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ESMTB
European Society for Mathematical and Theoretical Biology

Contents

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Letter from the President

Dear colleagues,

many of you will have received an email in which the following issues are discussed (if you haven't, please contact us at `info@esmtb.org`). However, since these issues are central to the work we have been doing, please let me restate the concepts and maybe enlarge a little bit in this issue of the Communications.

We are, I believe, at a turning point in the life of our Society. Biomathematics, theoretical biology, and theoretical (bio)medicine are assuming an ever increasing role in current scientific research and its application to societal issues. Besides the Society's traditional research themes (such as population dynamics or physiological modeling or stochastic processes in genetics), new developments are appearing at an ever faster pace: think of mathematical neuroscience, modeling for systems biology, or model-supported cardiac and orthopedic surgery. Time-honored pencil-and-paper, definition-theorem-proof approaches are being massively supplemented (not supplanted) by simulation and stochastic computation.

Our Society has the ambitious goal of representing this variety of endeavors, of competences and individual efforts in the European scene, which is where most of us naturally find ourselves operating. "Representing", however, is a big word. What is, really, the role of the Society? And how can we fulfill that role?

The main usefulness of a free professional association such as ours could be that it provides a forum to exchange opinions on the technical aspects of our work, as well as on the social and political issues that affect this work.

The technical exchange is well exemplified by ECMTB, our bi-annual conference. It is a good conference, in fact the reference event for mathematical biology in Europe, and is widely attended by researchers from all over the world, no problem there. Indeed, you are cordially invited to join us in ECMTB2020-Heidelberg in August/September 2020, where Anna Marciniak-Czochra will host us at the Mathematikon in a joint ESMTB-SMB event. We hope it will be even nicer than the already very nice ECMTB2018, when Maíra Aguiar hosted us at the Faculdade de Ciências of Lisbon University. Also, you may appreciate being notified of the upcoming workshops and summer schools our Society supports: if this is the case, send us an email and we will make sure you are on our mailing list. There are also other technical issues, which we have had as yet no time to address as they would deserve, for instance the formation of specific interest groups within ESMTB or the publication of white papers on particular topics of current interest.

The social and political issues are less clearly defined, but no less important.

One example is finding funds for our laboratories and departments. ESMTB is directly participating, for the first time, in a EU-funded call, with a COST proposal for a training network on cancer modeling. The funding that the Society would receive is not large, but the point is that we begin to be active in the fostering and facilitation of consortia formation to obtain research grants. The idea here is that ESMTB helps generating opportunities for the members and lends its credibility, as an established supra-national organization, to consortia aiming at European funding.

A second quite relevant socio-political issue is publishing research articles. We, as a professional association, must consider societal changes such as widespread and cost-effective Open Access, available without the imposition of de-facto limitations due to lack of resources in developing countries or niche scientific domains; such as the replacement of the traditional modality of reading (few) established journals front-to-back with the ad-hoc acquisition via Internet of the publications immediately relevant to the problem at hand, irrespective of the source; or such as the need for establishing qualitative standards for rigor and novelty in the current market-driven proliferation of titles and Editorial Boards, and explosive increase in published material.

Another important issue is the cross-

compatibility, exchange and improvement of post-graduate training in mathematical methods applied to biology and medicine: the interaction of mathematical and biological colleagues is better than in the past, but not quite as painless as we would hope; the recognition of interdisciplinary specialties is sorely lacking in the Universities of several European countries; the exchange of doctoral students could be greatly enhanced, with vast improvements in cross-fertilization among research units.

It is very likely that you have discussed these and other problems with your colleagues, and the point of the Society is to bring that discussion more effectively to a wider circle of researchers. To do that, our first priority in the past several months was the need to get reorganized: new banking, new member management software, new webpage, new legal address and updated administrative paperwork with the Authorities. And a new logo to top it off (do you like the range from continuous to discrete, going from the body to the wings of the butterfly? the dynamics in the shade?). We did a very substantial amount of work, of which our treasurer Bob Planqué carried the heaviest load.

Now, however, it is high time to go back from organizing the administrative machinery, and talk with you and with your colleagues (please feel free to diffuse this message to any of your colleagues who might be interested).

It would be interesting to see greater participation, both in terms of more new members, in terms of increasing the scientific diversity of the members, and in terms of improving the experience of involvement in Society activities of the existing members. Joining the Society now is rather painless: it is sufficient to go to www.esmtb.org → membership → application. Given the delay that has been necessary to effect all of the changes mentioned above, all who join or have already joined for 2019 will have a free membership renewal for 2020, valid for the several benefits including participation to ECMTB2020 Heidelberg at a discount.

But, why joining? What can ESMTB offer prospective members? We feel that the most important reason to join ESMTB is not the discounts on the registration for ECMTB and the many workshops, or the free electronic copy of JoMB. The main reason is to make a difference with our voice and our opinion in shaping the course that our professional association will follow, both scientifically and organizationally. The registration fee helps ESMTB recognize worthy students (through the prizes we offer and the workshops and schools we support) and spread the idea that theoretical biology and biomathematics are alive, well and relevant. With your participation in the General Assembly (G.A.) and by writing in the Newsletter and Communications you will expose inefficiencies, contradictions, wishful thinking and blind conservatism (please remember that soon after the 2020 G.A. all members will vote for the next Board). With your participation in the organization of the ESMTB seminars, workshops, summer schools and minisymposia you will push onto the stage the science you care about. And, best of all, you will meet other like-minded individuals all across Europe, old and young.

Please consider participating in those ESMTB initiatives that are relevant for you and your team. You may ask questions from or make proposals to any one of the current Board members, just write them an email: Susanne and Sílvia for communications and outreach, Luděk for student initiatives, Anna for Heidelberg2020, Sílvia for the newsletter, Toby for prizes and European policies and funding. If you want money, just ask Bob. If anything else comes to your mind, write Ellen, Maíra or myself.

Hope to hear from you,

Andrea De Gaetano
President of ESMTB

The Reinhart-Heinrich Doctoral Thesis Award 2018

The winner of the ESMTB Reinhart-Heinrich Doctoral Thesis Award for 2018 is Computer Science graduate Daniel Nichol, for his thesis **Understanding drug resistance through computational models of the genotype-phenotype mapping**. The award will be formally given in a ceremony at the ECMTB conference in Heidelberg in 2020. The awarding committee made the following statement: *Daniel Nichols thesis is likely to become a landmark in an issue of critical significance. It studies and proposes strategies to deal with drug resistance in the treatment of cancers and infectious diseases taking into account the genotype-phenotype mapping. New mathematical models are used to better understand the underlying mapping mechanisms, integrating genetics, environmental signals and stochasticity. The thesis gave rise to three papers already published in highly prestigious journals and to a few more papers under publication.* Dr Nichol completed his DPhil at University College Oxford. His supervisors were Peter Jeavons (Oxford, Computer Science) and Alexander R. A. Anderson (Moffitt, Integrated Mathematical Oncology). We congratulate him for his excellent and exciting work! First, he presents himself, and then follows an extended abstract of the thesis.

Daniel Nichol Personal statement

To predict this evolution we must first understand how genetic mutations are manifest as phenotypic change, and how these phenotypes are selected by druginduced environmental change. Studying this 'genotype-phenotype mapping' lies at the heart of my DPhil studies and my later modelling work as a postdoctoral training fellow in the Centre for Evolution and Cancer at the Institute of Cancer Research, London. I believe that it is only through an interdisciplinary approach combining modelling, large scale genomics, and experimental evolution that the evolution of drug resistance can be fully understood. Ultimately, if we can better predict the evolution and ecology of cancers, then we may be able to design better therapies by exploiting evolutionary trade-offs. The research I have undertaken in my DPhil was the first step towards this goal.

Thesis summary: 'Understanding drug resistance through computational models of the genotype-phenotype mapping' by Daniel Nichol

The emergence of drug resistance is ultimately driven by Darwinian evolution. These evolutionary dynamics are inherently two-tiered, with mutational processes at the genetic scale inducing variation in cellular phenotypes that are subject to natural selection. If we are to predict or reverse evolution, as we must to determine effective treatments for drug-resistant infections and cancers, then we must first understand the relationship between genetic and phenotypic change. This relationship, known as the genotype-phenotype (GP) mapping, is governed by a complex cascade of potentially stochastic molecular interactions that integrate genetic, epigenetic and environmental factors to determine cellular phenotype. In this thesis, we introduce mathematical models of the GP-mapping to explore how its structure influences the evolution of drug resistance, and how it determines the efficacy of novel therapeutic strategies such as drug holidays or adaptive therapy.

We begin by providing a comprehensive review of previous abstract modelling of the GP-mapping. Second, we demonstrate that models of GP-mappings can improve evolutionary predictions. Specifically, we show that through careful selection of drug sequences evolution could be 'steered' such that a highly drug resistant population does not emerge. Third, we introduce a novel model for

the GP-mapping wherein phenotypes arise stochastically. Through this model we explore the evolutionary dynamics of ecological 'bet-hedging', a common driver of drug resistance. We find that the structure of the GP-mapping can slow the evolutionary loss of this trait, preserving the survival mechanism when harsh environments occur very infrequently. Thus, the capacity to steer the evolutionary loss of bet-hedging is dependent on the structure of the GP-mapping. We next extend the bet-hedging model to account for epigenetic inheritance and the potential for phenotypic memory. Critically, we find that genetics, epigenetics and the GP-mapping interact non-additively to determine organismal fitness, indicating that evolution likely cannot be predicted without accounting for each of these biological processes. Finally, we explore how properties of the GP-mapping are manifested at the population scale and suggest experimental approaches to identify bet-hedging through population scale assays. The implications of our results for the treatment of drug-resistant diseases are explored throughout. Here, we provide an extended summary of the contents of the full thesis.

Introduction and Overview

The evolution of drug resistance represents a growing health crisis in the treatment of infectious diseases that necessitates immediate intervention. Similarly in the treatment of cancers, evolved secondary drug resistance is common, ultimately driving mortality. In both cases the same underlying evolutionary dynamics are at work. Therapeutic intervention induces strong selection pressures on a phenotypically heterogeneous population, driving the emergence of a resistant population and ultimately the relapse of refractory disease [1]. Evolutionary therapy aims to mitigate this process through timed interventions with alternative drugs, or breaks from drugs, informed by mathematical modelling. Critically, the success of this approach is dependent on our ability to predict evolution, and in particular, to predict when and how resistant phenotypes will emerge [2].

Phenotypic heterogeneity is often thought of as arising from rare, random mutations. However, isogenic populations can also generate phenotypically heterogeneous populations, either through stochastic cell-fate determination (bet-hedging), or through modulation driven by environmental cues (phenotypic plasticity). The relationship between genetics, environment and phenotype is encapsulated in the classical concept of the genotype-phenotype (GP) mapping which has been explored in numerous biological subfields [3]. Here, we propose that understanding the GP-mappings that underpin drug resistance will lead to better evolutionary predictions, and thus better therapy. To this end, we set out to derive GP-mapping models of the drivers of drug resistance, to explore their implication for evolutionary therapy, and ultimately derive conditions under which the drivers of adaptive phenotypic heterogeneity can be identified and potentially mitigated.

Aims: The aims of this thesis are three fold: First, to unify previous mathematical modelling of the GP-mapping in order to identify those sources of phenotypic heterogeneity that have been under-studied with respect to the evolution of drug resistance; second, to implement new models of the GP-mapping that account for these sources of phenotypic heterogeneity; and third, to demonstrate that coupling models of the GP-mapping with previous models of population dynamics can improve evolutionary predictions. This third aim is tackled three times with increasingly complex GP-mappings, each time starting from an abstraction of evolution and building theory towards experimentally testable predictions.

