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ESMTB European Society for Mathematical and Theoretical Biology

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Letter from the President

Dear colleagues and members of the ESMTB,

In her classic *Making Sense of Life*, E.F. Keller beautifully describes the cultural divide between biologists using experimental approaches and those who use mathematical and computational approaches. Asking how the zebrafish got its stripes, each biologist comes up with a radically different answer

A stereotypical experimentalist constructs knock-out phenotypes, obtains transcriptomics and proteomics datasets of striped and spotted fish, performs confocal microscopy, and so forth. He measures, measures, and measures again, and then constructs a narrative to connect his measurements without actually understanding how the system fits together.

The stereotypical mathematician takes a very different approach. She assumes a spherical fish and solves a set of equations sufficient to produce striped patterns. Then she picks out a few basic experimental facts and uses these as inspiration to simplify the equations to sufficient simplicity for proving existence and uniqueness of a solution.

The stereotypical computer scientist yet finds a third way of tackling the same problem. He constructs data structures and ontologies to describe the measurements. He develops data visualisation methods and large interactive touch screens in the computer science department to help the experimentalist who never gets to see it. Then each field publishes independently and rarely do they meet one another.

Fortunately things have changed. We can now safely take these crude generalisations for what they really are: stereotypes. All the approaches mentioned above are the area of active research, and of course for excellent reason: they are necessary groundwork. But, since roughly the last twenty-five years, experimental, computational and mathematical biologists have also been joining forces to analyse biological problems in an unprecedented way. It has led to numerous surprising insights into fields as diverse as taxonomy, biodiversity, development, behaviour, and gene regulation. Theories originally developed in the context of population dynamics and evolution have now brought new insights into fields traditionally considered the exclusive domain of molecular and cell biologists; think of immunology, viral evolution, tumour plasticity, antibiotic resistance and the dynamics of bacterial consortia.

Promoting such theoretical approaches and mathematical tools in biology and medicine has been the goal of the ESMTB since its founding in 1991, and it will continue to be the motivation for the new board of the period 2015-2017. It officially started at the ESMTB board meeting on 21st February 2015 in Vienna, Austria. I am sure to speak on behalf of the whole board by cordially thanking the five leaving board members for all their enthusiasm and great efforts over the last six years: our former president Andrea Pugliese, Miguel Herrero, Peter Jagers and Daphne Manoussaki. A special *thank you* is for our former treasurer Andreas Deutsch, who has served our society for the past twelve (!) years. Apart from the usual, financial tasks of the treasurer, Andreas kept our website http://esmtb.org running, administered our members, sent out payment reminders, made sure the flyers and *ESMTB Communications* were printed, and so forth.

A number of beautiful examples of the theoretical approaches that ESMTB will continue to promote were found among the applications for this year's Reinhart Heinrich thesis award for best PhD thesis. The two winners were Aurélie Carlier of Leuven University, Belgium and Juan Carlos López Alfonso of the Universidad Complutense de Madrid, Spain. Dr. Carlier has performed beautiful modelling work on the growth of new capillaries during

bone healing, while Dr. López Alfonso develop modelling and simulation approaches to optimize radiotherapy treatment against tumours. The research conducted for both theses has direct clinical relevance and was conducted in collaboration with experimentalists, as can be read in the thesis summaries from p. 16 onwards. As part of the award, the two winners will be invited to present a plenary talk at the next ECMTB conference.

This brings me to the ECMTB 2014 conference in Göteborg, Sweden, organised by the chair Torbjörn Lundh and his many colleagues of Chalmers University, the scientific committee, and so many other colleagues. I take this opportunity to cordially thank them for the enormous amount of work they did to make this conference a great success, as can be read in the report from p. 28, In the meantime, the organising team chaired by Markus Owen is busy preparing the 10th ECMTB conference, jointly with the Society for Mathematical Biology. ECMTB/SMB 2016 will be held from July 11th to July 15th, 2016 at the University Park Campus of Nottingham, UK. More information can be obtained at the conference website: http://www.ecmtb2016.org.

Other activities of ESMTB include the annual summer schools that we organize together with the European Mathematical Society, of which we are a member organization. The 2014 EMS-ESMTB Summer School was organized in August at the Linnasmäki Congress Centre in Turku, Finland on the *Dynamics of infectious diseases*. It was a great success, as you can conclude while reading the report starting on page 32. The 2015 edition of the summer school has been postponed, so there will be two summer schools in 2016. We are now in full preparation for the EMS-ESMTB school *Mathematical Modeling of Tissue Mechanics* that will be held from 25 to 29 July 2016 at the Lorentz Center in Leiden, The Netherlands, and a second school will be organized in Turku, Finland, also in 2016.

Apart from traditional communication channels, such as this edition of the *ESMTB Communications*, we are experimenting with Twitter and Facebook. As of the time of this writing, we have 271 followers of @ESMTBio and 108 likes of the more recent www.facebook.com/ESMTB. The channels are used to distribute job advertisements, conference announcements, interesting papers and trivia related to mathematical biology, so please *follow* @ESMTBio and *like* ESMTB. As a member of ESMTB I am sure you like us anyway, so why not express it by clicking on the infamous thumbs-up symbol? I hope you will use these electronic and paper communication channels to invite your colleagues to join the Society, and that we may occasionally use them to remind you to renew your membership for 2015. Beyond the practical advantages to members (free access to *Journal of Mathematical Biology*, discounts on Springer books, travel support for young researchers), we believe that ESMTB has a role in promoting exchanges of ideas, in forging collaborations at all levels, and in giving visibility to new research paths.

I look forward to meeting you at ECMTB 2016 in Nottingham, on Twitter (@ESMTBio) or on Facebook (ESMTB).

Roeland Merks
(@roeland_merks)

Minutes of the ESMTB Board meeting

Gothenburg, Sweden
15 June 2014

Meeting starts at 19.30

Present: Barbara Boldin (BB; Minutes), Reinhard Bürger (RB), Andreas Deutsch (AD), Peter Jagers (PJ), Torbjörn Lundh (TL; Organizer of ECMTB 2014), Roeland Merks (RM), Andrea Pugliese (AP), Ryszard Rudnicki (RR), Vitaly Volpert (VV)
Absent: Miguel Herrero (MH), Daphne Manoussaki (DM)

1. ECMTB 2014

The 9th European Conference on Mathematical and Theoretical Biology is well underway. The Board thanks PJ and TL for organization of the event. TL informs the Board that the conference has 600 registered participants. Springer offers an award of 1000 € for the best talk of the conference and an award of 500 € for the best poster presented during the conference. It is agreed that the Board alone will decide upon the winner of the best poster award, whereas all participants of the conference can vote for the best talk.

2. General Assembly during ECMTB 2014

The General Assembly of ESMTB will take place on Tuesday, 17 June 2014 at 17.00. One of the topics of the General Assembly is the forthcoming elections for the Board of ESMTB. At the end of 2014, five Board members (AD, MH, PJ, DM and AP) end their term on the Board of ESMTB. The others (BB, RB, RM, RR and VV) remain on the Board for additional three years.
In the autumn of 2014, electronic elections via ESMTB website will decide five new members that will join the Board of ESMTB for the period 2015-2020. The current Board has suggested some potential candidates and the following have accepted the Board's invitation and will run as candidates in the coming elections:

- Andrea De Gaetano (National Council of Research of Italy (CNR), Rome)
- Susanne Ditlevsen (University of Copenhagen, Denmark)
- Patsy Haccou (Leiden University College, the Hague, Netherlands)
- Frank Hilker (University of Osnabrück, Germany)
- Torbjörn Lundh (Chalmers and University of Gothenburg, Sweden)
- Anna Marciniak-Czochra (University of Heidelberg, Germany)
- Géza Meszéna (Eötvös University, Budapest, Hungary)
- Sergei Petrovskii (University of Leicester, UK)

During the General Assembly, some of these candidates will present themselves. For those who cannot be present, their written statements will be read out to introduce them to the audience and to present their planned contributions to the Society.
It is suggested that, in addition to the candidates proposed by the Board, ESMTB members can nominate themselves or other willing colleagues to run for the Board. Such proposals should be sent to AP by 11 July 2014. The electronic elections are planned for September 2014.

3. ECMTB 2016

ECMTB 2016 will take place between 11 June – 15 June 2016 at the University Campus of the University of Nottingham, UK. Markus Owen is the main organizer of the event.
For the first time in ECMTB history, the conference will take place only two years after the previous event. The Board members discuss whether ECMTB will thereafter adopt a two year gap, or return to triennial events. No final decision is made.

4. Report of the Treasurer

The end of 2014 brings with it the end of AD's very active and successful twelve year term on the Board of ESMTB. AD begins his final report by handing out printed reports and by reviewing the financial state of the Society:

- *Membership development:* data on ESMTB membership in the years 2003-2014 is presented. The number of memberships peaked in 2005 (in the year of ECMTB 2005 in Dresden). Despite the ECMTB in Krakow, the number of memberships decreased in 2011, the numbers are even lower in 2012 and 2013. Up until the start of ECMTB in Gothenburg, ESMTB had 111 paying members in 2014. Some more payments are expected until the end of 2014. AD adds that a positive effect on ESMTB memberships is observed from flyer distribution. The next reminder will be sent out in August or September 2014, before the elections for the new Board of ESMTB. AD presents 2014 membership data categorized by members' country of affiliation, membership type and payment categories. Membership fees remain the same as in the previous year and can be paid by bank draft transfer or by PayPal.
- *ESMTB Support:* in 2013, four requests for funding were received. The request to support MPDE in Osnabrück in August 2013 was later withdrawn. Three workshops (Mathways into cancer, Carmona, May 2013; Forum Biomath, Sofia, June 2013; Fourth Conference on Computational and Mathematical Population Dynamics, Taiyuan, May 2013) were financially supported by ESMTB, each with a contribution of 1000 €. In 2014, no requests have been received.
- *ESMTB Travel support:* in 2013, three applications were received for a travel support. Each was granted 500 € of support. Up until ECMTB 2014, twelve requests for travel support have been received in 2014.
- *ESMTB Account and audits:* auditors Carlos Braumann and András Czirók have reviewed and approved the Society's financial data for 2012 and 2013. AD presents Society's expenditures and revenues in 2013.

