once although we did not check the history ...

FUTURE EVENTS: BIOMATH TRIMESTER, LYON, 2013

Thematic program Mathematical Biology, Lyon, March-June, 2013. A thematic program will be held in Lyon, from March 4 to June 14, 2013, at Ecole Normale Supérieure de Lyon and Université Claude Bernard. The main topics to be addressed in this program are: cell biology, population dynamics, quantitative modelling for drug development, systems biology, and evolutionary biology.

The tentative schedule is as follows:

- Workshop "Biological invasions and evolutionary biology, stochastic and deterministic models", March 11-15, 2013
- Workshop "Cell biology", March 25-29, 2013
- Workshop "Quantitative modelling for drug development", April 11-12, 2013
- Summer school “Multiscale models in the life sciences”, Lyon, May 27-31, 2013. A summer school will be dedicated to recent progresses in multi-scale modelling, with applications in the life sciences. Grants will be available for PhD students.
- Conference in honour of Michael Mackey' 70th birthday, June 3-7, 2013

This program is funded by the “Laboratoire d'excellence” MILYON, an initiative from the French ministry of research.

Organizing committee: M. Adimy (INRIA), J. Bérard (UCBL), S. Bernard (CNRS, UCBL) H. Berry (INRIA), V. Calvez (CNRS, ENS de Lyon), F. Crauste (CNRS, UCBL), O. Gandrillon (CNRS, UCBL), E. Grenier (ENS de Lyon), Th. Lepoutre (INRIA), L. Pujo-Menjouet (UCBL), G. Raoul (CNRS, CEFE), B. Ribba (INRIA), V. Volpert (CNRS, UCBL), B. You (CHU Lyon).

Website: http://mathbio2013.sciencesconf.org/

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Reinhart-Heinrich Doctoral Thesis Award

ESMTB announces the annual Reinhart Heinrich Doctoral Thesis Award to be presented to the student submitting the best doctoral thesis within the current year 2012 in any area of Mathematical and Theoretical Biology.

Professor Reinhart Heinrich (1946 – 2006) started his research career in theoretical physics and then moved into biochemistry, becoming a full professor and head of theoretical biophysics at the Humboldt University, Berlin in 1990. He is considered a father of the field that is now named Systems Biology, since he investigated various topics such as modelling metabolic networks and metabolic control theory, modelling 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 that underlie observations, looking for different perspectives and connecting theoretical 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 decided to offer a Doctoral Thesis Award annually to commemorate Reinhart Heinrich and his legacy in mathematical and theoretical biology.

Prize Awarding Committee:

Carlos Braumann
Andreas Deutsch
Philip Maini
David Rand
Stefan Schuster (former assistant to Reinhart Heinrich)

Award

A summary of the thesis receiving the award will be published as the lead article in the 2013 issue of the European Communications in Mathematical and Theoretical Biology. The *award* includes*:*

- *an invitation to present a lecture at the forthcoming triennial ESMTB Conference (Gothenburg 2014) or, alternatively, a limited travel grant by ESMTB for a scientific visit of the recipient's own choice,*
- *1 year's free membership of ESMTB.*
- *A voucher for Springer books*

Application

Potential applicants may be nominated by any ESMTB member. To nominate a person for the Reinhart Heinrich Doctoral Thesis Award, the following information should be submitted to Andreas Deutsch (andreas.deutsch@tu-dresden.de):

1. Name, address, phone number, affiliation, and email address of the nominator.
2. Name, address, phone number, affiliation, and email address of the nominee.
3. A detailed statement describing why the nominee should be considered for the award.
4. An extended summary of the thesis (ca. 2-5 pages plus eventual pictures).
5. A CV of the nominee in some form.

Closing date for nominations is *30th November 2012*, by which time the thesis should have received final acceptance by the institution granting the doctoral degree.
Shortlisted applicants will be asked to send their full thesis.

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The picture on the front cover is taken from the dissertation of Stefan Hoehme.