Experimental validation: This work was completed in close collaboration with experimentalists at the Moffitt Cancer Center (Tampa, FL), the Cleveland Clinic (Cleveland, OH), and Case Western Reverse University (CWRU) (Cleveland, OH). These collaborations helped to ensure that throughout the thesis we always worked toward generating experimentally verifiable hypotheses. Owing to time constraints, experimental results were not complete before these thesis was submitted but have since validated a number of theoretical predictions and been published. Where appropriate

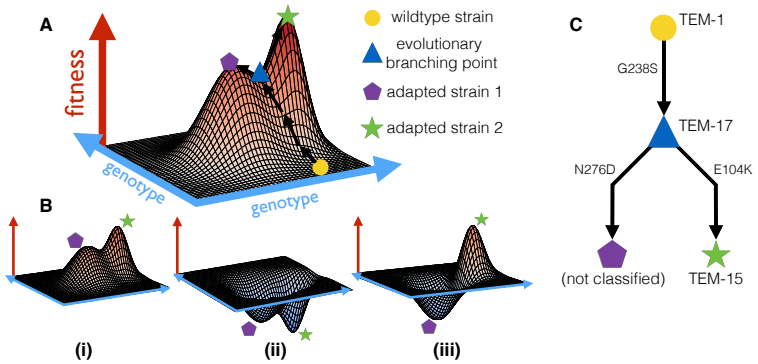

Figure 1: **Collateral sensitivity need not be repeatable. A)** Evolution from a wild–type genotype (yellow circle) need not be repeatable owing to the potential of branching points in the fitness landscape (blue triangle). **B)** Patterns of collateral response that can arise from evolutionary divergence: **i)** guaranteed cross–resistance, **ii)** guaranteed collateral sensitivity, **iii)** collateral response determined by which evolutionary trajectory occurs. **C)** A model predicted evolutionary branching point in the TEM gene under the antibiotic cefotaxime [10].

these validation experiments are highlighted below.

GP-mappings and Phenotypic Heterogeneity

The genotype-phenotype (GP) mapping is central to successful predictions of evolution. With the advent of single-cell sequencing it becoming clear that whilst mutations often drive phenotypic diversity, monoclonal cells exhibit phenotypic heterogeneity. Deconvolving the drivers of this heterogeneity is a difficult task, owing to the overwhelming complexity of intra-cellular signalling cascades. Mathematical models provide a means to understand this complex process, just as modelling has helped elucidate other complex ecological and evolutionary systems. Models of the GP-mapping arise many biological fields, often with recurrent properties, permitting us to gain intuition for one system from the study of another. For example, in attempting to understand drug resistance, studies of RNA secondary structure provide insight into the role of neutral mutations and studies in plant biology provide mathematical formulations of the 'reaction norm' governing phenotypic plasticity. The mathematical basis of these results is independent of the specific domains in which they were derived. We present a unification of GP-mapping results under a common framework through which evolutionary questions can be interpreted beyond the fields in which they originally arose. Our survey highlights aspects of the GP-mapping that are under-studied evolutionary medicine; namely bet-hedging which forms the basis of the much of this thesis.

Predicting Evolution from GP-mappings

The central tenet of our work is that models GP-mappings can improve evolutionary prediction. To demonstrate this fact we began by exploring the simplest GP-mapping - the fitness landscape. By consideration evolution under the constraints of a fitness landscape, we showed that drug ordering determines the degree of resistance that arises. We utilised empirically-derived fitness landscapes for *E. coli* to provide evidence that rational drug sequencing can partially mitigate resistance, whereas arbitrary sequencing may promote it [4]. Absent clinical guidelines regarding drug sequencing we argue that current practice may promote drug resistance just as irresponsible dosing can.

Our modelling suggests that evolution may be predictable but not necessarily repeatable (Figure 1). Evolution need not arise in the same way in independent instances, but evo-

lutionary trajectories can be sufficiently constrained for predictions to be made. An immediate consequence of this observation is that predictions of collateral sensitivity made using low-replicate-number evolutionary experiments may have overstated therapeutic benefit; predicting a collaterally sensitive response where cross resistance can occur. As such, we introduce the concept of *collateral sensitivity likelihoods* as a metric to account for stochasticity in the evolution of drug resistance. Following the submission of the thesis, this non-repeatability was confirmed through high-replicate experimental evolution coupled with targeted whole-genome sequencing [5]. These results have motivated changes in our own experimental evolution protocols undertaken in collaboration with microbiologists at CWRU, Ohio. We anticipate they will also impact how others will undertake experimental evolution studies in future.

Non-genetic Heterogeneity and the Evolution of Bet-Hedging

Resistant phenotypes can arise stochastically within an isogenic population. A clinically important example is the emergence of drug-tolerant bacterial 'persister cells' that allow bacterial populations to survive antibiotic therapy before outgrowing to re-establish a pathogenic population [6]. In our review of GP-mappings we identified that this phenomenon is under-represented in theoretical models. Inspired by the milieu of intracellular chemical reactions that govern cellular phenotypes, we implemented a new model of bet-hedging using stochastic chemical reaction network models previously studied in the context of biological computing [7] (Figure 3). Specifically, we modelled phenotypes as determined by the stochastic simulation of a bistable switch with genetically determined initial conditions [8].

Mathematical studies have demonstrated that bet-hedging can be selectively advantageous in stochastically fluctuating environments but can incur a fitness cost in fixed environments. This represents an apparent paradox of bet-hedging: how can bet-hedging persist over long time-scales in environments where natural selection acts to remove it? We performed invasion analysis to demonstrate that the structure of the GP-mapping itself can act to slow the evolutionary loss of bet-hedging by inducing diminishing fitness benefit in successive mutations towards a one-phenotype strategy. This result is not solely an interesting evolutionary result, but has profound impact for evolutionary therapies targeting diseases with bet-hedging-driven resistance mechanisms. Through agent based modelling of populations subject to drug holidays, we demonstrated that where evolutionary loss is fast, treatment holidays may induce increased susceptibility to drugs targeting proliferative cells, whereas where evolutionary loss is slow, this strategy is likely to fail. Thus, we argue that understanding of the precise molecular drivers of bet-hedging may hold the key to predicting and reversing some important forms of drug resistance.

Non-genetic Inheritance and Evolution of Phenotypic Memory

Previous models of bet-hedging assume that offspring are assigned a phenotype with a fixed probability. Often, this probability is taken as dependent on the parent cell phenotype, which represents a type of stochastic inheritance or 'memory'. We set out to explore how this memory may arise and whether it impacts the evolutionary fate of a bet-hedging population. We first extended the bistable switch model by introducing the epigenetic inheritance of the intracellular factors that comprise the switch. These inherited molecules interact with the genetically-determined initial 'burst' of expression to bias the switching behaviour (Figure 3). Once the switching has occurred, the molecules are modelled as subject to decay throughout the life of the cell, in turn determining the number inherited epigenetically at the next reproduction event. This mode of epigenetic inheritance is observed in human cell lines where the relative abundance of epigenetically inherited stress protein (p53) and mitogen (CCND1) determine cell-cycle arrest or proliferation [9].

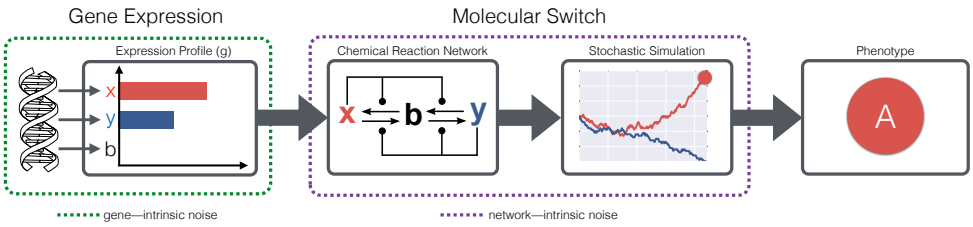

Figure 2: **The chemical reaction network model for bet-hedging.** Gene expression profiles are assumed to be fixed for each genotype and serve as initial conditions for the stochastic simulation of a bistable chemical reaction network (purple box) that determine cellular phenotype.

We next derived a multi-scale model that approximates the stochastic growth dynamics of a population endowed with bet-hedging with memory. We explored the selective advantage of memory and whether the evolution of memory and bet-hedging might be predictable. Surprisingly, we found that memory is not universally beneficial and that the sign of the fitness contribution is dependent on both the associated GP-mapping and the genetic configuration of the population. This phenomenon mirrors sign epistasis in population genetics, wherein a mutation can be either beneficial or deleterious dependent on the genetic background in which it occurs. Thus, mirroring our results for fitness landscapes, we find a rugged landscape of bet-hedging mechanisms on which the evolution of bet-hedging need not be repeatable. We infer that knowledge of both genetic and epigenetic inheritance, along with the GP-mapping, is required to make successful evolutionary predictions. To conclude this chapter, we explored the impact of bet-hedging and memory on the efficacy of evolutionary therapies. Critically, we found that despite the difficulty in making evolutionary predictions, therapy can be partially optimised in a mechanism-agnostic way; namely through optimised timing of a metronomic dose that maximises the killing of proliferative cells whilst minimising toxicity.

GP-Mappings at the Population Scale

Throughout our modelling we identified the common theme that successful evolutionary predictions are likely to be predicated on knowledge of the underlying GP-mapping. Unfortunately, where stochasticity drives phenotypic heterogeneity through bet-hedging, this mapping is believed to comprise complex molecular pathways that are difficult to characterise. With this issue in mind, we conclude the thesis by identifying population-scale manifestations of the GP-mappings that can be identified with presently available experimental assays. Specifically, through simulations we identified the phenotype distributions and spectra of mutational frequencies arising from populations endowed with bet-hedging and mutation driven resistance. These models are employed to undertake two case studies: first, we identify memory in bet-hedging as a possible explanation of persister-cells that expand in frequency in confluent populations; and second, we develop a means to detect bet-hedging-driven resistance from matched pre- and post- therapy bulk whole-genome sequencing.

Conclusions

The aim of this thesis was to explore the extent to which evolution can be predicted to optimise evolutionarily-informed therapies. Our work began with the observation that understanding the drivers of phenotypic heterogeneity is key to successful prediction. Through a survey of GP-mapping studies we identified bet-hedging as an under-studied driver of resistance. With this in mind, we first used the fitness landscape model to demonstrate how model GP-mappings can improve evolutionary predictions. Second, we introduced a new model of bet-hedging and demonstrated that the evolutionary dynamics of bet-hedging are closely linked to the specific

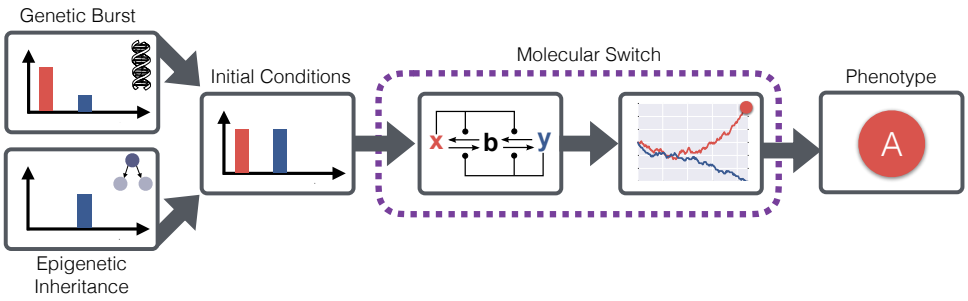

Figure 3: **The extended chemical reaction network model for bet-hedging with memory.** Following division, daughter cells inherit a number of molecules determined by the parental cell age. These molecules are combined with a fixed gene expression profile (genotype) and serve as initial conditions for the bistable chemical reaction network model of the GP–mapping. The inheritance of molecules from the parent cell biases the switch towards the phenotype of the parent, inducing phenotypic memory.

mechanisms through which it arises. Third, we extended our bet-hedging model to account for phenotypic memory, demonstrating that the selective advantage of memory is contingent on the precise machinery of bet-hedging. These findings indicate that the evolution of bet-hedging need not be repeatable, and thus that successful evolutionary predictions will depend on characterisation of both the modes of inheritance and the precise molecular switching. Finally, we undertook two model-driven case studies to demonstrate how the properties of bet-hedging can be identified at the population scale. We anticipate that studies such as these represent the first step towards developing the necessary model systems through which GP-mappings can be studied. Throughout this thesis we have employed abstract models as a means to generate biological hypotheses, but have done so with pragmatic goals; namely, how can evolutionary therapy be improved?