AD's successor will be elected among Board members during the first meeting of the newly formed Board at the start of 2015. All present Board members express their strong support of the candidate Frank Hilker (FH; University of Osnabrück, Germany), who has shown will and enthusiasm in taking over as Society's treasurer if elected to the Board. AD once again expresses his belief in FH to provide a smooth transition of duties and in serving the Society well as its treasurer.

5. Communication/Information/Promotion

In addition to being the Society's treasurer, AD has been very active in promoting the Society by taking care of ESMTB website and in disseminating information via flyers and ESMTB Infoletter. It is agreed that BB will take over ESMTB Infoletter in 2015. Either BB or RM will take over as caretakers of ESMTB website.
All Board members thank AD for his hard work on the Board of ESMTB and his many valuable contributions to the Society

6. ESMTB Communications

The 2014 issue of ESMTB Communications was finished, printed and disseminated in time for ECMTB in Gothenburg, largely thanks to the efforts of VV. The Board members thank VV for his hard work. Several issues of the Communications were distributed also during the conference in Gothenburg.
The printing and dissemination of ESMTB Communications has been done by AD in Dresden. With the election of the new Board, a new solution will have to be found for printing and distribution of the Communications. All Board members would will continue their work on the Board after 2014 agree to check the costs in their home countries. Depending on the costs, the final decision about future ESMTB Communications production will be made later.

7. Reinhart Heinrich award

The Reinhart Heinrich award annually honours the best PhD thesis in the field of mathematical and theoretical biology. The awarding committee currently consists of Nico Beerenwinkel, Carlos Braumman, Andreas Deutsch, Philip Maini and Stefan Schuster. AD reports that eleven applications were received by the committee in 2013. ECMTB 2014 will host RH award winners of 2011 (Stefan Höhme; University of Leipzig) and 2012 (Christoforos Hadjichrysanthou; City University London), who will present their award winning theses in an invited lecture.

AD informs the Board that he is willing to continue for one more year as head of the RH awarding committee.

8. EMS – ESMTB Summer schools

The 2014 EMS-ESMTB Summer School will take place between the 17 August and 24 August 2014 at the Linnasmäki Congress Centre in Turku, Finland. The focus of the school will be the *Dynamics of infectious diseases.*
Some suggestions are made for the EMS-ESMTB Summer School in 2015. RM volunteers to explore possibilities to organize the 2015 summer school at the Lorentz Center in Leiden, The Netherlands. A suggested topic for the summer school is tissue modelling.
In a meeting of AP with Jose Carrillo, the Chair of the Applied Mathematics Committee of the EMS, EMS has expressed a wish to organizing some more common activities. In particular, it is suggested that a 2-3 week workshop might be organized in the near future to promote mathematical biology among mathematicians. Some ideas are discussed for a possible venue for such an event.

The meeting ends at 21.30 with a thank you to all of the present outgoing Board members (AD, PJ and AP) for their hard work on the Board of ESMTB and their many contributions to the Society.

Barbara Boldin
Secretary of ESMTB

Minutes of the GENERAL ASSEMBLY OF ESMTB
17 June 2014
Assembly starts at 17.10
ESMTB president Andrea Pugliese welcomes the Assembly. Present are ESMTB Board members except Miguel Herrero and Daphne Manoussaki, ECMTB 2014 organizer Torbjörn Lundh, Rueben O'Dea (representative of the organizing committee of ECMTB 2016) and roughly 30 interested conference participants.

1. Report by the President

Andrea Pugliese (AP, ESMTB President) thanks the organizers of ECMTB 2014 for an interesting and successful conference. The conference hosts 600 registered participants.
AP summarizes some activities of the Society:

- ESMTB website www.esmtb.org is maintained by Andreas Deutsch, the Society's treasurer
- ESMTB Infoletter is sent out monthly to all ESMTB members
- ESMTB Communications are edited by Vitaly Volpert are published annually

One of the main activites of ESMTB is support and organization of summer schools. The joint EMS-ESMTB 2013 summer school took place in Lyon (see Communications 2013), the 2014 EMS-ESMTB summer school is The Helsinki Summer School on Mathematical Ecology and Evolution: Dynamics of Infectious Diseases (see http://mathstat.helsinki.fi/research/biomath/summerschool2014/).

2. Report by the Treasuer

Andreas Deutsch (AD, ESMTB Treasurer) will end his twelve year term on the Board of ESMTB at the end of 2014. AD presents his final report to the Assembly:

- *Membership development:* data on ESMTB membership in the years 2003-2014 is presented. The number of memberships peaked in 2005 (in the year of ECMTB 2005 in Dresden). Up until the start of ECMTB in Gothenburg, ESMTB had 111 paying members in 2014. Some more payments are expected until the end of 2014. AD adds that a positive effect on ESMTB memberships is observed from flyer distribution. The next payment reminder will be sent out in August or September 2014, before the elections for the new Board of ESMTB. AD presents 2014 membership data categorized by members' country of affiliation, membership type and payment categories. A novel category is 'life membership'. Membership fees remain the same as in the previous year and can be paid by bank draft transfer or by PayPal. Payments by bank transfer are encouraged.
- *ESMTB Support:* in 2013, four requests for funding were received. The request to support MPDE in Osnabrück in August 2013 was later withdrawn. Three workshops (Mathways into cancer, Carmona, May 2013; Forum Biomath, Sofia, June 2013; Fourth Conference on Computational and Mathematical Population Dynamics, Taiyuan, May 2013) were financially supported by ESMTB, each with a contribution of 1000 €. In 2014, no requests have yet been received.
- *ESMTB Travel support:* in 2013, three applications were received for a travel support. Each was granted 500 € of support. Up until ECMTB 2014, twelve requests for travel support have been received in 2014.
- *ESMTB Account and audits:* auditors Carlos Braumann and András Czirók have reviewed and approved the Society's financial data for 2012 and 2013. AD presents Society's expenditures and revenues in 2013.

- *ESMTB Communication/Information/Promotion:* in addition to being Society's treasurer, AD is in charge of ESMTB website as well as printing and distribution of ESMTB Flyers and ESMTB Communications.

AD's successor will be elected among Board members during the first meeting of the newly formed Board at the start of 2015. If elected to the Board of ESMTB, Frank Hilker (FH; University of Osnabrück, Germany) is willing to take over as Society's treasurer. AD expresses his belief in FH to provide a smooth transition of duties and in serving the Society well as its treasurer.

3. Elections for the new ESMTB Board

The end of 2014 marks the end of term for five ESMTB Board members (Andrea Pugliese (current ESMTB President), Andreas Deutsch (current ESMTB Treasurer), Peter Jagers, Miguel Herrero and Daphne Manoussaki). Five members (Roeland Merks (current ESMTB Vice president), Barbara Boldin (current ESMTB Secretary)), Reinhard Bürger, Ryszard Rudnicki and Vitaly Volpert remain of the Board for another three years.

Electronic elections for five new Board members will be held in Autumn 2014 via ESMTB website. The current Board has suggested a number of candidates and the following have accepted the Board's invitation and will run as candidates in the coming elections:

- Andrea De Gaetano (National Council of Research of Italy (CNR), Rome)
- Susanne Ditlevsen (University of Copenhagen, Denmark)
- Patsy Haccou (Leiden University College, the Hague, Netherlands)
- Frank Hilker (University of Osnabrück, Germany)
- Torbjörn Lundh (Chalmers and University of Gothenburg, Sweden)
- Anna Marciniak-Czochra (University of Heidelberg, Germany)
- Géza Meszéna (Eötvös University, Budapest, Hungary)
- Sergei Petrovskii (University of Leicester, UK)

Andrea De Gaetano, Frank Hilker, Torbjörn Lundh, Anna Marciniak-Czochra and Géza Meszéna introduce themselves to the Assembly and present their planned contributions to the Society. If elected to the Board, Frank Hilker has expressed will and enthusiasm to take over the duties of Society's Treasurer. As other candidates could not be present at the Assembly, the President reads out their written profiles.

The president asks for additional nominations but none is put forward during the Assembly. ESMTB members can nominate themselves or other willing colleagues to run for the Board. Such proposals should be sent to AP by 11 July 2014.

The profiles of all elections candidates will be available at www.esmtb.org and sent to all Society members together with the electronic ballot information before the elections. Electronic elections are planned for September 2014.

4. **ECMTB 2016**

Rueben O'Dea, a representative of the organizing commitee of ECMTB 2016 (led by Markus Owen) introduces some initial plans for ECMTB 2016 in Nottingham. The conference will take place from 11 July – 15 July 2016 at the University Campus of the **University of Nottingham and will be a joint event with the Society for Mathematical Biology (SMB).**

Andrea Pugliese once again thanks the organizers of ECMTB 2014 and all the Board members who will step down at the end of 2014. The meeting ends will applause.