References

[1] Greaves, M. and Maley, C. C. Clonal evolution in cancer. Nature, 481(7381):306–313, 2012.

[2] Gatenby, R. A., Silva, A. S., Gillies, R. J., and Frieden, B. R. Adaptive therapy. Cancer Research, 69(11):4894–4903, 2009.

[3] Pigliucci, M. Genotype–phenotype mapping and the end of the genes as blueprint metaphor. Philosophical Transactions of the Royal Society B: Biological Sciences, 365(1540):557–566, 2010.

[4] Nichol, D., Jeavons, P., Fletcher, A. G., Bonomo, R. A., Maini, P. K., Paul, J. L., Gatenby, R. A., Anderson, A. R., and Scott, J. G. Steering evolution with sequential therapy to prevent the emergence of bacterial antibiotic resistance. PLoS Computational Biology, 11(9):e1004493, 2015.

[5] Nichol, D., Rutter, J., Bryant, C., Hujer, A. M., Lek, S., Adams, M. D., Jeavons, P., Anderson, A. R., Bonomo, R. A., and Scott, J. G. Antibiotic collateral sensitivity is contingent on the repeatability of evolution. Nature Communications, 10(1):334, 2019.

[6] Lewis, K. Persister cells, dormancy and infectious disease. Nature Reviews Microbiology, 5(1):48–56, 2006.

[7] Cardelli, L. and Csikász-Nagy, A. The cell cycle switch computes approximate majority. Scientific Reports, 2:656, 2012.

[8] Nichol, D., Robertson-Tessi, M., Jeavons, P., and Anderson, A. R. Stochasticity in the genotype-phenotype map: Implications for the robustness and persistence of bet-hedging. Genetics, 204(4):1523–1539, 2016.

[9] Yang, H. W., Chung, M., Kudo, T., and Meyer, T. Competing memories of mitogen and p53 signalling control cell-cycle entry. Nature, 549(7672):404, 2017.

[10] Mira, Portia M and Crona, Kristina and Greene, Devin and Meza, Juan C and Sturmfels, Bernd and Barlow, Miriam Rational design of antibiotic treatment plans: a treatment strategy for managing evolution and reversing resistance PloS one,10(5):e0122283.

Reports from 2018 travel grant awardees, supported by an ESMTB travel grant

ESMTB Travel Support

The ESMTB provides travel support to mathematical/theoretical biology events such as meetings, conferences, workshops or schools. Support is provided only to ESMTB members, so that an applicant needs to be an ESMTB member at the moment of submitting the application. The maximum amount of travel support provided by the ESMTB per single application is currently set to 350 euro. However, funding will in most cases be only partial, in order to support a greater number of applicants. In general, preference will be given to:

- applicants who have been members of the ESMTB for a longer time,
- doctoral students and post-docs, but graduate students and senior scientists may also apply,
- applicants who present a paper or poster at the attended event,
- applicants who did not receive travel support from the ESMTB before,
- applicants in conditions of economic hardship.

Details and the application form are available at `https://www.esmtb.org/Travel-Support`

In 2018, 20 travel grants were awarded, with total support of 4610 EUR. Most applications concerned participation at the ECMTB2018 conference in Lisbon, followed by the ESM-ESMTB Summer School on Mathematical Ecology and Evolution 2018 in Turku.

The awardees are asked to write a brief report about the event. Here we present some of the reports the awardees sent to us upon returning from the event they were attending. The original reports are slightly edited and shortened yet their spirit remains unchanged.

Report by Aurélien Velleret on the ESM-ESMTB Summer School on Mathematical Ecology and Evolution 2018, Turku

This school was one of the best opportunities for me to advance in my future career. It was quite dense but very well organized. The conditions were optimal for us to learn a lot and exchange between the students and the teachers in a very friendly and open manner. The fact that we were all staying for the week in this rather remote place – with a nice forest nearby – contributed much to this atmosphere. Indeed, I liked much the informal meetings during lunches, dinners or in the evenings (more than the breaks where I rather wanted some rest). The expeditions at Turku and the experience of sauna were also great and made me feel at ease in the group, leading to easier interactions (probably also in the future!). The lessons were of great quality and variety. Since I consider these methods and topics as potential future area of research, it was a wonderful opportunity to consolidate my knowledge.

Among all presented courses, the Sebastian Schreibers course was probably the one I expected the most, since it dealt with these issues of maintenance of ecological diversity in the context of a (usually random) changing environment. In fact, my PhD deals with the survival of populations submitted to a risk of extinction given a change of the environment and the stochastic emergence of new fixed mutations in the population. So there is clearly some insight that I could have through the models he presented, notably on this notion of a species being able to invade a stochastic dynamics with possibly many others. Even after my PhD, I would really enjoy to work on more carefully on these subjects, possibly wondering about an extinction of a species not completely excluded and yet a priori very exceptional.

I was also very glad we could have an opportunity to work between the students on articles related to one of the course and present at the end some conclusions to the other groups. Quite naturally, Ive chosen Schreibers group and the

articles were very interesting (in fact, we chose to focus only on one of the two for the presentation). I must say I was probably the most familiar with the probabilistic notions presented (branching processes, generating functions), so that I was often in charge of explaining them. Yet, there was a real dynamics of group and we were left very autonomous on the way we managed the job, with of course the support of Sebastian Schreiber to deal with our difficulties in understanding. It was a great experience and a very nice way to interact with the other members of my group.

Finally, the short presentation of each students, done in the two first evenings, was a useful way to present ourselves to the others and present our main subject of interest for following discussions. As we were quite numerous (above 30), it was indeed quite dense and I was glad it was at least split in two evenings. In conclusion, I highly appreciated the contents I studied thanks to this Summer School and the wonderful conditions we were in!

Report by Sara Hamis on the "Mathematical perspectives in the biology and therapeutics of cancer" workshop at CIRM, Marseille The workshop brought together mathematicians, clinicians and biologists, comprised a symposium, a series of invited and contributed talks and posters, the majority of which investigated aspects of cancer mathematically. An impressive array of invited speakers from well-renowned cancer research institutes and universities shared their expertise to a highly interested audience. Multiple cancer-related concepts of clinical importance were discussed, such as tumour growth, intratumoural heterogeneity, angiogenesis, drug resistance, treatment responses and treatment optimisation. In an effort to portray these cancer aspects sensibly using mathematics, several mathematical modelling techniques were proposed. Mechanistic and phenomenological, discrete and continuous, deterministic and probabilistic models were all presented and motivated. Mathematically, problems were solved both analytically and numerically and cancer was investigated, on various scales, ranging from macroscopic population scales down to patient, tumour, cell and subcellular scales. Overall, the great variety mathematical techniques to investigate various cancer issues provided a nice up-to-date overview of what fellow researchers are working on right now.

In addition to mathematical presentations, more biology-centered talks were presented by clinicians and biologists, providing us mathematicians with useful insights. These talks instigated well-needed discussions attempting to answer the questions (1) What can we (mathematicians) do to help clinicians/scientists advance cancer research and clinical protocols? (2) What information do we (mathematicians) need from clinicians/scientists in order to progress mathematical oncology?

Furthermore, in the spirit of interdisciplinary collaborations, a fruitful symposium was held on Wednesday morning. Speaking at the symposium were people from French cancer research institutes including Christine Chomienne, the director of ITMO Cancer Aviesan and Research and Innovation department INCA. We (the audience) received useful advice on how to establish successful collaborations with clinicians/scientists, and how to formulate prosperous grant applications. Personally, as a young researcher who wishes to continue in the field of mathematical oncology, I found this symposium to be highly interesting and important as it provided useful information on how to achieve successful research (beyond mathematical aspects).

To summarise the scientific content of this workshop in three words, it was interdisciplinary, well-delivered and current. I enjoyed every single talk and poster. In addition to learning from other peoples presentations, I was gratefully given the opportunity to present my research on modelling effects of hypoxia-activated prodrugs (talk) and chemotherapeutic drug resistance (poster). Presenting my work in front of an audience of experts (most of whom I have cited) was a humbling and exciting experience. Scientific content aside, the workshop was fantastically well-organised, fun and friendly. The conference center and the geographical lo-

cation is absolutely gorgeous, and an unforgettable hike in the Calanques was arranged for adventurous conference participants. I would highly recommend fellow young researchers in the field of mathematical oncology to attend any upcoming similar events.

Finally, I would like to add that I am very thankful to the workshop organisers for accommodation funds and to ESMTB for the travel grant. Without the support I could not have attended this workshop.

Participants of the "Mathematical perspectives in the biology and therapeutics of cancer" workshop organized at CIRM, Marseille

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Report by Tatjana Jakushina on the Lisbon ECMTB2018 conference The 11th European Conference on Mathematical and Theoretical Biology (ECMTB 2018) was one of the most important events related to the Year of Mathematical Biology 2018. The organization of the conference and the quality and diversity of presented researches was very impressive. This event gathered around 700 participants from 60 countries, including both influential scientists and young specialists. It was an invaluable experience to attend such a broad range of sessions and have an opportunity to discuss the most relevant problems in mathematical biology.

The conference program included nine plenary talks, one of which was the BS-EMS Lecture by Samuel Kou. Among other impressive lectures, I found the talk Models of learning and evolution: what do they have in common? by Eors Szathmaary one of the most inspiring. In this presentation, three main questions shedding light on the relation between evolution and learning processes were discussed. First, whether true evolutionary dynamics can unfold in the brain. Second, whether associative, reinforcement and deep learning dynamics could play a role in the evolution of ecosystems, developmental genetic regulatory networks and evolutionary transitions in individuality. Third, whether similar algorithms could realize either of them in some natural systems. This talk was thought-provoking, providing many ideas for further research in artificial evolution and multilevel selection.

Another plenary speaker that I want to mention specifically was Eva Kisdi with a talk Adaptive dynamics and the evolution of diversity. This presentation was dedicated to an important approach in evolutionary theory and its possibility to explain the enormous diversity of living forms. That lead to a series of problems: the existence of the upper bound to the number of species, the possibility of natural selection to lead to extinction, and the difference between variation and speciation.

More than 400 contributed talks were arranged in parallel and contributed sessions and minisymposia, covering a wide range of cutting-edge topics. I attended talks in Evolutionary Dynamics, Mathematical methods in Biology, and Population Biology sessions, prioritizing the fields that are relevant to my current projects. Moreover, I still address the conference materials for useful references. A series of results on replicator equations, host-parasite dynamics, and spatially distributed populations was especially interesting. Many different techniques represented the spatial evolution problem: Wright island models, static and random graphs for replicator dynamics, Wright-Fisher diffusions. New modeling frameworks were suggested, such as numerical simulations of nonlocal agent-based models can be combined with the analysis of corresponding continuum models or spatially explicit 3D-individual-based models. One minisymposium dealt with the dynamical behavior of systems of ordinary differential equations arising from chemical reaction net-

works. In particular, the authors investigated the boundaries and general techniques to find first integrals and conservative oscillations.

This conference provided fantastic networking opportunities due to its social program and an extensive poster session. I found this experience has improved my presentation skills and more importantly, my confidence in the current project.

Report by Sophie Meakin on the 10th Summer Institute in Statistics and Modeling in Infectious Diseases (SISMID), University of Washington, Seattle The school offered fifteen 2.5 day courses in a range of methods of statistical analysis and modern modelling techniques. ESMTB kindly awarded me a travel grant to help cover the expenses of the summer school; I was also awarded a scholarship from the Department of Biostatistics at the University of Washington. I elected to take courses on Markov chain Monte Carlo methods, integrating novel data streams into epidemiology, and contact network epidemiology.

The first course I attended was an introduction to Markov chain Monte Carlo (MCMC) methods for infectious diseases, taught by Elizabeth Halloran, Vladimir Minin and Kari Auranen. MCMC is widely used in epidemiological modelling research and thus an important technique to be able to understand and apply. I took this course specifically to learn how to implement MCMC for parameter estimation and data augmentation. The course covered both the theory behind MCMC methods and computer sessions implementing various results in R. This latter part of the course was particularly useful, especially being able to discuss the practical choice of the sampling distribution and convergence with the module leaders. I will use the methods in my research in modelling emerging infectious diseases to estimate key epidemiological parameters.