Barbara Boldin
Secretary of ESMTB

Minutes of the ESMTB Board meeting

*Vienna, Austri21th February 2015*Meeting starts at 9:30.Present: Barbara Boldin (BB; Minutes), Reinhard Bürger (RB), Andrea De Gaetano (ADG), Susanne Ditlevsen (SD), Anna Marciniak-Czochra (AMC), Andreas Deutsch (AD), Mats Gyllenberg (MG; editor-in-chief of Journal of Mathematical Biology), Frank Hilker (FH), Eva Hiripi (EH; Springer representative), Torbjörn Lundh (TL), Roeland Merks (RM; Chair), Andrea Pugliese (AP), Ryszard Rudnicki (RR), Vitaly Volpert (VV)

Round of introductions and welcome.

1. **Board elections and constitution of the ESMTB Board for 2015-2017**

   A brief summary of Board elections. At the end of 2014, five members of the Board of ESMTB (Andrea Pugliese (ESMTB President), Andreas Deutsch (ESMTB Treasurer), Peter Jagers, Miguel Herrero and Daphne Manoussaki) ended their term on the Board of ESMTB. The other Board members (Barbara Boldin, Reinhard Bürger, Roeland Merks, Ryszard Rudnicki and Vitaly Volpert) continue for the next three years.

   During the 9th ECMTB in Gothenburg in June 2014, the General Assembly of ESMTB nominated eight candidates to replace the outgoing members of the Board for the 2015-2020 mandate. The candidates were Andrea De Gaetano, Susanne Ditlevsen, Patsy Haccou, Frank Hilker, Torbjörn Lundh, Anna Marciniak-Czochra, Géza Meszéna and Sergei Petrovskii. In August 2014, 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 Board of ESMTB. The results of the elections were as follows:

Candidate:	Number of votes:
Andrea De Gaetano	40
Susanne Ditlevsen	44
Patsy Haccou	29
Frank Hilker	52
Torbjörn Lundh	40
Anna Marciniak-Czochra	40
Géza Meszéna	28
Sergei Petrovskii	32

The five new members of the Board are thus Andrea De Gaetano, Susanne Ditlevsen, Frank Hilker, Torbjörn Lundh and Anna Marciniak-Czochra.

The constitution of the new ESMTB Board. All members of the Board are present at the meeting and cast their votes to elect the President, Vice president, Treasurer and Secretary of ESMTB for the 2015-2017 period. The results are as follows: Roeland Merks is elected as Society's President, Torbjörn Lundh as the Vice President, Frank Hilker is elected as the new Treasurer and Barbara Boldin is re-elected as Society's Secretary.

The ESMTB Board for the 2015-2017 mandate:

Roeland Merks (President)
Torbjörn Lundh (Vice president)
Barbara Boldin (Secretary)
Frank Hilker (Treasurer)
Reinhard Bürger
Andrea De Gaetano
Susanne Ditlevsen
Anna Marciniak-Czochra
Ryszard Rudnicki
Vitaly Volpert

2. Report by the outgoing ESMTB President

AP briefly summarises the 9th ECMTB that took place in Gothenburg during 15th-19th June 2014. The conference was a success and AP thanks TL for wonderful organisation. AP highlights the Society's support to students and meetings. The Society should continue to organise schools and workshops and work on attracting new members. Ties with other related Societies are nurtured: AP highlights ongoing communications with Jose Carrillo (EMS) and initiatives to organise more joint events in the future.

3. Report by the outgoing ESMTB Treasurer

AD begins his final report as ESMTB's Treasurer by handing out a printed summary and describing his work since he took over as Society's Treasurer in 2003.

- *Membership development.* AD presents the data on ESMTB memberships in the years 2003-2014. The number of memberships peaked in 2005 (in the year of ECMTB in Dresden). In 2014, ESMTB had 228 members. The distribution of ESMTB members over countries and membership types is presented. In 2012 a new category "life membership" was introduced. Membership fees can be paid either by bank draft transfer or PayPal. The former is strongly encouraged since it incurs not costs to ESMTB.
- *ESMTB Support.* ESMTB offers support for schools and workshops as well as individual travel support for students. AD describes which schools and workshops were the recipients of ESMTB support in the years 2005-2014. In 2014, MPDE in Torino was supported in the amount of 1000 €. In addition, 17 out of 19 applicants were granted 500 € each in 2014. In 2015, one application for support of a school has been received thus far and the Board will discuss its support.

Å ESMTB Account. Revenues are exclusively from membership fees. AD shows the revenues and expenditures in 2014 and concludes by presenting the ESMTB balance: at the end of 2014, the Society's account balance was + 18.851,79 €.

In addition to working as ESMTB Treasurer, AD has done an immense job for Society's promotion, including maintaining the Society's website, printing and distributing ESMTB flyers and posters, printing of ESMTB Communications and distributing Society's Info-letter. FH, the newly elected Treasurer of ESMTB, will continue and build on AD's excellent work related to Society's finances. The other tasks previously performed by AD are assigned to new Board members (see Communication/Information/Promotion).

AD highlights the importance of increasing Society's visibility and in particular of promoting the Reinhart Heinrich award. ESMTB annually gives out the Reinhart Heinrich award to honour the best PhD thesis in mathematical and theoretical biology (see The Reinhart Heinrich award section).
It is generally agreed that many more scientists work in the field of mathematical and theoretical biology today compared to previous decades. Yet, this increase is not reflected in ESMTB membership numbers. Benefits of ESMTB membership are discussed. Some ideas to increase the Society's appeal are circulated, in particular of attracting applied mathematicians endeavouring to work in the field of mathematical and theoretical biology. ADG expresses some doubts about the current formulation of the Society's mission (as expressed in the ESMTB flyer). It is agreed that suggestions for a new formulation will be circulated and discussed among ESMTB Board members and an update will be decided upon during the next meeting of the Board. In particular, the newly formulated mission should make clearer the Society's objectives, its place in the scientific community and should establish the qualities that

distinguish it from sister societies (e.g. SMB). ESMTB could provide a database of programmes in mathematical and theoretical biology at universities in Europe and could do more to promote exchange of students of mathematical and theoretical biology between European universities within existing exchange programmes (e.g. Erasmus).

4. Journal of Mathematical Biology and Springer

Journal of Mathematical Biology is the official journal of ESMTB. Currently, the editors-in-chief are Mats Gyllenberg (present at the meeting) and Mark Lewis. The editorial board of the journal includes a member of the current Board (RB) and the outgoing ESMTB president (AP). EH, the editor for Biomathematics and Statistics at Springer, presents the publisher's report on the Journal of Mathematical Biology:

- The number of manuscripts annually submitted to the Journal of Mathematical Biology is increasing. In 2014, the number of new submissions was close to 500. The acceptance ratio remains roughly constant and is around 25%. MG adds that the fraction of submissions that are sent out for review has increased. In order to handle the increased number of accepted manuscripts, issues of JMB now contain more pages. In 2015, 14 issued are planned, each having 250 pages. EH presents the data on average review process duration and average handling times and is happy to report that the backlog has decreased from 14 months in the previous years to 10 months. Decreasing the backlog further is one of the tasks for the future. EH presents the distribution of submitted and accepted manuscripts according to the corresponding author's country of residence.
- Different subscription types are presented and data concerning manuscript downloads is shown, including the top 10 downloaded papers of 2014. Most visitors are referred to JMB via Google. The number of subscriptions to printed issues decreases fast. There are however no plans to abandon the printed issues of JMB. Abstracting of JMB and impact factors are discussed. Top ten cited articles are mentioned.
- EH highlights that ESMTB members are given free access to electronic issues of JMB and are offered a special rate for printed issues. In addition, Springer contributes to the Reinhart Heinrich award by offering a 200 € worth of Springer books to Reinhart Heinrich award winners.
- EH introduces the new Springer journal, The Journal of Mathematical Neuroscience and asks for help in promoting the journal.

MG and the Board members thank EH for the extensive report. MG adds that

- Ideas for special issues, review state-of-the-art articles and Perspectives articles are most welcome. One idea put forward is a special issue or a review article on *image analysis.*
- Free downloads of JMB articles during ECMTB in Nottingham (and future ESMTB conferences) would be welcome.
- Plagiarism is less common than a few years ago.
- The impact factor of JMB remains high (close to 2.4). The journal is highly respected and it is important to keep the quality of the contributions high.

The Board thanks MG for his excellent work as JMB's editor-in-chief.

5. ECMTB 2014

TL reflects on the very successful ECMTB in Gothenburg in June 2014, describes the application for grants, the scientific committee and scheduling of the conference, including the scientific and social programme. TL concludes by handing out financial reports of the conference.

6. ECMTB 2016

The next ECMTB will take place between 11th-15th June 2016 at the University Campus of the University of Nottingham, UK. The conference will be a joint ESMTB-SMB conference and will, for the first time in ESMTB history, take place only two years after the previous event. Markus Owen, the main organiser of the event, could not attend the Board meeting in Vienna. RM gives an update on his behalf: the conference venue is set and the scientific committee is working on the list of plenary speakers. SD and VV are representatives of the Board in the scientific committee, which also includes AD. It is advised that the organising committee of ECMTB 2016 collaborates with TL and makes the most of his experience with organising the conference in Gothenburg. Several suggestions are put forward:

- Choose a standard format for mini-symposia (for example 4 talks of 30 minutes)
- Engage the scientific committee in scheduling of mini-symposia and contributed sessions. In particular, the scientific committee can advise to merge similar topics and minimise overlap between mimi-symposia and contributed sessions
- It is important to have a preliminary schedule to allocate time for special events (e.g. award talks, meetings of ESMTB and SMB etc.).