The second course I attended covered topics in modelling with novel data streams, such as Google trends and Twitter, into epidemiological modelling. The course was led by Mauricio Santillana, Alessandro Vespignani and Elaine Nsoesie. I took this course primarily to learn a new approach to epidemic modelling, as well as to understand the challenges and limitations of using online data. The course covered a wide range of topics, including: accurate estimation of current disease incidence using data from Google trends and Twitter; using the Global Epidemic and Mobility Model (GLEAM), a worldwide metapopulation model for infectious diseases that draws together real-world population and mobility data; and practical web-scraping methods to collect Twitter, Amazon and Yelp data. I was especially interested to learn how to use GLEAM as it ties in well with my own research and will be a very useful tool. In addition, I have learnt a range of practical methods such as data management using Python's Pandas library.

The final course I attended was on contact network epidemiology, led by Joel Miller and Thomas Hladish. Contact networks are one modelling paradigm used to describe the mixing patterns of a population: nodes represent individuals and edges between nodes represent disease-transmitting interactions. The course was a balance of both analytic and computational methods in network epidemiology, for example: deriving analytic epidemiological models on contact networks; finding closed-form expressions for the basic reproduction number and final size distribution for these models; an introduction to NetworkX, a Python library that can be used to simulate epidemics on networks. I found all aspects of this course both interesting and relevant: my own research is currently focussed on metapopulation models (networks where nodes are populations rather than individuals), but I found that many of the analytic methods for contact networks could be translated to think about metapopulation models, which has given me ideas how to approach some challenges I am facing in my own research.

Overall, my experience at SISMID was fantastic: I learnt a lot of new statistical and mathematical methods that will be very useful in the rest of my PhD, and met many wonderful people (staff and fellow students) who I look forward to meeting at future conferences.

ECMTB 2020

The **12$^{\text{th}}$ European Conference on Mathematical and Theoretical Biology (ECMTB 2020)** will be held in **Heidelberg, Germany, from 31$^{\text{st}}$ August to 4$^{\text{th}}$ September 2020**. The conference will be hosted at Heidelberg University, in the campus located in the old town: Neue Universitt, Universittsplatz 1, 69117 Heidelberg. This will be a joint event between the European Society for Mathematical and Theoretical Biology (ESMTB) and the Society for Mathematical Biology (SMB).

We invite all researchers and students interested in mathematical and computational biology to join us on this exciting scientific event! Applications for Minisymposia, Contributed Talks and Posters will be open soon on the Conference webpage `http://www.ecmtb2020.org`.

To stay updated on the latest news on the ECMTB 2020, follow us at

`https://www.facebook.com/ecmtb2020/`

Looking forward to seeing you in Heidelberg,

Anna Marciniak-Czochra
(on behalf of the Organising Committee)

ESMTB
European Society for Mathematical and Theoretical Biology

Report from the 11th European Conference on Mathematical and Theoretical Biology (ECMTB 2018) July 23-27, 2018, Lisbon, Portugal

By Maíra Aguiar, Carlos Braumann, Nico Stollenwerk (Conference Chairs)

Biomathematics is a fast growing subject in Europe and to celebrate the importance of applications of mathematics to biology and life sciences, the Year of Mathematical Biology 2018 (YMB) was declared, a joint initiative of the European Mathematical Society (EMS) and the European Society for Mathematical and Theoretical Biology (ESMTB). With many events organized, including thematic programs and conferences and workshops, the **11th European Conference on Mathematical and Theoretical Biology (ECMTB 2018)** (`http://www.ecmtb2018.org`) was the main event of the YMB.

Traditionally organized by the ESMTB, the ECMTB 2018 was this time (and for the first time) also organized by the EMS, having the Portuguese Mathematical Society (SPM) as co-organizer. The conference venue was the Faculty of Sciences of the University of Lisbon, in Portugal (FCUL), hosted by its research centre, Centro de Matemática, Aplicações Fundamentais e Investigação Operacional (CMAFcIO - Centre for Mathematics, Fundamental Applications and Operational Research). The ECMTB 2018 had the patronage of His Excellency the President of the Republic of Portugal and was granted the UNESCO seal by the National UNESCO Committee. Besides the sponsorship of the three organizing societies, it has been sponsored by several Portuguese research centres (CMAFcIO, CMA, CIMA, CEAUL) and the Portuguese Foundation for Science and Technology (FCT), Instituto Gulbenkian de Ciência, international publishers (Springer, MDPI, PLOS One, Elsevier, EMS-PH, IOP Publishing. Oxford University Press, Wiley), the Bernoulli Society, the Portuguese Statistical Society, the Centro Internacional de Matemtica and other organizations and companies.

From July 23 (July 22 for those attending the early registration and cocktail welcoming party) to July 27, the city of Lisbon (Portugal) welcomed the more than seven hundred participants from 80 countries with a pleasant weather (it was cooler than the usual hot weather typical of this time of the year, a blessing for participants from Central and Northern Europe com-

ing from unusually high temperatures in their home countries). The record number of participants (only beaten by joint ESMTB-SMB Conferences) is a sure sign of the growing importance of Mathematical Biology.

After the opening ceremony, there was a Tribute to Karl Peter Hadeler by **Odo Diekmann**, immediately followed by the opening plenary conference, a Bernoulli Society-European Mathematical Society Joint Lecture, by **Samuel Kou** (Harvard University, USA), on the exciting topic of "Big data, Google and disease detection: A statistical adventure". The other plenary conferences were on equally exciting topics and were given by the eminent scientists **Helen Byrne** (Oxford University, UK, "Mathematical approaches to modelling and remodelling biological tissues"), **Antonio DeSimone** (SISSA, Italy, Biological and bio-inspired motility at microscopic scales: locomotion by shape control), **Eva Kisdi** (University of Helsinlki, Finland, "Adaptive dynamics and the evolution of diversity"), **Mirjam Kretzschmar** (University Medical Centre Utrecht, The Netherlands, "Modelling the waning and boosting of immunity"), **Eva Löcherbach** (Cergy-Pontoise University, France, "Modeling interacting networks of neurons as processes with variable length"), **Andrea Pugliese** (University of Trento, Italy, "Epidemic models structured by parasite load and immune level"), **Eörs Szathmáry** (Eötvös Loránd University, Hungary, "Models of learning and evolution: what do they have in common?") and **Kees Weijer** (University of Dundee, UK, "Analysis of collective cell behaviours underlying primitive streak formation in the chick embryo"). One of the recent winners of the Reinhart Heinrich Best Ph. D. Thesis Award, **Jochen Kursawe**, was able to come and give the traditional winner talk on "Quantitative approaches to investigating epithelial morphogenesis".

ECMTB 2018 had also a very rich programme of 36 cutting-edge Mini-symposia, 60 Contributed Talk parallel sessions and 2 Poster sessions (in a nice get together coffee +cocktail break), totalling 455 oral communications and 119 posters covering all areas of Mathematical and Theoretical Biology. There were 4 poster prizes given by a jury and sponsored by publishers (Elsevier, MDPI, Springer). The reader can take a look at the Programme (`http://www.ecmtb2018.org/files/files/ecmtb_booklet_a4.pdf` or the short version `http://www.ecmtb2018.org/ActMap`) and the Book of Abstracts with ISBN: `http://www.ecmtb2018.org/files/files/BookOfAbstracts_ECMTB2018_inclusions.pdf`.

Moreover, the ECMTB Mentorship Programme was set up to facilitate research and career interactions between junior and more senior scientists attending the meeting.

The General Assembly of the ESMTB took place on July 26 and it was opened to members and non-members of the Society. Several issues

concerning the working of the ESMTB and the development of Mathematical and Theoretical Biology were discussed, followed by further discussions over a wine tasting event.

The social programme provided ample opportunities for scientific exchange and personal contacts. Besides the already mentioned social activities and the coffee and the lunch breaks, there were excursions and a conference dinner that started with a Tuna (which is a not a fish, but a typical Portuguese University playing and singing student group) and was followed by dancing.

The ESMTB, to celebrate the Year of Mathematical Biology 2018 and wishing to extend its membership to other researchers in the area, invited every participant registered for the ECMTB 2018, that was not yet an ESMTB member, to become a member. The Society welcomes those accepting such invitation by exempting them of the first year membership fee. Note that the invitation is still standing (see detailed information on `http://dev.ecmtb2018.org/RegRules`).

On behalf of the Organizing Committee, we thank the organizing societies for their trust, the Scientific Committee, the sponsors, the plenary speakers, the organizers of the Minisymposia, the session chairs, the mentors and mentees, the jury of the poster prizes, the student helpers and the hard-working and skilful members of the Secretariat (Ana Rita Ferrer, Ana Isabel Figueiredo, Joana Guia). We are especially grateful to all the participants, for whom this Conference was organized, for having made it a memorable event and a landmark in the growing path of Mathematical and Theoretical Biology.

Educational corner: Limit cycles in a general predator-prey model

By Luděk Berec

In each issue we present some short educational text about a subject in mathematical biology. If you think some subject should be treated in the next issue, please let us know. Enjoy!

Introduction

The Rosenzweig-MacArthur model of predator-prey dynamics, combining logistic prey growth with a type II predator functional response, is a classic among models of predatory interactions [2]. Its immortality is assured above all by an occurrence of the so-called *paradox of enrichment*, when enriching the system by supplying more resources on which the prey sustains may jeopardize the very prey and predator existence. Mathematically, this is a consequence of a Hopf bifurcation at which a stable coexistence equilibrium gives way to stable limit cycles of increasing amplitude. The Hopf bifurcation occurs when the vertical predator nullcline and the peak of the humped prey nullcline pass one another. One can find anecdotal mentions that this also happens in some other predator-prey models, but I am aware of no detailed analytical account of this in the literature. Therefore, I offer this text for interested readers, assuming just some elementary knowledge of modelling predator-prey dynamics. I also encourage the readers to try and extend this analysis to some more predator-prey model not covered here.

Let us consider the following predator-prey model:

$$\begin{aligned} \frac{dN}{dt} &= N\,g(N) - f(N)\,P \\ \frac{dP}{dt} &= e\,f(N)\,P - mP \end{aligned} \tag{1}$$

Here N and P stand for prey and predator density, respectively, while e and m represent the consumption efficiency and the per capita mortality rate of the predator, respectively. Moreover, $g(N)$ is the per capita prey growth rate in the absence of predators, and $f(N)$ is the predator functional response (neglecting any interference or facilitation among predators). With $g(N) = r(1 - N/K)$ for some positive parameters r and K, and the Holling type II functional response $f(N) = \lambda N/(1+h\lambda N)$ for some positive parameters λ and h, the model (1) becomes just the Rosenzweig-MacArthur model of predator-prey dynamics.

In the following, I assume that the functions g and f are continuous and continuously differentiable at any $N \geq 0$. Moreover, for the per capita prey growth rate g I assume that $g(0) > 0$, $g'(N) < 0$ for all $N \geq 0$ and $g(K) = 0$ for some $K > 0$. These assumptions imply that prey growth is logistic-like and that $g(N) < 0$ for all $N > K$. For the predator functional response f I assume that $f(0) = 0$ and $f'(N) > 0$ for all $N \geq 0$, which implies $f(N) > 0$ for all $N > 0$. Moreover, I assume that f is saturating for large N, that is, $\lim_{N\to\infty} f(N) = c < \infty$.

Model equilibria and their stability

There are several equilibria (N, P) of model (1). There are two boundary equilibria that always exist, the *extinction equilibrium* $E_0 = (0, 0)$ and the *prey-only equilibrium* $E_K = (K, 0)$. If any coexistence equilibrium exists it has to lie on the predator nullcline defined by the equation $f(N) = m/e$. This equation has no solution for $m/e \geq c$ yet has a unique solution when $m/e < c$. In the latter case, the predator nullcline is

$$N = N^* = f^{-1}(m/e) > 0 \tag{2}$$

and N^* is the N-coordinate of any potential coexistence equilibrium.