7. Future ECMTB

The Board discusses whether ECMTB will return to the triennial cycle after 2016 or continue with a two-year interval. A two year cycle offers several advantages, including more opportunities for PhD students to present their work and more chances to promote the Society. An obstacle might be a lack of potential hosts. AP introduces two potential hosts for the 2018 conference and another candidate emerges as the host of the 2010 event. ADG suggests that, instead of at University premises, ECMTB may be organised in a conference centre/hotel in a tourist resort with sufficient capacities. ADG offers to explore this possibility further. These suggestions give hope that ECMTB may successfully switch to a biennial cycle. The Board therefore decides to pursue this goal and AP offers to check whether any of the two potential hosts of ECMTB 2018 can confirm their willingness to organise the event.

8. EMS-ESMTB schools

Plans for the 2015 joint EMS-ESMTB summer-school have been delayed. There will be two schools in 2016: in addition to the delayed school (on Tissue modelling at the Lorenz Centre in Leiden, The Netherlands), wheels are in motion for the 2016 Helsinki summer school in Turku, Finland.

9. ESMTB Communications

VV briefly describes the making of ESMTB Communications. The last issue was presented and distributed during ECMTB 2014 in Gothenburg. Currently, around 300 copies are printed in Dresden with the total cost of about 1000 €. The next issue is in preparation. Once more, there is a discussion whether to increase the scientific content in the Communications. This idea is, however, not generally accepted.
The editorial Board of the Communications currently consists of Wolfgang Alt, BB, AD, RM, AP and VV. AD proposes to step down and SD volunteers to join the editorial board. EH volunteers to help with promotion of ESMTB Communications.

10. Communication/Information/Promotion

Distribution of duties after AD's departure. In addition to taking care of Society's finances, AD has been responsible for Society's website, printing and distributing of ESMTB flyers and posters and distributing ESMTB Info-letter. These duties are now assigned to other Board members as follows:

- The Society's website will from now on be maintained by RM and Bob Planque from VU University Amsterdam, who has kindly offered assistance in this matter. RM offers to help with the distribution of flyers and possibly with printing of ESMTB Communications
- AMC volunteers to continue the Society's Info-letter.

Twitter/Facebook. ESMTB has a Twitter account (@ESMTBio) with around 250 followers. There is potential to better use the Twitter account to promote Society's activities, inform of open positions and university programs in mathematical and theoretical biology, include announcements about the Journal of Mathematical Biology etc. For further promotion, RM and TL may set up a Facebook account for ESMTB.

11. The Reinhart Heinrich award

AD reports that 6 applications were received for the 2014 Reinhart Heinrich award. The winner will be announced soon and a report on the Reinhart Heinrich award will be included in the 2015 issue of ESMTB Communications.
The current award committee is led by AD and includes Nico Beerenwinkel, Carlos Braumman, Philip Maini and Stefan Schuster. AD suggests to step down in the near future and suggests RB as his successor.

12. Ties with other Societies

ESMTB is a member of EMS and ICIAM. EMS and ESMTB organise joint summer schools. In recent months there has been ongoing communication with Jose Carrillo (EMS) and AP (ESMTB) with the aim of organising additional joint events. Ties with ICIAM have weakened in the past year. The Board agrees to work on strengthening these ties and to have a representative of the Board of ESMTB at the next meeting of ICIAM.
FH remarks that reciprocal ESMTB-SMB membership does not guarantee voting rights to ESMTB members in SMB elections, while SMB members with reciprocal ESMTB membership can vote in ESMTB elections. RM offers to explore this issue with the Board of SMB.

13. Closure

The Board thanks RB for organisation of the meeting. The outgoing president (AP) and the outgoing Treasurer (AD) are thanked for their excellent contributions to the Society.

The next ESMTB Board meeting will take place in October 2015 in Copenhagen.

The meeting ends at 19.00.

Barbara Boldin
ESMTB Secretary

The Reinhart Heinrich thesis award

Multiscale modelling of angiogenesis during normal and impaired bone regeneration

Extended Abstract of the Doctoral Thesis by Aurélie Carlier
Supervisors: Profs. H. Van Oosterwyck and L. Geris

Introduction

Bone is a truly remarkable and interesting tissue. Not only provides the human adult skeleton support and protection for various organs in the body, the collection of 206 bones also stores minerals, produces blood cells and allows movement. Moreover, unlike other adult biological tissues, bone is the only tissue that can heal without the production of scar tissue. The regeneration of bone tissue is a complex, well-orchestrated process of cell recruitment, proliferation and differentiation regulated by several biochemical and mechanical factors. Briefly, the characteristic course of long bone healing can be subdivided in three main stages: (i) the "inflammation phase" where the trauma site becomes hypoxic and is invaded by inflammatory cells, fibroblasts and mesenchymal stem cells, (ii) the "reparative phase" which starts with the production of a cartilaginous and fibrous tissue template, later invaded by new blood vessels and replaced by a bony callus through endochondral ossification, (iii) the final "remodeling phase" during which the woven bone is replaced by lamellar bone and the vasculature is reorganized (Figure 1).

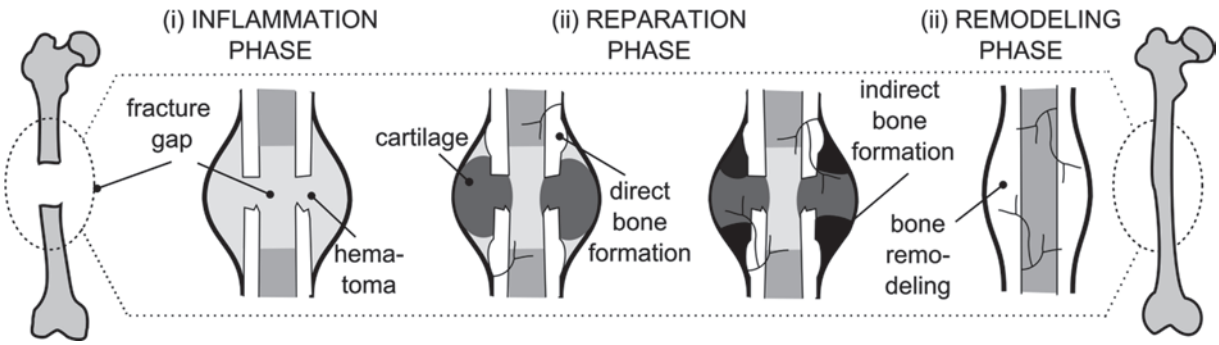

Figure 1: Schematic representation of the three different phases of fracture healing (adapted from [1]).

Unfortunately, the conditions for spontaneous bone healing are not always present, leading to a delayed union or a non-union in 5 to 10% of all cases (e.g. annually this comes down to over 6 million fractures in the USA alone). In order to address the key mechanisms that lead to fracture non-unions, determine the factors predictive of fracture complications and establish optimal patient-specific therapeutic strategies, this PhD project used an interdisciplinary approach, combining experimental work with modelling efforts.

Establishing a multiscale computational framework

This PhD project has developed a multiscale model of angiogenesis (i.e. the formation of a new blood vessel network) during bone fracture healing. More specifically, at the tissue level the spatiotemporal evolution of 10 continuous variables is captured with partial differential equations (PDEs) of the taxis-reaction-diffusion type (Figure 2). As such the various key processes of bone regeneration are modelled by the following variables: mesenchymal stem

cell density (c_m), fibroblast density (c_f), chondrocyte density (c_c), osteoblast density (c_b), fibrous matrix density (m_f), cartilaginous matrix density (m_c), bone matrix density (m_b), generic osteochondrogenic growth factor concentration (g_{bc}), vascular growth factor concentration (g_v) and oxygen concentration (n). Note that only one generic osteochondrogenic growth factor (g_{bc}) is included, whose influence on differentiation is steered to either chondrogenesis or osteogenesis depending on the local oxygen concentration.

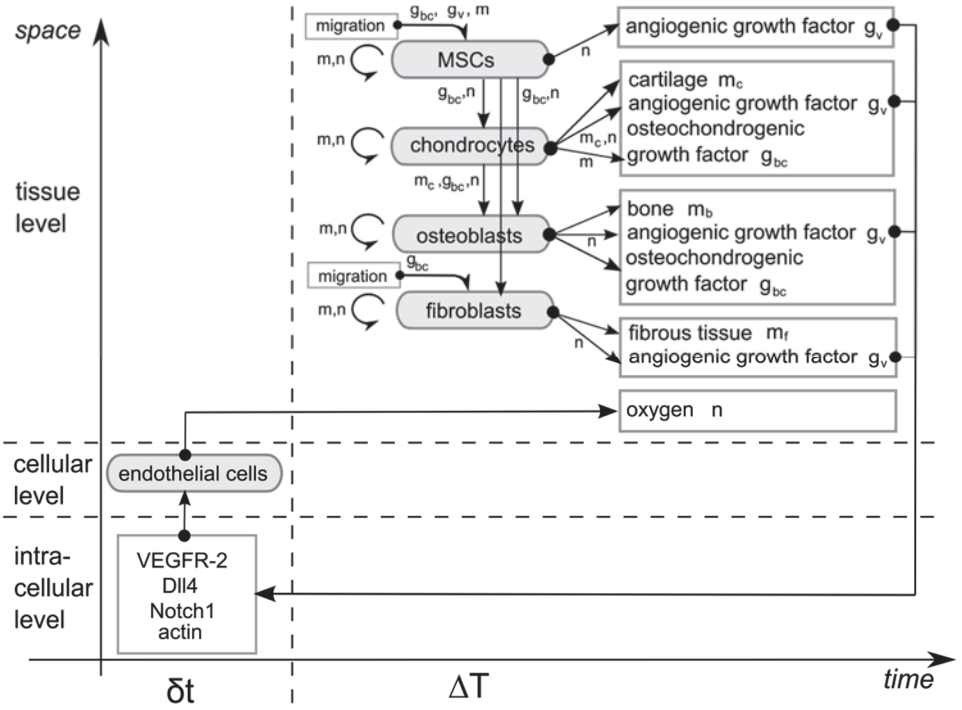

Figure 2: Schematic representation of the multiscale bone regeneration model. $m=m_f+m_c+m_b$ represents the total tissue density. The intracellular variables govern the endothelial cell (EC) behavior. At the tissue scale, cells can migrate (only MSCs and fibroblasts), proliferate (circular arrows), differentiate (vertical arrows), produce growth factors and extracellular matrix. Blood vessels are a source of oxygen which influences proliferation, differentiation and hypoxia-dependent angiogenic growth factor production. Variables influencing a tissue level process are indicated next to the corresponding arrow.