The prey nullcline is defined by the formula

$$P = \frac{N\,g(N)}{f(N)} \tag{3}$$

which is well-defined except possibly at $N = 0$. It follows from the formula (3) that the prey nullcline is positive for $N < K$ and negative for

$N > K$. Therefore, the predator and prey nullclines intersect in the first quadrant and hence a coexistence equilibrium exists if and only if $N^* < K$ or equivalently $ef(K) > m$. Note that this final condition has an obvious biological interpretation: if it holds then the predator population increases when rare if it is introduced into the prey population at its carrying capacity K; otherwise the predator population goes extinct. In any case, if $ef(K) > m$ then

$$P^* = \frac{N^* g(N^*)}{f(N^*)} = \frac{e}{m} N^* g(N^*) > 0 \qquad (4)$$

is the P-coordinate of any potential coexistence equilibrium. Since N^* is unique, so is $P^* = (e/m) N^* g(N^*)$ and hence the coexistence equilibrium (N^*, P^*).

The Jacobian matrix corresponding to the model (1) is

$$J(N,P) = \begin{bmatrix} g(N) + N g'(N) - P f'(N) & -f(N) \\ eP f'(N) & ef(N) - m \end{bmatrix} \qquad (5)$$

Evaluated at the extinction equilibrium $E_0 = (0,0)$, it reduces to

$$J(0,0) = \begin{bmatrix} g(0) & 0 \\ 0 & -m \end{bmatrix} \qquad (6)$$

Since $g(0)$ is positive, E_0 is a saddle point. At the prey-only equilibrium $E_K = (K, 0)$, the Jacobian matrix is

$$J(K,0) = \begin{bmatrix} K g'(K) & -f(K) \\ 0 & ef(K) - m \end{bmatrix} \qquad (7)$$

Since $K g'(K)$ is negative, E_K is locally asymptotically stable provided that $ef(K) < m$ and unstable if $ef(K) > m$. Note that the latter condition coincides with the existence condition of the coexistence equilibrium. Hence, E_K is locally asymptotically stable if no coexistence equilibrium exists and is unstable once a (unique) coexistence equilibrium exists.

At the coexistence equilibrium (N^*, P^*), the Jacobian matrix corresponding to the model (1) becomes

$$J(N^*,P^*) = \begin{bmatrix} g(N^*) + N^* g'(N^*) - P^* f'(N^*) & -m/e \\ eP^* f'(N^*) & 0 \end{bmatrix} \qquad (8)$$

Let us now analyse the determinant and trace of this matrix. Since

$$\det J(N^*,P^*) = mP^* f'(N^*) > 0 \qquad (9)$$

the product of two eigenvalues of the matrix (8) is positive and this rules out a saddle point. Moreover,

$$\operatorname{tr} J(N^*,P^*) = g(N^*) + N^* g'(N^*) - P^* f'(N^*) \qquad (10)$$

Let us now play with the right-hand side of equation (10):

$$\begin{aligned} & g(N^*) + N^* g'(N^*) - P^* f'(N^*) \\ =& g(N^*) + N^* g'(N^*) - N^* g(N^*) \frac{f'(N^*)}{f(N^*)} \\ =& \frac{(g(N^*)+N^* g'(N^*))f(N^*) - N^* g(N^*) f'(N^*)}{f(N^*)} \\ =& f(N^*) \frac{(g(N^*)+N^* g'(N^*))f(N^*) - N^* g(N^*) f'(N^*)}{(f(N^*))^2} \\ =& f(N^*) \left[\frac{N g(N)}{f(N)}\right]'\Big|_{N=N^*} \end{aligned}$$

The expression in square brackets is the prey nullcline, so $[N g(N)/f(N)]'|_{N=N^*}$ is the slope of the prey nullcline at $N = N^*$. Moreover, as $f(N^*) > 0$ the trace of the Jacobian matrix at (N^*, P^*) has the same sign as the slope of the prey nullcline at N^*. Since we know the determinant of the Jacobian matrix at (N^*, P^*) is positive, (N^*, P^*) is locally asymptotically stable if $\operatorname{tr} J(N^*, P^*) < 0$. This occurs if and only if the prey nullcline is decreasing at N^*. On the contrary, (N^*, P^*) is unstable if $\operatorname{tr} J(N^*, P^*) > 0$ which occurs if and only if the prey nullcline is increasing at N^*.

Let us now assume that the predator nullcline $N = N^*$ intersects the prey nullcline $P = N g(N)/f(N)$ at a local minimum or maximum of the latter. This implies $\operatorname{tr} J(N^*, P^*) = 0$. Since the determinant of the Jacobian matrix

corresponds to the product of its eigenvalues and the trace of the Jacobian matrix corresponds to the sum of its eigenvalues, the eigenvalues have to be purely imaginary with a nonzero imaginary at any local extremum of the prey nullcline. Thanks to continuous changes of eigenvalues with changes of model parameters, the eigenvalues have to be imaginary with a negative real part when $\operatorname{tr} J(N^*, P^*)$ is slightly lower than zero and imaginary with a positive real part when $\operatorname{tr} J(N^*, P^*)$ is slightly higher than zero. Thus, there is a potential for a Hopf bifurcation to occur if the other (rather technical) conditions of the Hopf theorem [2] are met.

Importantly, these results imply that if the prey nullcline $N\,g(N)/f(N)$ is monotonically decreasing for all $N > 0$ then the coexistence equilibrium (if it exists) is always stable. On the other hand, if $N\,g(N)/f(N)$ initially increases and then decreases with increasing N, or vice versa, then stability of the coexistence equilibrium (if it exists) changes if the model parameters change such that the predator nullcline $N^* = f^{-1}(m/e)$ and the peak of the prey nullcline transverse one another.

Special cases

Linear functional response If $f(N) = \lambda N$ for some $\lambda > 0$, then

$$\begin{aligned} \operatorname{tr} J(N^*, P^*) &= \lambda N^* \left[\frac{N\,g(N)}{\lambda N}\right]'\Big|_{N=N^*} \\ &= N^*\,g'(N^*) < 0 \end{aligned}$$

So the coexistence equilibrium (N^*, P^*), if it exists, is always stable.

Exponential prey growth If $g(N) = r > 0$, then

$$\begin{aligned} \operatorname{tr} J(N^*, P^*) &= f(N^*) \left[\frac{rN}{f(N)}\right]'\Big|_{N=N^*} \\ &= r\,\frac{f(N^*) - N^* f'(N^*)}{f(N^*)} \end{aligned}$$

Since $f(N^*) > 0$, it is $\operatorname{tr} J(N^*, P^*) < 0$ if and only if $f(N^*) - N^* f'(N^*) < 0$ which is equivalent to

$$f'(N^*) > \frac{f(N^*)}{N^*}$$

This is the well-known *Gause's condition of coexistence equilibrium stability* for the predator-prey model with exponential prey growth [1].

Rosenzweig-MacArthur model Assuming logistic prey growth $g(N) = r(1 - N/K)$ for some positive r and K, and a Holling type II functional response $f(N) = \lambda N/(1 + h\lambda N)$ for some positive λ and h, the existence condition $f(K) > m/e$ becomes $e > mh(1 + 1/(h\lambda K))$. Moreover, the prey nullcline

$$P(N) = \frac{N\,g(N)}{f(N)} = \frac{r}{\lambda}\left(1 - \frac{N}{K}\right)(1 + h\lambda N) \tag{11}$$

is an equation for inverted parabola with $P(0) = r/\lambda > 0$, which is humped in the first quadrant as soon as

$$P'(N)\big|_{N=0} > 0 \quad \Leftrightarrow \quad h\lambda K > 1$$

Otherwise, if $h\lambda K < 1$, $P(N)$ is monotonically decreasing with increasing N in the first quadrant and the coexistence equilibrium (N^*, P^*), if it exists, is therefore stable.

If $h\lambda K > 1$, so the prey nullcline is humped in the first quadrant, the hump occurs at the prey density

$$N_h = \frac{h\lambda K - 1}{2h\lambda} \tag{12}$$

As a consequence, an increase in the prey carrying capacity K moves N_h to the right, yet has no effect on the predator nullcline $N^* = m/[\lambda(e - mh)]$ (recall from the above that $f(K) > m/e$ implies $e > mh$). Therefore, if originally $N_h < N^*$ (stability) then by increasing K eventually $N_h > N^*$ and the coexistence equilibrium (N^*, P^*) becomes unstable. Moreover, a Hopf bifurcation occurs at $N^* = N_h$, and a unique stable limit cycle arises. System destabilization via a Hopf bifurcation may occur also due to changes in other model parameters, such as due to decreasing predator mortality rate m; N^* then moves to the left while N_h stays unaffected.

Type III functional response A form commonly used to model the Holling type III func-

tional response is

$$f(N) = \frac{aN^2}{1+bN^2} \tag{13}$$

Let us first assume $g(N) = r$ (exponential prey growth), but $f(N) = aN^2$. This gives

$$\operatorname{tr} J(N^*, P^*) = a(N^*)^2 \left[\frac{rN}{aN^2}\right]'\Big|_{N=N^*} = -r < 0$$

So the coexistence equilibrium (N^*, P^*), if it exists, is always stable. Quadratic functional response thus stabilizes predator-prey dynamics.

However, the situation is a bit more complicated when the form (13) is used. The prey nullcline is then

$$P = \frac{r}{aN}\left(1 - \frac{N}{K}\right)(1 + bN^2)$$

and the trace of the Jacobian matrix at the coexistence equilibrium is

$$\operatorname{tr} J(N^*, P^*) = r\left(\frac{2bm}{ae} - 1 - \frac{2bm}{aeK}\sqrt{\frac{m}{ae-bm}}\right)$$

Obviously, this expression is negative for the predator mortality rate m close to zero as well as for m attaining ae/b from the left, but if $m > ae/(2b)$ the trace may go positive. If that is the case, the prey nullcline has both a local minimum and a local maximum in the first quadrant (Fig. 4a). Hence, when increasing m, the coexistence equilibrium is initially stable, then a stable limit cycle emerges in a Hopf bifurcation, but eventually the coexistence equilibrium returns to being stable in another Hopf bifurcation (Fig. 4b).

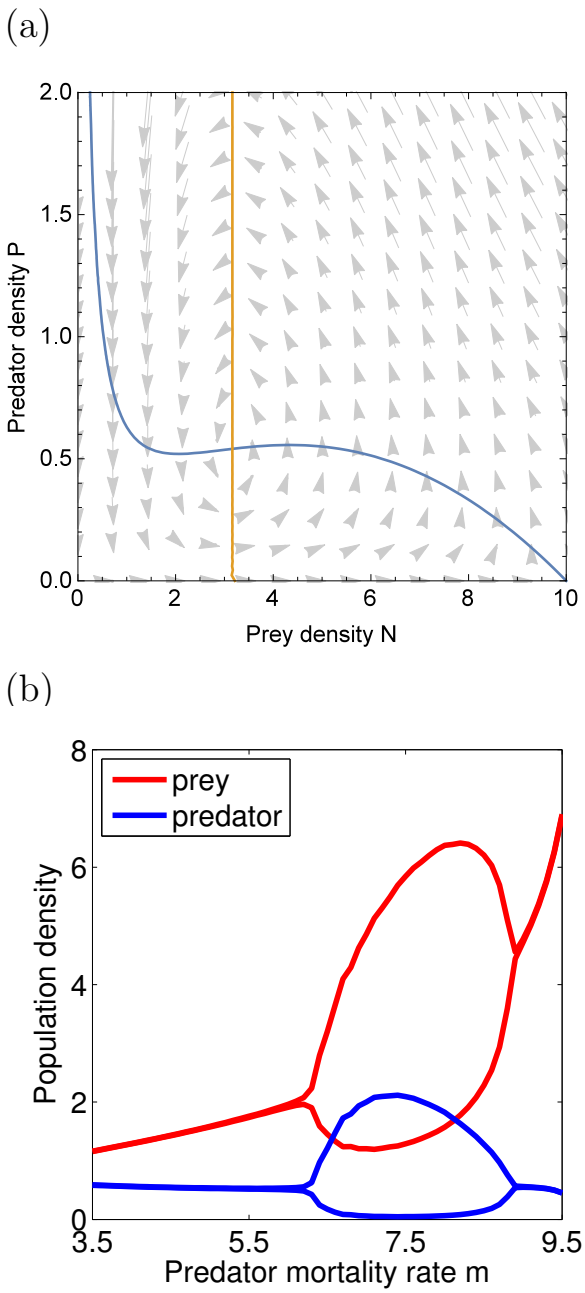


Figure 4: Impact of a Holling type III functional response. (a) An example phase portrait with a cubic prey nullcline that has both a local minimum and a local maximum in the first quadrant. (b) A corresponding bifurcation diagram with two Hopf bifurcations. Parameters: $r = 1$, $K = 10$, $l = 2$, $h = 0.2$, $e = 2$, and $m = 8$ in panel (a).

References

[1] Gause, G.F., Smaragdova, N.P. and Witt, A.A., 1936. Further studies of interaction between predators and prey. *Journal of Animal Ecology*, 5, 1–18.

[2] Kot, M., 2001. *Elements of mathematical ecology*. Cambridge University Press.

European teams in mathematical biology

In each issue we present some of the European groups working in the field of mathematical biology. We try to cover different subjects and geography. If you think some group should be portrayed in the next issue, please let us know. Enjoy!

StAMBio University of St Andrews Mathematical Biology Group

The research group is based within the School of Mathematics and Statistics of the University of St Andrews. We are an interdisciplinary group of mathematicians who develop, analyse and simulate mathematical models to study the key mechanisms that underpin the dynamics of biological systems. Our current research interests include multiscale models of cancer growth and treatment, models of infectious diseases and immune competition, biological pattern formation and morphogenesis, free boundary problems in biology, stochastic models of signalling and gene regulatory networks, evolutionary dynamics in structured populations and mathematical models arising from theoretical ecology.

At present the group consists of five members of staff, four postdoctoral fellows and three PhD students, whose research profiles are briefly described below.

STAFF MEMBERS

Mark A. J. Chaplain (Head of the Group)

My main area of research is Mathematical Oncology the application of mathematical modelling to cancer growth and treatment. I am interested in all aspects of cancer modelling gene regulatory networks, avascular growth, the immune response to cancer, angiogenesis, invasion and metastasis, multiscale modelling techniques, chemotherapy and radiotherapy treatment. I am also interested in theoretical ecology, specifically host-parasitoid systems.

Jochen Kursawe

I develop and apply mathematical and computational methodology to understand embryonic development. I collaborate with experimental biologists to research how individual cells make decisions (e.g. to divide or differentiate) and how multiple cells interact to form healthy and viable tissues. My work includes analysing the dynamics of gene regulatory interactions and modelling mechanics of single cells and cell-cell interactions. My aim is to decipher fundamental mechanisms that underlie the robustness of embryonic patterning and morphogenesis.

Tommaso Lorenzi

The focus of my research is on mathematical models of complex living systems formulated in terms of nonlinear partial differential equations and corresponding stochastic individual-based models. These models can support a deeper theoretical understanding of the mechanisms underlying a variety of emergent behaviours observed in nature. Moreover, they pose a series of analytical and numerical challenges which make them interesting mathematical objects per se.

Giorgos Minas

I study noisy, dynamic and complex biological processes, such as gene regulation, signalling and development. The target is to develop an integrated, multi-level approach that combines stochastic modelling and mathematical analysis with computational, statistical and machine learning methods. The ultimate goal is to answer fundamental biological questions such as how cells adapt to multi-dimensional signals received in their ever-changing environments.

Nikolaos Sfakianakis

The focus of my research is the multiscale study of cancer and spans from lamellipodium dynamics and live cell motility, to cancer growth and tissue formation, and to the role of stemness in health and disease. The tools I employ come from several (sub-)fields of Applied Mathematics: modelling, scientific computing, numerical analysis, and analysis of partial differential equations.

POSTDOCTORAL FELLOWS

Ruth Bowness

I am a Medical Research Council Fellow and Academy of Medical Sciences Springboard Award Holder. My research involves using differential equations and individual-based models to describe infectious disease spread within the human body, and to simulate and compare treatment strategies. My current projects include multiscale within-host modelling of tuberculosis disease progression and treatment, and within-host modelling of antimicrobial resistant infections.

Sara Hamis

As part of an interdisciplinary team with researchers at Ninewells hospital, I am currently working on developing new paradigms for overcoming drug resistance in cancer. Mathematical and computational biology are my main research interests, and I work with multiscale, hybrid individual-based models.

Fiona R. Macfarlane

The main focus of my research is the development of individual-based models describing tumour-immune competition and tumour growth. More recently, I have been working on the derivation of partial differential equation models from stochastic individual-based models of cell populations.

Cicely K. Macnamara

Currently I am working as part of SofTMech an EPSRC-funded centre for Mathematical Sciences in Healthcare. I work on an individual-based, force-based model for tumour growth and the interactions with the extra-cellular matrix. My other research interests include cancer-immune dynamics; intracellular dynamics, including gene regulatory networks and cancer invasion.

PHD STUDENTS

Linnea C. Franssen

I am an EPSRC-funded PhD student in my final year. I focus on modelling cancer cell invasion and secondary metastatic spread. For this, I use spatially explicit hybrid modelling techniques to account for the evolution of individual cancer cells and connected clusters of cancer cells, and for the transition between those states. I have developed the first cell-based spatially explicit framework of metastatic spread and currently work on a 3D in silico model that captures cancer cell invasion observed in in vitro assays.

Chiara Villa

I started my PhD in 2018, under the supervision of Mark Chaplain and Tommaso Lorenzi. I am originally from Italy and I studied in St Andrews for an MMath degree in Applied Mathematics. I work on continuous models of phenotypic selection in vascular tumours, and mechanochemical models of pattern formation and tumour invasion.

Yunchen Xiao

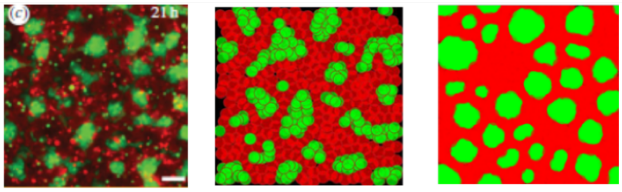
I started my PhD in 2018, under the supervision of Mark Chaplain and Len Thomas (Statistics). My interest in Mathematical Biology began during a summer research internship with Tommaso Lorenzi. My Masters dissertation was entitled 'Mathematical models of cell dynamics in acute myeloid leukaemia'. My current research interests are: parameterising mathematical models of tumour-induced angiogenesis and tumour invasion & metastasis, along with parameter estimations and selecting among competing models using Approximate Bayesian Computation methods.

More about our research and possible PhD and postdoc opportunities can be found at `http://www.mcs.st-and.ac.uk/mathbiol/`

MAMBA (Inria, CNRS and Sorbonne Université)

MAMBA is not only a fast moving venomous snake but also the name of our team, an acronym for "Modelling and Analysis for Medical and Biological Applications". Located both in the Jacques-Louis Lions Laboratory of Sorbonne Université and in the Inria Paris Research Centre, our team gathers 8 permanent researchers, and 20 post-doctoral and Ph.D students. It aims at developing mathematical models, simulations and numerical algorithms to solve problems from life sciences involving dynamics of biological systems such as protein intracellular spatio-temporal dynamics, cell motion, early embryonic development, tissue growth and regeneration, cancer evolution, healthy and tumour growth control by pharmacological means, protein polymerisation occurring in neurodegenerative disorders and control of mosquito populations (to prevent epidemics of vector-borne diseases like zika or dengue). It is the evolution of the BANG project-team, headed by Benoît Perthame during 11 years (2003-2013).

Data and image analysis, statistical, ODE, PDE, SDE, stochastic processes and agent-based approaches are used either individually or in combination, with a strong focus on PDE analysis and agent-based approaches. In order to develop a unified framework to describe the systems of interest at different scales (microscopic to macroscopic scales), a large activity of the team consists in investigating the link between these different models.



Many projects within our team are guided or directly address questions or applications in biology, biotechnology or medicine and are carried out in close collaboration with specialists in biology or medicine. In this context, our ongoing collaborations with biologists and physicians, the collaboration with St Antoine Hospital within the Institut Universitaire de Cancérologie of Sorbonne Université and Hopital Paul Brousse (IUC, Luis Almeida, Jean Clairambault, Dirk Drasdo, Benoît Perthame) and close experiment-theory collaborations characterized by associated researchers at the Leibniz Institute for Working Environment and Human Factors in Dortmund (Dirk Drasdo), Germany, are key points in our project. A very strong link has also been developed with the Wolfgang Pauli Institute in Vienna, especially with C. Schmeiser and his collaborators (Marie Doumic, Benoît Perthame, Diane Peurichard), through an Inria "associated team", a format to promote close interactions and exchanges with other institutions. The mosquito population control studies (Luis Almeida, Pierre-Alexandre Bliman) are also developed in close collaboration with life scientists from Institut Louis Malardé (French Polynesia), Instituto de Medicina Tropical Pedro Kouri (Cuba) and Instituto Oswaldo Cruz (Brazil).

Our main objective is the creation, investigation and transfer of new models, methods and algorithms. In selected cases software development as that of CellSys and TiQuant (Dirk Drasdo and Stefan Hoehme) is performed. More frequently, the team develops "proof of concept" numerical codes in order to test the adequacy of our models to experimental biology.

Some very recent research examples:

Cancer:

- Proposal of strategical principles in cancer therapeutics using asymptotic analysis and optimal control for cell population dynamic models. Ref.: C. Pouchol, J. Clairambault, A. Lorz, E. Trlat, JMPA, 2018.
- Quantitative cell-based model predicts mechanical stress response of growing tumor spheroids over various growth conditions and cell lines, Ref: P Van Liedekerke, J Neitsch, T Johann, K Alessandri, P Nassoy, D. Drasdo. PLoS Comp Biol, 2019.

Protein polymerisation:

- On the asymptotic distribution of nucleation times of polymerization processes. Ref : P. Robert and W. Sun, SIAM App Math., 2019.
- A new variant of the Becker-Döring system, to model sustained oscillations observed in protein fibrils depolymerisation experiments, Ref: M. Doumic, K. Fellner, M. Mezache, H. Rezaei, JTB, 2019.

Vector-borne diseases:

- Implementation of control strategies for sterile insect techniques, P.-A. Bliman, D. Cardona-Salgado, Y. Dumont, O. Vasilieva, Math Biosci., 2019.
- Preventing epidemics of vector-borne diseases (like dengue or zika) thanks to the control of mosquito populations, Ref: L. Almeida, Y. Privat, M. Strugarek, N. Vauchelet SIAM J. Math. Anal., 2019

Cell multiscale models:

- Particle interactions mediated by dynamical networks: assessment of macroscopic descriptions, Ref : J. Barré, J.A. Carrillo, P. Degond, E. Zatorska, D. Peurichard, Journal of Nonlinear Science, 2017 (+ illustration)
- Traveling wave and aggregation in a flux-limited Keller-Segel model, V Calvez, B Perthame, S Yasuda, 2019.
- Developing a new mathematical framework to model reaction-diffusion in developing organisms: Ref : F. Rossi, N. Pouradier Duteil, N. Yakoby, B. Piccoli, Proc. 2016 IEEE CDC, 2016.

Photos from left to right then up to bottom: Luis Almeida, Federica Bubba, Marie Doumic, Gaëtan Vignoud, Jean Clairambault, Jieling Zhao, Markus Schmidtchen, Dirk Drasdo, Julia Delacour, Mathieu Mezache, Cécile della Valle, Pierre-Alexandre Bliman, Adrien Ellis, Alexandre Poulain, Nastassia Pouradier-Duteil, Philippe Robert, Benoît Perthame, Xinran Ruan, Valeria Caliaro, Diane Peurichard

Other members: Jules Dichamp, Florian Joly, Noemi David, Jorge Estrada Hernandez, Emma Leschiera, Jesus Bellver Arnau, Giorgia Ciavolella, Gisselle Estrada Rodriguez.

Minutes of the ESMTB board meetings

Heidelberg, March 8, 2019.