The formation of the blood vessel network is modelled at the level of the individual endothelial cell with a discrete agent-based approach where the vessel diameter corresponds to the grid cell size at which the continuum model is solved (i.e. 25 µm). The model includes three different processes that determine the development of the discrete vascular tree, i.e. sprouting (the formation of a new branch, headed by a “tip cell” or “leader cell”), vascular growth (the extension of the branch due to the growth of “stalk cells” or “follower cells”) and anastomosis (the fusion of two branches). The sprouting behavior of the endothelial cells is captured with 8 intracellular variables, unique to every endothelial cell (Figure 2). The rules that capture the intracellular dynamics and the lateral inhibition mechanism during tip cell selection were derived from the agent-based model of Bentley et al. [2]. The growth of a blood vessel is modeled by computing the movement of the corresponding tip cell where the tip cell speed depends on the active VEGFR-2 concentration and the tip cell direction is influenced by chemotactic (angiogenic growth factor) and haptotactic (collagen fibers in the extracellular matrix) signals. When a tip cell encounters another blood vessel or when it migrates outside the geometrical domain, an anastomosis is formed during which the leading endothelial cell loses its tip cell phenotype. The newly established connection between the vessels allows for blood flow and the delivery of oxygen and nutrients. As such, only the ECs that are part of a vascular loop are sources of oxygen (Figure 4).

The complete description of the equations, boundary and initial conditions, the geometrical domain, the parameter values and implementations can be found in [3-5].

Towards clinical applications

In the multiscale computational platform many cellular processes, like survival, proliferation and differentiation are (non-linearly) dependent on oxygen concentration and since they all have a specific range of oxygen concentration at which they are “optimized” (maximally affected), it becomes virtually impossible to intuitively predict the resulting bone healing outcomes. As such, for the first time, a powerful framework is established which allowed us to investigate the complex non-linear, oxygen-dependent dynamics of blood vessel formation, oxygen supply, oxygen diffusion, oxygen consumption, cellular proliferation and cellular differentiation during normal and impaired fracture healing [4]. After corroborating the predictions of the multiscale model for normal fracture healing with experimental data, the model was used to understand the underlying mechanisms of impaired healing for three clinical cases: the permanent failure of bone healing in large bone defects, the implantation of bone grafts in a damaged environment and the impaired healing of bone fractures in patients in which the bone formation is genetically disrupted.

In large bone defects, an extensive sensitivity analysis showed that the initial conditions (i.e. the amount of osteoprogenitor cells, growth factors and the oxygen concentration initially present in the fracture zone) have an important impact on the final amount of bone formation. They are however not sufficient to result in complete healing of critical size defects due to the delayed vascularization of the central callus area, leading to hypoxic conditions and cell death. Inspired by the importance of a timely vascularization as well as by the limited biological potential of the fracture hematoma, the influence of the host environment on the bone healing process in critical size defects was explored further (Figure 4). The model results indicated clearly that the contribution of the host environment, and more specifically its role as a source of vascularization, is critical for successful bone healing. The predictions also showed that the lack of adequate vascularization can be compensated by a continuous delivery of osteoprogenitor cells from the overlying muscle. Consequently, the effectiveness of a therapy (consisting of the injection of cells, growth factors or a combination thereof) is dependent on the timing of the treatment as well as the host environment since the latter can serve as a source of additional osteoprogenitor cells, growth factors or vascularization to populate the fracture callus and increase the biological potential thereof (Figure 3). In order to illustrate the model’s potential, several treatment strategies were designed and tested for effectiveness taking into account the specific role of the host environment. This resulted in a qualitative correspondence between the predicted outcomes of certain treatment strategies and experimental observations [4].

During autologous bone grafting, bone is harvested from one anatomical site and transplanted to another site in the same patient. Although this treatment is still considered the “gold standard” for several complex orthopedic cases, it has several limitations which include donor site pain, increased blood loss, increased surgery time, increased risk for donor site infection and limited supply. As such, novel therapies try to “engineer” a patient-specific bone graft by seeding cells and growth factors on biocompatible scaffolds. In order to help identify the components and sequence of events that are essential for a successful

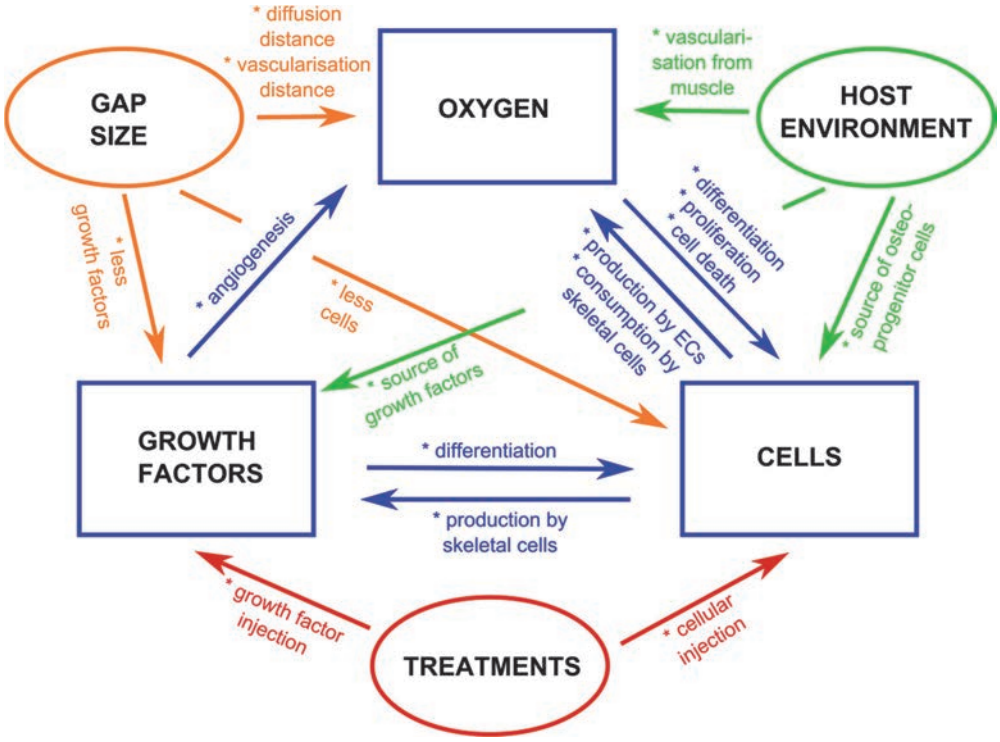

Figure 3: Schematic overview of the complex spatiotemporal interplay between the amount of oxygen, growth factors and cells as well as the gap size, host environment and administered treatments.

tissue engineering construct, an improved comprehension of bone graft healing and its interaction with the host environment is imperative. The geometrical domain of the bone regeneration model was adapted to the experimental set-up in which an autograft was implanted in a compromised host environment, created by inserting a filter in between the overlying muscle and the graft. The multiscale bone regeneration model accurately predicted the experimentally observed bone formation patterns in normal (without filter) and impaired bone graft healing (with filter) (Figure 4). Moreover, the computational model was able to add credibility to the experimental hypothesis of an oxygen-dependent switch in cell fate which resulted in an altered healing pattern in a compromised host environment. Similar to the previous findings, the results highlight again the important role of vascularization for the clinical success of bone grafting strategies [6].

Congenital pseudarthrosis of the tibia (CPT) is a rare disease which normally presents itself during early childhood. It is characterized by anterolateral bowing of the tibia and develops into spontaneous fractures in the distal tibia. Usually the bone regeneration is insufficient and a pseudarthrosis is formed at the fracture site. An adequate treatment is currently lacking, often resulting in multiple revision surgeries and occasionally even amputation. The exact etiology of CPT is still highly debated. However, 40-80% of the CPT-patients are carriers of a mutation in the NF1 gene, leading to an altered phenotype of the skeletal cells. In order to improve the understanding of the role of NF1 haploinsufficient skeletal cells in impaired bone healing, eight factors described to contribute to the poor fracture healing outcome in CPT patients (i.e. increased invasion of fibrous lesion cells, increased fibroblastic proliferation, increased fibroblastic differentiation, reduced osteogenic differentiation, reduced endochondral ossification, reduced cartilage formation, increased fibrous tissue formation and increased angiogenic growth factor production) were investigated in the bone regeneration model. By altering these eight factors, the computational model predicted the experimentally observed “hamartoma” formation, i.e. a disorganized mass of bone and fibrous tissue. As such the computational model which is, to the best of the author's knowledge, the first in its field,

showed that the presence of a NF1 mutation, resulting in aberrant behavior of skeletal cells, leads to the formation of a pseudarthrosis (Figure 4). Preliminary results also indicated that through various combinations of altered parameter values, the different degrees by which CPT presents itself might be captured by the computational model [7]. Moreover, a minimal set of parameter values that needs to be altered in order to produce the aberrant phenotype, could be defined. Besides exploring the underlying mechanisms of action of CPT, the bone regeneration model also demonstrated that the effectiveness of a BMP-therapy is dependent on the timing at which the treatment is initiated as well as on the degree of severity of CPT.