Present: the complete board (Maíra Aguiar (MA), Ellen Baake (EB; minutes), Luděk Berec (LB), Sílvia Cuadrado (SC), Andrea De Gaetano (AdG; chair), Susanne Ditlevsen (SD), Toby Lundh (TL), Anna Marciniak-Czochra (AMC), Bob Planqué (BP)

Board meeting 9:00-13:00

- The informal decisions taken via email ballot since the Lisbon meeting were unanimously approved. The list of informal decisions is attached to the minutes.
- Identity and journal representation of the Society: The core business of ESMTB, namely mathematical and theoretical biology, is characterised by research combining insight into a biological problem with a non-trivial conceptual/mathematical core (ideally yielding a high convex sum). Neither the branch of the mathematics nor the branch of biology involved is important.

  JOMB, the official journal of ESMTB, does not cover all of this. Nevertheless, with a clear majority (7 in favour, 2 abstentions), the board decides not to suggest any changes to the scope of the journal, in order not to interfere with its mathematical focus, clear profile, and immaculate reputation. While it seems to be difficult to have more than one official journal, possibilities should be explored to support, endorse, or advertise another journal to keep the balance; the board is unanimous on this. It might also be a good idea to suggest special issues of JOMB with a more computational focus.
- Various suggestions for the logo of the society are discussed. The general preference is for a butterfly, landing on an Lorenz attractor shadow, its body an integral sign, and its wings dissolving into discrete objects (indicating a transition from continuous to discrete).
- Guidelines for supporting meetings and events: The following rules are agreed on.
  - The scope of the meeting must be within the scope of ESMTB.
  - At least one of the organisers is member in good standing, where age and amount of membership are considered as additional aspects.
  - If the registration fee for the event $\leqslant$ 200 EUR, then ESMTB members get a 50 EUR discount. If the registration fee is more than 200 EUR, they get at least a 100 EUR discount. The treasurer is the contact for the organisers to check membership status for those requesting the reduced registration fee.
  - Meeting participants will be offered ESMTB membership at a fee reduced by 50 percent. There is no reduced fee for ESMTB membership for school participants, since we already have a discounted membership fee for students (25 EUR).
  - The event should give visibility to ESMTB via a link to the Society's webpage, public recognition of the endorsement, and visibility to ESMTB throughout event
  - The organiser(s) undertake(s) to write a post-event report, to be published in the Communications.
  - The organiser(s) undertakes to offer each participant the possibility to be included in the ESMTB contact list. Participants should be asked if they want to be part of the ESMTB email list and to receive our info letter. That should be done during the online registration and for those who accept (data privacy rules?), the email/institution info should be shared with the Society.

  - Travel support will be handled separately.
  - An upper limit of 9000 EUR per year applies; it will be distributed in 2 rounds (deadlines June 30, Dec. 30, with a decision 2 weeks later) Requests will be handled by treasurer. He makes (or sollicits) a realistic estimate of how much conference needs and presents it to board, who decides.

- Member enrolment campaign: The board is close to finalising lists of researchers working in mathematical and theoretical biology/medicine. Maira will draft a message advertising membership in ESMTB, and Andrea will bulk mail the letter under his own name.

- Special interest groups within the Society ('subnetworks'): For some thematic groups, there is the desire to use the functioning infrastructure of ESMTB, such as the web page to advertise acitivities, and the communications to report on current developments. If such structures develop within ESMTB (rather than building up duplicate structures), this also gives additional visibility to ESMTB. In SMB, such structures are called subgroups; we might call them focus groups. Members are expected to be ESMTB members. The current suggestion for a focus group on multiscale methods, made by AMC, will serve as a pilot project, to be communicated as a currently-emerging group, welcoming others. AMC will take care of the details.

- Funded Research (H2020/FP9) action group: This initiative will facilitate the participation in consortia who send grant proposals to H2020/FP9. AdG and TL will take this in hands. In particular, the infrastructure of ESMTB will be used to distribute the news about these opportunities, establish contacts, and facilitate the formation of the corresponding groups.

- ESMTB web page: BP reports on the status of the new web page, which is being completely restructured.

- EMS web page: Susanne has editing responsibility for the year of mathematical biology. In the future, the corresponding page should become a part of the ESMTB web page.

- Membership fee structure: It is decided that a 'light' membership (free access to JOMB, reduced fee at meetings, no eligibility for travel grants) will be offered to those based in underfavoured nations (BP will identify a suitable list) and western PhD students in their first year. Full student memberships with benefits will apply to all other PhD students. No change of fee structure is envisioned here, apart from a 1-year free membership for recipients (and first rankings) of the society prizes (that is, the winner of the Arino prize, the top-5 for the Heinrich prize, and the winners of the ECMTB poster prize; the latter gets a second year if already a member). Whether there should be elected (rather than ordinary) members (as with ISI) is to be rediscussed in the future.

- Reinhart Heinrich awards procedures: Some subtle changes will have to be made, and decided upon by email ballot.

- Upcoming events:
  - ICIAM July 2019 in Valencia: Maybe SC can attend as ESMTB representative.
  - ECMTB 2020 in Heidelberg: Originally planned for August 3–7, 2020, a shift to the 1st week of September is now preferred, due to building availability. AMC will negotiate this with SMB. AdG will then get in touch about the scientific board according to decision in Lisbon.

Meeting with Springer and JOMB managing editor (14:00–16:00)

Guests: Lynn Brandon, Elena Griniari (Springer), Mats Gyllenberg (JOMB managing editor, ME)

The following topics were discussed.

- Elena Griniari reports that, due to a reorganisation at Springer, responsibility for JOMB has moved to Lynn Brandon.
- The Springer representatives report on facts and figures on JOMB: From 2017 to 2018, submissions have increased from 500 to 512 (with an upward trend over several years), downloads have increased (from a median of 262 to a median of 287), the number of published papers has increased from 122 to 128, the number of online-first papers has increased, and the turnaround time to first decision has decreased to 60 days.
- Scope of the journal: The ME confirms that a condition for publication in JOMB is some kind of mathematical sophistication, where modelling also counts as mathematics.
- Perspectives section: There are very few Perspectives articles; there should be more. Current Perspectives editor is Helen Byrne; the ESMTB board should appoint a contact person (it is later decided that this will be SD), who will identify topics and authors and sollicit manuscripts. It is discussed whether the Perspectives are to be understood as representing policies of the board, which express opinions, beliefs, or convictions, which then belong to the 30 pages that are reserved for ESMTB every year and need not be peer-reviewed; or whether they are scientific papers, which are peer-reviewed and fall under the final responsibility of the ME. It is also discussed whether the Perspectives may be published on ESMTB web page and in the Communications. This would require publication under a different licence. SD will negotiate these questions with Springer and clarify the format and the workflow.
- Special issues: More special issues should be sollicited. The workflow is that the ESMTB board identifies (preferrably at least two) guest editors, who have to be approved by the ME, and make a plan (authors and topics) of the issue that has to be approved by the board and the ME. The guest editor has the role of an assocoiate editor, which means that the final decision on a paper rests with the ME, who is responsible for all of scientific quality of the journal. (This is a general Springer policy; in practice, decisions of the ME against an AE or GE are extremely rare.)
- The 30 pages reserved in JOMB for issues of ESMTB seem to have become mostly obsolete since scientists do no longer read paper issues cover to cover, but individual electronic articles. A sub-page of the journal or a web page would be more appropriate. It should be discussed how this can be realised.
- Springer inquires into the collaboration on a book series (such as Springer Briefs, a collaboration with the Bernoulli Society; these are small books of 50-125 pages). A similar cooperation with ESMTB might involve lecture notes for summer schools, or longer review articles.
- The cooperation agreement between ESMTB and Springer is inconsistent w.r.t. the responsibilities in appointing new AEs. Is this the responsibility of the ME alone, or is there cooperation with the ESMTB board?
- Sponsoring: Springer has previously sponsored poster prizes in the ECMTB conferences and will consider doing so also for the 6-9 smaller events supported by ESMTB per year.
- Transfer to BMB: The question is raised whether there should be the possibility of transfer of manuscripts from JOMB to BMB. The usefulness of this is unclear.

- EMS: The ME reports that the EMS will increase grants to summer schools, EMS distinguished speakers at conferences, and similar issues, and encourages ESMTB to apply for such funding (deadline September 30, 2019, for events in 2020). It is also important that ESMTB should be represented at ECM 2020.

Board meeting 16:00-17:30

- Financial situation: BP reports that we currently have a balance of EUR 70.000. Payment of membership fees by credit card has become available. Problems with institutional membership remain to be resolved.
- Support for meetings: It is agreed that the treasurer hands out money for meetings before the event.
- Free membership: It is agreed that Angelique Stephanou is to receive a free membership for a couple of years, as a thank you for her role as our representative in France.
- Communications: they may now be printed in Prague, at the cost of 1 EUR for printing, and 4 EUR for sending. It is discussed whether hardcopies are still required. After all, all other societies still do it this way. The decision is delegated to SC, SD, and LB.

Lisbon, July 2018, at ECMTB2018

The meeting was distributed across the following time slots: July 24, 12:30-14:00; July 25, 12:30-14:00; July 26, 12:30-14:00; July 27, 15:45 17:45. These minutes also contain a report on the general assembly on July 26, 16:40-17:30.

Present: Maíra Aguiar (MA), Ellen Baake (EB; minutes), Andrea deGaetano (AdG; chair), Susanne Ditlevsen (SD), Torbjörn Lundh (TL), Anna Marciniak-Czochra (AMC), Robert Planqée (RP).
Absent (with apology): Silvia Cuadrado (SC), Luděk Berec (LB)

1. Meeting with Springer and JOMB managing editor (July 24, 12:30-14:00)

Guests: Elena Griniari (Springer), Mats Gyllenberg (JOMB managing editor).

The following topics were discussed:

- The contract between Springer and the ESMTB (attached to the minutes) dates from 2010 and must be updated. The current benefits for ESMTB members are: free online access to JOMB, discount on the printed copy of 25%, and a discount of 20% on Springer books in biomathematics for a two-month period every year (currently this period is set to April-May). The modalities of ordering with this privilege should be publicised on the internet pages of ESMTB one month ahead of the privilege period each year (so far, this did not happen; we should see to it in the future). The new contract will be negotiated in due course. On the technical side, it will be article-based rather than page-based. Further aspects are discussed within the board later during the week.
- 30 pages per year can be used for societal issues; this has not been much used in the past.
- The 'Perspectives' section aims at 1-2 articles per year on recent developments or emerging fields. Current editor is Helen Byrne.
- Special issues on specific topics (with guest editors) are welcome. They may be initiated via proposals of 1-2 pages. There have recently been several special issues on the occasion of birthdays, and memorial issues; but this should be discontinued.
- Review articles are welcome (there are too few). They are solicited by invitation by the editors or the ESMTB. It is discussed whether review authors should get a Springer book for free, rather than a free JOMB subscription.
- Promotional materials from Springer can only be sent to mailing lists if individuals

have agreed to receive them.

- Development of the journal: Submissions are stable at around 500 per year. At least 50% are rejected without review. Of the remaining ones, roughly 50% finally make it into the journal. In light of the high rejection rates, a transfer desk to other journals (such as Bulletin of Mathematical Biology) would be welcome.
  Impact factor, citations, and downloads have increased, the turnaround times have decreased. Elena Griniari presents a report including detailed journal statistics.
- The JOMB editorial board currently consists of 17 persons, plus the two managing editors. 7 out of the 17 are Europeans, 2 are female. The board should be enlarged; preferentially in the directions of evolution, stochastics, and/or epidemiology.
- It is discussed whether the scope of JOMB should be opened up into the direction of computational biology. Mathematical Biosciences did enlarge its computational section. It is discussed whether computational biology is a case for JOMB; or whether the journal should stick to its proof-oriented focus, which gives it a well-defined and high reputation in mathematics. Another possibility would be to widen our scope by supporting a computational journal; options are discussed.
- It might be helpful to name a liaison officer for the journal.