Conclusion

In summary we can state that the bone regeneration model, established in this PhD work through an interdisciplinary approach, does not only predict the bone fracture healing process in small and large defect sizes, it also captures the fundamental mechanisms of bone formation. Indeed, the multiscale bone regeneration model accurately predicts the experimentally observed bone formation patterns in normal and impaired bone graft healing as well as the aberrant healing in NF1 patients (Figure 4). The common thread that is weaved throughout all the results discussed above, is angiogenesis. The model results clearly show that the newly formed blood vessels will supply the necessary oxygen to ensure cellular survival, proliferation and growth factor dependent differentiation, finally resulting in the successful completion of the bone regeneration process. As such, we can conclude that a complete cortical bridging of a challenging critical size defect, or a successful incorporation of a graft in a compromised host environment, or the formation of a bony union in NF1 patients will only occur if growth factors, osteoprogenitor cells and vasculature are simultaneously present in the callus area (Figure 3). Consequently, the most stringent factor that is lacking in a certain area or at a certain time point will be an ideal candidate for future treatment strategies. Although more clues are needed to complete the bone regeneration puzzle, the computational framework allowed us to step closer to the prevention and effective treatment of complex orthopedic cases. Future research should focus on the refinement and validation of the framework so that it ultimately can assist in bringing novel treatment strategies for challenging orthopedic cases from bench to bed side [8].

Acknowledgements

I greatly thank my supervisors Profs. H. Van Oosterwyck and L. Geris for their excellent support, scientific expertise and inspiring discussions. My sincerest appreciation also goes to the awarding committee for awarding my thesis with the Reinhart Heinrich Doctoral Thesis Award 2014. I would also like to thank the ESMTB for giving me the opportunity to present my research results here. Finally, I would like to acknowledge the financial support of the Research Foundation Flanders (FWO-Vlaanderen).

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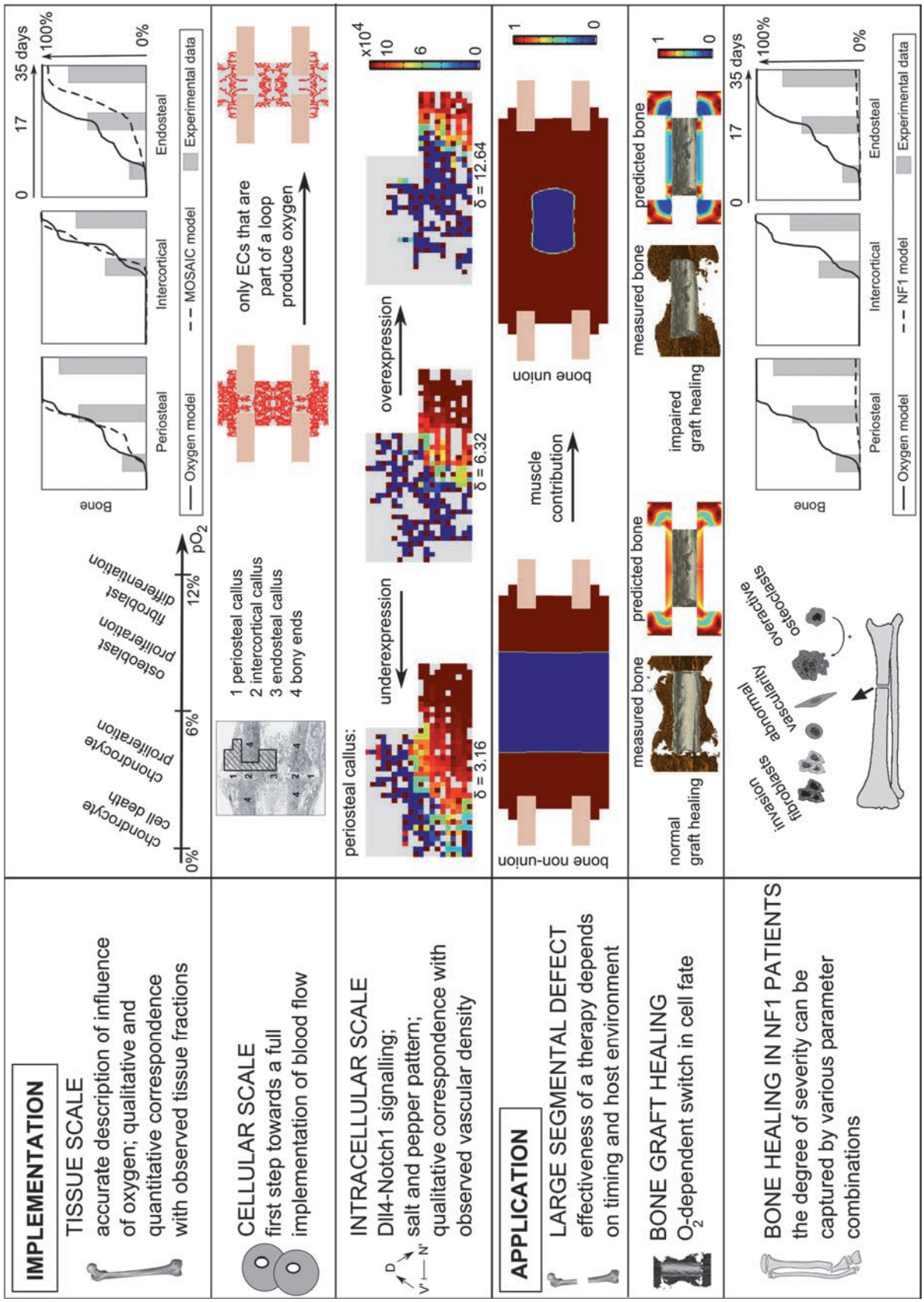
Figure 4: Schematic overview of the major contributions of this PhD work.



Modeling and optimization of radiotherapy treatment plans

Extended Abstract of the Doctoral Thesis by Juan Carlos López Alfonso
Supervisors: Profs. Miguel A. Herrero, Juan B. García-Archilla and Dr. Luis Núñez Martín

In spite of the great efforts made over many years in the fight against cancer, improving the treatment, whence the prognosis of this disease remains one of the biggest challenges in medicine nowadays. Ever since the discovery of X-rays by Wilhelm Conrad Röntgen in 1895, radiotherapy has played a major role in the treatment of solid tumors for curative and palliative purposes. In particular, this therapeutic technique is designed to shed ionizing radiation to induce damage in pathological tissues, while at the same time avoiding as much as possible undesirable side effects on nearby organs. According to recent estimates, no less than 50% of all cancer patients receive radiotherapy during their illness, whether on its own or as an adjunct to chemotherapy, surgery or other medical procedures. Technical and methodological advances during the last century have allowed radiation oncologists to achieve local tumor control in a considerable number of patients diagnosed with solid tumors. However, locoregional recurrence and treatment of disseminated tumors remain a formidable problem in many situations. For these reasons, it is necessary to improve currently used diagnosis, planning and therapeutic techniques. In this context, the development of new mathematical models and more sophisticated computer-based methods are expected to provide significant tools towards curing this disease whenever possible and to improve the patients' quality of life in all cases.

The aim of this thesis was precisely to develop mathematical models and computer-based algorithms to assist in the decision-making process whereby actual radiotherapy treatment plans are designed and selected [1]. More precisely, a multi-parameter variational problem was first formulated, and then numerically solved, whose solutions provide optimal radiation dose distributions satisfying standard clinical and technical requirements [2], [3]. In addition, an agent-based model of heterogeneous tumor growth based on specific biological and radiobiological assumptions was proposed, and tumor response to different homogeneous and heterogeneous radiation dosimetries was investigated [4]. Finally, a decision-support tool was developed to assist radiophysicists during planning in the choice of tentative treatment plans, a process that to this day largely relies on personal experience and thus highly subjective. In what follows, the main chapters of this thesis are briefly summarized.

Selecting radiation therapy dose distributions by means of constrained optimization problems

The main steps in planning radiotherapy consist in selecting for any patient diagnosed with a solid tumor i) a prescription radiation dose on the tumor, ii) dose constraints for the critical structures delineated and iii) a fractionation scheme specifying the number and frequency of therapeutic sessions during treatment. In particular, dose tolerance limits to nearby organs at risk and the prescription dose are usually defined depending on the tumor type and location without any direct reference to quantitative radiobiological assessment. Interestingly, several mathematical models for the effect of radiation on biological matter have been reported. However, although they are widely acknowledged by clinicians, the difficulty to obtain accurate *in vivo* measurements of the radiobiological parameters involved has severely restricted their application in current clinical practice.

The goal here was to propose a mathematical model to select radiation dose distributions as solutions of suitable variational problems, under the assumption that only partial information on radiosensitivity parameters is available. The functional to be minimized represents a weighted sum of radiobiological effects directly related to target dose coverage and sparing of healthy tissues. In addition, standard clinical and technical constraints are also accounted for. A comparison of the proposed dose distributions with those actually delivered in a number of clinical cases strongly suggests that model solutions can be instrumental in deriving good quality tests to select radiotherapy treatment plans in rather general situations (see for instance Figure 1). Moreover, a strategy was implemented to eventually obtain optimal dose distributions with which competing tentative plans designed over a same treatment planning system should be compared. It is worth noting that, solutions of this model can be obtained for any type of tumor regardless of its location, as well as for different intratumoral regions or several tumors identified for the same patient.