2. Wednesday, July 25, 12:30-14:00

The following topics were tackled:

- The e-vote decisions taken via email ballot since the Warsaw meeting were unanimously ratified. The list of e-vote decisions is attached to the minutes.
- ESMTB 2020 will take place in Heidelberg, August 3-7, 2020, organised by AMC. It will be a joint conference with the SMB. A two-tier procedure is envisaged for the scientific board, namely: 2 persons from the ESMTB board, 2 from the SMB board, and 1 local person will decide about the plenary speakers and the number of minisymposia. The second tier, including the first one plus an additional 4 people from ESMTB, 4 from SMB, and 2 locals will decide about the minisymposia themselves and the contributed talks. The locals will decide about the posters. AdG will discuss this suggestion with the SMB.
- Bank account: Treasurer, president, vice president, and secretary should have access to the new bank account (to be opened in France since the society is registered in France).
- Web page: The web page must move out of Dresden by October 1st at the latest. RP takes care of this, decides what is necessary, and buys expertise where required (in particular, web design).
- Memberships: ECMTB participants that are not ESMTB members and have paid the full conference fee can apply for membership for one year without fees.
- EC H2020: AdG presents plans of the European Society of Oncology Surgery, and the European Society of Intensive Care, for joint proposals with ESMTB within the H2020 framework. These proposals will set up a framework within which individual PIs can then apply for funding. The board approves these plans.
- Next board meeting: will be in Heidelberg in March or April 2020, organised by AMC.

3. Ovide Arino outreach award on Thursday, July 26, 12:30-14:00

Guests: Jean-Luc Gouzé, representative of the Societé Francophone de Biologie Theoretique (SFBT); Rafael Bravo; Suzanne Touzeau

It is agreed that the Ovide Arino outreach award, to be co-sponsored by SFBT and ESMTB, will be awarded on the occasion of ECMTB every two years. The prize will amount to 1000 Euros of personal

money, to which SFBT and ESMTB will contribute equally. The prize will go to a person from a non-favoured country, maybe at the early postdoc level, who has done outstanding work in connection with a European group. The jury will consist of 5 persons: 2 from ESMTB, 2 from SFBT, and one from an underprivileged country. The jury will agree on the rules, assisted by TL, due to his experience with the Heinrich Prize.

As to the jury, the board approves the nomination of Rafael Bravo and Suzanne Touzeau for ESMTB. For SFBT, Angelique Stephanou is suggested, together with Julien Arino (the son of Ovide Arino and a mathematician himself) or a substitute. SFBT will decide about these suggestions. The fifth member will be chosen and invited to join the committee by the four above members.

4. General assembly, Thursday, July 26, 16:40-17:30

The current board introduces itself: Members are MA (Vice president), EB (Secretary), LB, SC, AdG (President), SD, TL, AMC, RP (Treasurer).

The board reports on important current developments, namely communication (SD), prizes, schools, grants (TL), administration (EB), members, finance, web page (RP), ECMTB (MA, AMC), and Horizon2020 (AdG). MA, in the name of the previous and the current board, thanks Andreas Deutsch for his extended service to ESMTB; Mats Gyllenberg informs about JOMB.

AdG then initiates a discussion with the participants about the future role of ESMTB. The 'wishlist' includes: networking (information about who does what where), the option to pay membership fees by credit card (rather than PayPal), satellite meetings to ECMTB, lobbying for the area, improved information about job offers, and mandatory membership for ECMTB participation.

5. Friday, July 27, 12:30-14:00

The following topics were tackled:

- Acta Mathematica Hungarica offers a special issue with proceedings of ECMTB. The board decides against this (it's too late, and the board lacks the necessary manpower to appropriately compile the proceedings).
- Thursday, October 10, 2018, is the Day of Mathematical Biology. The board will think about possible means of promotion (press, radio) and send suggestions to TL.
- Reinhart Heinrich Prize: The procedures are contained in the attached document. This year, there have been very few suggestions; when soliciting new members, one should, at the same time, solicit suggestions for the prize. Two members of the committee will step down next year and will have to be replaced.
- ICIAM: In this year's ICIAM meeting in Philadelphia, ESMTB was represented by Alex Ostermann (Austria). At the next meeting (spring 2019) in Valencia, AdG will attend.
- EMS: This year's EMS meeting was attended by AMC.
- ESMTB communications: appear once per year (more is not feasible). There is some discussion about size, format, and paper versus electronic; it is decided to stay with paper.
- ESMTB logo: It is agreed that the logo is ugly and should be changed. Suggestions will be discussed via email, and the layout should be done by a designer (MA will ask the designer of the ECMTB18 logo).
- Finance: ESMTB will receive from ECMTB18 a 10 EUR flat rate per participant paying a non-member regular fee (MA will do the exact sums in Sep.).
- ECMTB20: There is nothing to decide today. The next steps will be to decide about the scientific committee, and on the fee structure.

- Upcoming meetings supported by ESMTB:
  - Helsinki summer school on mathematical ecology and evolution (Turku, August 2018)
  - Dynamical systems applied to the natural sciences (Naples, Feb. 2019, MA)
  - Summer school on theoretical ecology (Sicily, autumn 2019).
  - SD will apply for funding for the 5th international conference on mathematical neuroscience (June 2019, Copenhagen). (The general procedure is application via email to AdG, then the board votes about a support of 1000 Euros if possible.)
- Travel grants: the board acknowledges LB's written report.
- Emails to ESMTB (via info@esmtb.org): The current situation is unsatisfactory; this will change after the migration.
- Honorary memberships: It has been brought to our attention that some key figures in the development of ESMTB (founding members etc.) are now retired professors and have no access to research funds. We may think whether to institute some sort of (lifetime?) honorary membership, cost-free, to keep these individuals within the Society. If we so decide, then we would have to set up some kind of system for proposing candidates and deciding on granting membership.
  The board decides against honorary memberships, not least because ordinary members pay their fees from their personal salaries (rather than institutional funds) as well, and the persons in question certainly have generous pensions. Furthermore, they could have become life members during their active carreer, thus saving money anyway.
- Role of JOMB for ESMTB:
  - As mentioned before, we can use space (two pages per issue) in the journal for societal issues. It is argued that this does not make too much sense these days because people do not use journals this way any more (they download individual articles rather than looking at journal issues cover to cover). The board agrees that we keep this point in mind for the renegotiations of the contract.
  - In comparison with SMB, our situation is unfortunate. SMB has Bulletin of Mathematical Biology and gets a share of the profit, because SMB has the name rights and could negotiate accordingly. It is discussed whether and how the situation can be improved.
- Projected and upcoming big conventions: ICIAM in Valencia (2019); global convention on mathematical biology (SMB, ESMTB, Chinese Society of Mathematical Biology, Japanese Society of Mathematical Biology) in China 2022; ICIAM in Tokio 2023; ICIAM 2024 somewhere in Europe.

E-vote decisions of the ESMTB board, Jan. 2018 – Feb. 2019

- January 17, 2018: In lack of a further volunteer, for the moment ESMTB will continue with a single ICIAM contact point (AdG). If at any time one of us will feel interested in joining, they should notify the board.
- January 28, 2018: With 6 expressed favorable votes the board decides to grant to the event "Mathematics for Biomedicine", Turin, October 8-11, 2018, the sum of 1000 Euro.
- February 6, 2018: With 6 votes we define as "Member in good standing" only mem-

bers who have paid their dues for the current year at the time they submit the application (for travel grant, reduced-fee registration or other).

- February 8, 2018: With a majority, it is set that the society will reimburse either the direct beneficiary or a reliable proxy upon presentation of the relevant receipts.
- February 9, 2018: TL will act for the board to draft the necessary regulations for the administration of the Reinhard Heinrich and possible other future awards granted by ESMTB, as well as to represent ESMTB in the necessary discussions with the Heinrich Prize Committee and other prize-related activities.
- March 2, 2018: The board has voted to accept a MoU modification such that the ECMTB2018 organisers will not pay ESMTB the originally agreed 10 EUR per participant for those participants who have benefited from the 50 EUR discount because they are ESMTB members in good standing.
- March 21, 2018: AMC will be our representative with EMS. Check that we will pay or have paid our EMS and ICIAM dues for 2018.
- April 29, 2018: Given the need to proceed expeditiously in effecting the variation of the society's official registered address, the president convened today an electronic meeting of the board, explaining that the building where the society has its previous official address, in the campus of the Faculty of Medicine of the University of Grenoble, no longer exists. The kind offer to locate the official address of ESMTB within the same campus, in a different building, was accepted by the board with 8 favorable votes and 2 abstained out of 10. The new official address of the society is henceforth: Société Européenne de Biologie Mathématique et Théorique / European Society for Mathematical and Theoretical Biology (ESMTB), Laboratoire TIMC-IMAG, Pavillon Taillefer, Faculté de Médecine de Grenoble, 38706 La Tronche cedex, France. The board wishes to express sincere thanks to Dr. Angelique Stephanou, to Prof. Philippe Cinquin and to the staff at TIMC-IMAG for their precious collaboration.
- May 17, 2018: The board accepts the resignation of Prof. Frank Hilker, tended by him to all board members by email message. Since the statutes of the society do not foresee the possibility to replace a board member before the regular periodic elections, the board will henceforth count nine members until the next mandate starting January 2021.
- June 28, 2018: The board approves the proposal of the Societé Francophone de Biologie Théorique to co-sponsor the Ovide Arino Outreach Award.
- November 13, 2018: the Board decides that in case financial support for a scientific event (meeting, conference, workshop, school) is asked of the Board by a Board Member, by a Board Member's institutional colleagues or staff, or for an event of which the Board Member is an organizer or co-organizer, the implicated Board Member shall abstain from the evaluation of the request and from the Board's decision to grant such request.
- December 11, 2018: ESMTB will support the Samos workshop/summer school at the usual conditions (1500 Euro contribution and agreed upon visibility).
- January 28, 2019: ESMTB will support the Conference on Discrete Models of Complex Systems, 15-17 July 2019, with the standard amount of 1500 Euro.

Ellen Baake
ESMTB Secretary

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 2019 in any area of Mathematical and Theoretical Biology, see `https://esmtb.org/Reinhart-Heinrich-Award`.

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
Reinhard Buerger, Carlos Braumann, Helen Byrne, Mirjam Kretzschmar, Stefan Schuster (former assistant to Reinhart Heinrich)

Award

- Publication of a summary of the thesis receiving the award as lead article in the 2020 issue of the European Communications in Mathematical and Theoretical Biology.
- 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 recipients 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 Stefan Schuster (`stefanschu@gmail.com`):

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 ***31st January 2020.***

Only theses that have been accepted in 2019 can be considered. The acceptance date is the date at which the thesis is considered by the institution as fulfilling all the requirements for the granting of the doctoral degree, even if such degree will be formally attributed at a later date. It is the successful thesis defense date if no changes are demanded or, when changes in the thesis are required, the date when such changes are accepted by the institution.

Shortlisted applicants will be asked to send their full thesis.

CALL FOR MEMBERSHIP FEES 2019

The **European Society for Mathematical and Theoretical Biology (ESMTB)** was founded in 1991 during the first European Conference on Mathematics Applied to Biology and Medicine in l'Alpes d'Huez, France. The mission of the ESMTB is to promote theoretical approaches and mathematical tools in biology and medicine in a European and wider context. This goal is pursued by the organization and support of summer schools and conferences, by the European Communications and the information on our web-site. ESMTB annually honours the best PhD thesis in the field of mathematical and theoretical biology with the Reinhart Heinrich Doctoral Thesis Award. ESMTB is a nonprofit organisation. The ESMTB board organizes the activities of the society according to the ESMTB statutes.

Membership benefits include:

- Full online subscription to the **Journal of Mathematical Biology** (Springer Verlag)
- Members are eligible, during a two-month period each year, for a **discount of 20% on all Springer books** in the area of mathematical biology.
- **Travel Support** for mathematical/theoretical biology meetings
- Endowing the **Reinhart Heinrich best doctoral thesis award**
- **Reduced fees** for selected conferences and schools
- **Reduced subscription rates** for selected journals
- **Voting** in society elections

Please register at http://www.esmtb.org.

Membership Fees per year:

The **Individual Annual Membership Fee** is:

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

The **Institutional Annual Membership Fee** is: 200 Euro

The Life Membership Fee is:

1. 750 EUR (age 40 or above)
2. 500 EUR (age 50 or above)
3. 250 EUR (age 60 or above)

Further information:
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