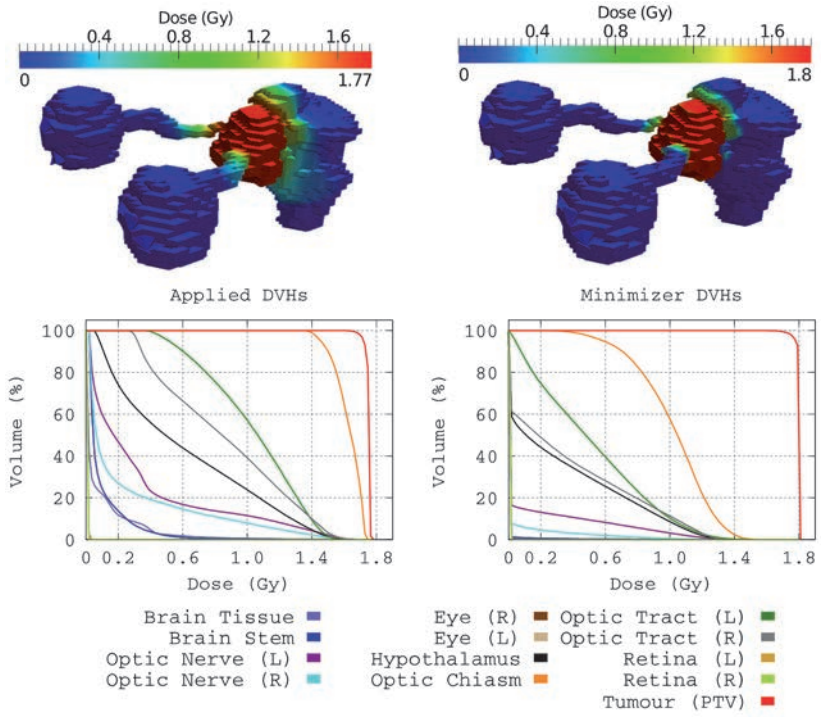


Figure 1: [Top]: A comparison of an applied radiation dose distribution (left) and the corresponding optimal dose distribution (right) obtained from the proposed model. [Bottom]: Dose-volume histograms of the applied (left) and optimal (right) dose distributions for each organ at risk involved and the target volume. Notice the better performance of the optimal dose distribution, with respect to tumor dose coverage and sparing of organs at risk, when compared to the actual treatment delivered.

Estimating dose painting effects in radiotherapy: a mathematical model

The onset of radioresistance, and its resulting poor prognosis, is strongly correlated with the development of significant intratumoral heterogeneity. For that reason, there is a growing interest in the clinical significance of tumor heterogeneity, which is supposed to be a determinant factor in tumor progression and recurrence. Extensive genetic variations in tumor cells due to intratumoral evolution have been recently demonstrated. Moreover, tissue-level heterogeneity due to variations in vascular density and blood flow has been clinically observed (see Figure 2). In recent years, accumulating evidence suggests that tumor heterogeneity is a key factor in the development of therapeutic resistance, and therefore in radiation therapy

outcomes. As a consequence, increasing attention is being paid to “dose painting” (or “dose sculpting”), a technique that consists in prescribing different radiation dosimetries to non-intersecting regions within a given tumor, so that irradiation be boosted in more radioresistant (for instance, hypoxic, quiescent, etc.) regions. However, current medical techniques are unable to deduce clinically relevant information about tumor heterogeneity by means of non-invasive methods. As a consequence, radiation dosimetries are prescribed under the assumption that the malignancy targeted is of a homogeneous nature.

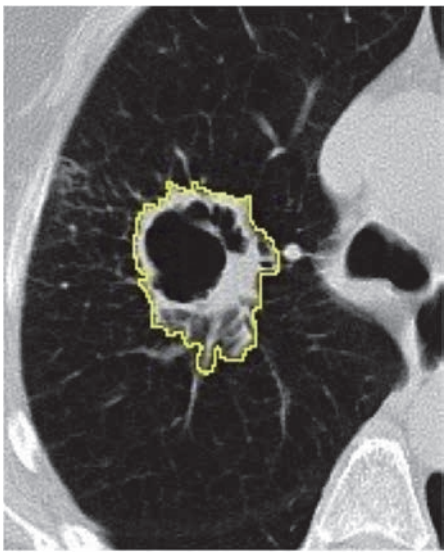


Figure 2: A CT scan of lung showing a cancer in the right upper lobe (circled) with regions of necrotic (dead) and viable tissue (Courtesy of Dr. Robert A. Gatenby, Moffitt Cancer Center, Tampa, USA).

A mathematical model of tumor growth was proposed to gain insight about two key issues: how heterogeneity emerges in growing tumors, and what are the most suited dose distributions to achieve control in heterogeneous tumors. To that end, the effect of different dosimetries on heterogeneous tumors was explored by means of an individual cell-based model. A case was considered where two tumor cell phenotypes are present, which have been assumed to strongly differ in their respective cell cycle duration and radiosensitivity properties. As a result of such differences, the spatial distribution of the corresponding cell phenotypes can be predicted with the tumor growth (see Figure 3). In particular, starting from an initial configuration where a majority of cancer cells (CCs) and a minority of cancer stem cells (CSCs) are present and randomly distributed, a robust emerging feature was obtained. Namely, most of the CSCs concentrate within the tumor core as tumor grows, provided that the CSC cycle is significantly longer than that of CCs, as well as CSCs remain a small fraction of the total tumor population. As a consequence, and assuming also that CSCs are more resistant to radiation than CCs, heterogeneous dosimetries can be selected to enhance tumor control by boosting radiation in the region occupied by the more radioresistant tumor cell phenotype. It was also shown that, when compared with homogeneous dose distributions as those being currently delivered in routine clinical practice, such heterogeneous radiation dosimetries are always better than their homogeneous counterparts.

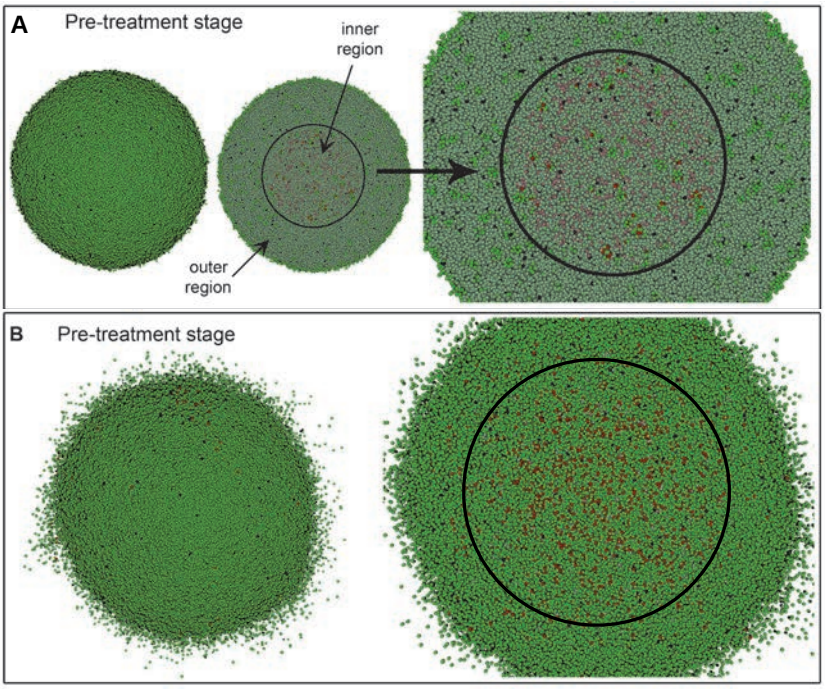


Figure 3: Simulated growth of a heterogeneous tumor with low (A) and high (B) migration rates. Depicted in green and red are CCs and CSCs respectively. [Left]: Tumor stages when radiation therapy is started (about 10^6 cells in total) and [Right] 3D transversal cuts performed in the middle of the solid tumors (left), so that its interior could be seen. Notice that in (A) the more radioresistant cell phenotype CSC is confined within the tumor bulk when irradiation is started. However, when the high migration rate is considered (B), CSCs are not fully concentrated in the tumor core, but it is possible to define the inner region where at least 80% of CSCs are located.

A decision-support system to select dosimetry plans in radiotherapy

Radiotherapy treatment plans are selected by radiophysicists and clinicians out of a small number of competing tentative plans simulated on a commercial treatment planning system. These commonly differ from each other in few variations in the number, incidence angles, weights and/or intensity of radiation beams converging on the target volume. For any tentative plan, planning systems provide dose-volume histograms (DVHs) for each critical structure delineated, as well as the isodose curves over the whole treatment domain. The choice of the treatment plan is then made, regardless of further physical and radiobiological quantities, mainly upon comparison of the DVHs and isodose curves for each tentative plan considered. The plan closest to achieving the clinical requirements is selected and delivered to the patient. Nevertheless, such decision-making process largely relies on the professional experience of the planner and thus highly subjective. Actually, considerable skills are required to pick up the most suitable tentative plan from a mere inspection of the DVHs and isodose curves, which may look quite similar. This makes it difficult to tell by mere inspection which plan may yield better therapeutic outcomes, as well as to predict the impact of small modifications on any of them.

A decision-support tool based on DVHs was proposed to assist clinicians during radiotherapy treatment planning. For any tentative plan, estimates of dose coverage on the target volume, as well as sparing of nearby organs at risk and healthy tissue are defined. These partial metrics

are then combined into a dose distribution index (DDI), which provides a unified score for each tentative plan considered. To compute the DDI, only DVHs obtained from treatment planning systems and the prescription dose on the target are required. In order to validate the DDI scoring tool, a large cohort of head and neck cancer patients was considered. For each patient, three tentative plans were designed, one of which was eventually delivered. We thus were able to compare the plan with lowest DDI score and that actually applied to each patient. To further assess the information provided by the DDI, a sequence of complexity increasing treatment plans for a prostate cancer patient was also investigated. We demonstrate that the DDI can be used to assess the quality of a given treatment plan, as well as to compare rival tentative plans. DDI provides an unambiguous and non-subjective tool for dosimetry comparison of competing plans with similarly looking DVHs. Moreover, the DDI can be easily computed for any tumor type and location irrespective of the treatment planning system and radiotherapy technique considered. In order to simplify the use of this decision-support tool in routine clinical practice, a user graphical user-interface was developed (see Figure 4). The proposed tool is not meant to be a replacement for clinical decisions. Instead, it is expected to provide a precise assessment of the impact of such decisions over the anatomical and pathological regions considered.

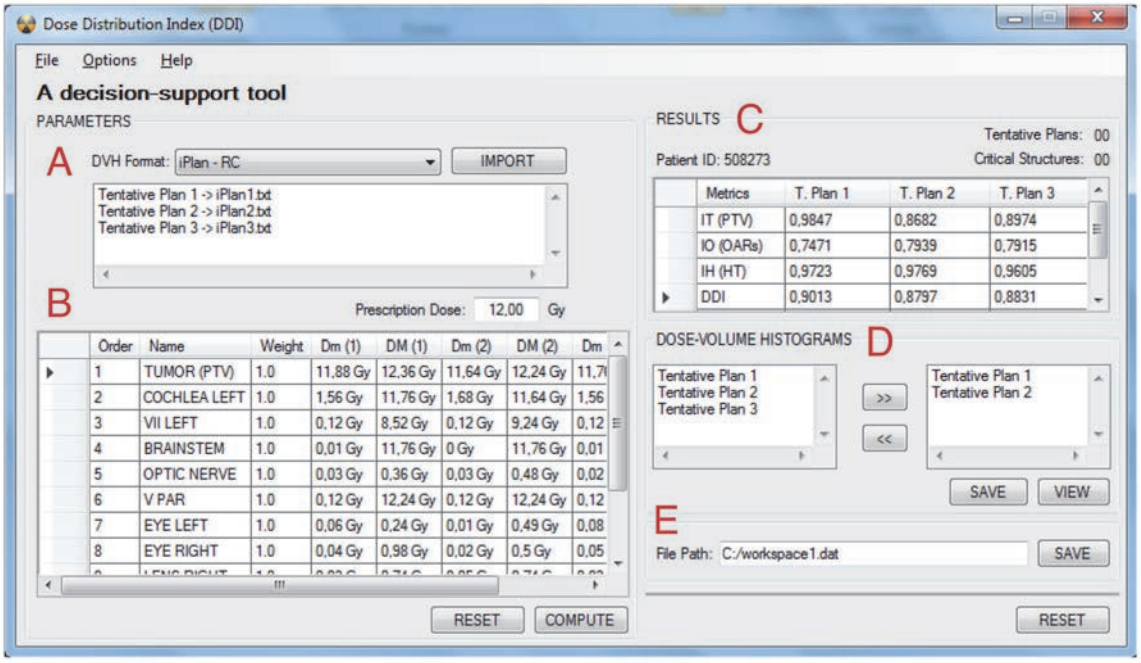


Figure 4: A user-friendly graphic interface to assess and compare tentative treatment plans using the proposed DDI. This software allows to A) import tentative plans, B) edit the DDI parameters, C) compare the resulting scores, D) visualize the DVHs and E) make a backup of the workspace.

Conclusions

Summing up, in this thesis some mathematical models and computer-based procedures have been proposed to assist radiation oncologists during treatment planning. These models are expected to aid the improvement of radiotherapy clinical practice, a goal that has always been present during this study.

Acknowledgements

I greatly thank my supervisors for guiding me professionally throughout my thesis, as well as for their advice, enthusiasm and support. Each of them has been an inspiration to me. I also thank the Spanish Ministry of Economy and Competitiveness (MINECO) for their (FPI) PhD fellowship program. I would also like to thank the awarding committee for the Reinhart Heinrich Doctoral Thesis Award 2014, as well as for giving me the opportunity to present a summary of my thesis here.

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ECMTB 2014

Every fourth year there is a world cup in football. And every third year there is a European Conference on Mathematical and Theoretical Biology, ECMTB. Many of us let these meetings be milestones in our attempts to order the past and to plan for the future. At ECMTB you meet "the usual suspects" to continue your conversation from last time, but you also make new acquaintances and find out what new questions that are "hot" in a similar manner as new techniques and tactics are picked up by coaches at the football's world cup.

In the eighties, IFK Göteborg became the UEFA Champions twice, but last year Göteborg, or as it is internationally know as: Gothenburg, hosted the 9th ECMTB in June 15-19, 2014. It was a warm week with long sunny days and many parallell talks to navigate between. Prestigious prizes were awarded, books where displayed and important planned and spontantious meetings took place in every corner. There was a reception in the city hall and there were excursions one afternoon where hiking in the woods turned out to be the most popular activity, followed by the archipellago expedition. The was a General Assembly and we had a banquet with harring, snapps, dancing and strawberries. Finally, after the official closure of the conference, some stayed one extra day to more seriously celebrate midsummer eve with wreaths and Maypole-dancing in broad daylight.

So, what were the new trends at this meeting? This is always a subjective impression, but let me just come with one observation. While trying to schedule all the 271 contributed talks interfoliated with the 42 minisymposia in order to avoid as many scientific collisions as possible, it became very clear that cancer modeling, in all its shapes and expressions, is a highly active and vital field. For more details on the program, plese see ecmtb2014.org.

I would like to thank all of you who came to the ECMTB in Gothenburg last year and made the meeting so enjoyable and productive. See you already next summer in Nottingham!

Torbjörn Lundh

- 627 delegates
- 4 lunches
- 1 conference dinner
- 42 mini symposia
- 271 contributed talks
- 8 coffee breaks
- 1 midsummer celebration
- 19 hours of daily sunshine


ECMTB 2016
Nottingham
11-15 July 2016

The 4th Helsinki Summer School on Mathematical Ecology and Evolution

Dynamics of Infectious Diseases

Linnasmäki Congress Centre, Turku, Finland
17 – 24 August 2014

Director: Mats Gyllenberg
Department of Mathematics and Statistics, PO Box 68
FIN-00014 University of Helsinki, Finland
email: mats.gyllenberg@helsinki.fi

Contact: Eva Kisdi
Department of Mathematics and Statistics, PO Box 68
FIN-00014 University of Helsinki, Finland
email: eva.kisdi@helsinki.fi

Website: http://mathstat.helsinki.fi/research/biomath/summerschool2014/

Scientific programme
Lectures: The main part of the school consisted of five series of lectures, 7h long each, given by outstanding invited lecturers. These were the following:
* Odo Diekmann (University of Utrecht): Population dynamics of infectious diseases
* Frank Ball (University of Nottingham): Stochastic models of epidemics
* Thomas House (University of Warwick): Networks and epidemics
* Michel Langlais (University of Bordeaux): Spatial dynamics of infectious diseases
* Troy Day (Queen's University, Canada): Evolution of hosts and pathogens

Discussion groups: Each series of lectures was accompanied by a discussion group working on selected research papers. The students signed up to a discussion group in advance (max 10 students per group) and studied the corresponding working papers prior to the school. During the school, the students had in-depth discussions with each other and with the lecturer to clear all details and relate the working papers to the broad context of mathematical epidemiology. The time slots dedicated to these discussions are marked as "workgroup" in the attached programme (5h total, plus intense work also in free time). The groups reported back to the school by giving a ca 20 min presentation each on the last day, with a minimum of 3 presenters per group. The resulting presentations were of high quality and showed a very good understanding of the topics discussed.

Student self-introduction: To help people of similar interests to find each other and engage in informal discussions, Monday evening was reserved for the students to introduce themselves in a short presentation of their research. In addition, mini-posters presenting each student's work were displayed throughout the school.

Exam: The student participants were offered to take an exam in the form of take-home essays. Each course of the school had a separate essay topic, such that a student taking the exam is expected to write five short essays. The essays are submitted electronically and graded by the lecturers as pass/fail. Students who have passed at least 4 out of the 5 courses are awarded 8 ECTS credits by the University of Helsinki.

Results and impact

The school was an ideal opportunity to deepen the knowledge of the students in mathematical epidemiology, an important area of applied mathematics with high relevance to society. The students were at an impressively high scientific level, so that the school could achieve its aim of bringing the participants to the research frontiers. The one-week school was a period of very intense work both during the lectures and during the group discussions. The lectures were given by some of the most outstanding researchers of the field, and they have put very considerable effort into this school. As expected, the result was an outstanding scientific programme. The group discussions provided an efficient way of in-depth learning. In addition, the Reader gives all participants a timely and top-grade overview of mathematical epidemiology.

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 2015 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 includes:
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 2016 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*

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 2015*, 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 thesi

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Further information:
Prof. Frank Hilker, ESMTB treasurer
Institute of Environmental Systems Research
Osnabrück University
frank.hilker@uni-osnabrueck.de