European Communications in Mathematical and Theoretical Biology
2020, No. 23

Communications

ESMTB
European Society for Mathematical and Theoretical Biology

Contents

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

Letter from the President

Dear colleagues,

it is early fall of 2020, in approximately one month the elections for the new Board of the Society will be held, and in three months the old Board members will make place for the newly elected ones. It is an appropriate time for a critical appraisal of what has been done over the past three years and how things appear on the horizon.

I believe that it can be safely stated that the new Board will start from a much improved general situation with respect to what we old Board inherited. Thanks mainly to a very successful Lisbon ECMTB2018 the Society's finances are in good shape, even after supporting 20 or so local meetings and schools throughout 2018-2019-2020. After many years of interruption we successfully restored the legal address of the Society, thanks mainly to the selfless help of the colleagues from CHURG/SIIM at the Université de Grenoble, Angelique Stephanou first of all who labored through the lengthy French bureaucratic process. Together with the resolution of the administrative situation, we managed to open the Bank account for the Society in Grenoble, finally achieving the long, long-due transition of the financial management from the tender, loving care of Andreas Deutsch, who had sustained it from Dresden for more than 12 years: under the present arrangement, the account is finally in the name of the Society itself, and will not need to be changed as the Society Administrators change, thereby obviating the problems that did plague such switches in the past. We (Bob Planqué) switched to the Wild Apricot membership management system, actuating a change already advocated by the past ESMTB Board. In the process, we also transferred from Dresden the webpage, rebuilding it entirely, changed the logo (we hope most of you like it), and maintained the possibility of accepting payments by credit card. We conducted one campaign for new memberships, with some success: unfortunately, Covid-19 interfered with the effort of registering new members by forcing Anna Marciniak and her organizer team to postpone our flagship conference, ECMTB 2020 Heidelberg to 2021, the conference being the most evident aggregation moment, being attended typically by more than 700 participants. In order to strengthen the relationship between our European Society and the rest of the world, and in order to emphasize our investment in the new generations, a new "Ovide Arino Outreach Award" has been created in collaboration with the Société Francophone de Biologie Théorique. For it and for our long-standing Reinhart Heinrich Award, streamlined procedures have been put in place, including mechanisms for the renewal of the respective Award Committees. We have participated in one H2020 COST project proposal and regularly taken our place in the EMS and ICIAM meetings, giving our small contribution to the discussion and promotion of sensitive societal issues impacting mathematical biology across the Continent and the world. The negotiations with Springer Verlag, about the new agreement regulating the relationship between the Society and the Journal of Mathematical Biology, are well under way and seem to be arriving to a mutually satisfactory arrangement: barring unforeseen occurrences, we ought to be able to finalize the Agreement before December, leaving to the new Board one less problem to be solved.

Much remains to be done in the future: intensifying the relationships between ESMTB and national societies, improving and synchronizing the offer of Summer Schools and other educational initiatives, achieving ESMTB-organized EU-funded projects (particularly in collaboration with European societies in other domains such as medicine), recognizing and supporting special-interest groups within our constituency (e.g. cancer modeling), establishing closer ties and fruitful interchange between theoretical biology and more computational side-fields (such as computational genomics, bioinformatics, quantitative pharmacology), giving more space and attention in our initiatives to somewhat neglected sub-domains (such as mathematical statistics) and to biological applications of traditionally "pure" mathematical disciplines

(for example differential geometry or fractional differential equations). For all of this and more, best luck to the new Board!

It has been an honor serving the Society for these three years and it has been a real pleasure collaborating with the colleagues of the Board over these years.

Very affectionate regards,

Andrea De Gaetano
President of ESMTB

ESMTB Board Elections

The board of ESMTB consists of 10 members. Each member is elected for 6 years, and board elections are taking place every 3 years, where half the board is being replaced. The next elections will take place in **October 2020**.

The European Society for Mathematical and Theoretical Biology (ESMTB) supports and promotes excellence activities on theoretical approaches and mathematical tools in biology and medicine in a European and wider context. This goal is pursued by encouraging community networking and scientific collaboration, as well as the organization of summer schools and conferences, in particular of the biannual European Conference in Mathematical and Theoretical Biology (ECMTB). Applications for travel grants and prizes such as the Reinhart Heinrich Doctoral Thesis Award and the Ovide Arino Outreach Award are granted every year and published on the ESMTB Communications, available for download on our website `www.esmtb.org`.

The activities of the Society are mainly conducted by the elected Society Board: Board members run for six years; half of the board is replaced every three years to ensure an overlap of new and experienced board members. The Board conducts its actions through one-day meetings (held approximately twice a year): a local workshop is usually organized concomitantly with the Board meetings. Board meetings are also held during the General Assembly (G.A.) held on the course of the European Conference in Mathematical and Theoretical Biology. A substantial part of the work and decisions are done, of course, by e-mail.

In 2020 the ESMTB members will elect (via electronic ballots managed by the current Board) five new Board members, whose period of office will run from January 2021 through December 2026. The candidates are now known. Read the statements from all ten: `https://esmtb.org/ESMTB-2020-Election-Candidates`.

The election will take place between 1 and 31 October, 2020, where active members will express a preference for up to 5 candidates via their personal area within the ESMTB website. All active members will receive an email with a link to the elections page.

Results will be announced by October 31st, 2020 and a joint Board meeting will be scheduled for December 2020, in order to effect the transition between the old and new Board members.

Current (2018-2020) board members:

- Andrea De Gaetano (president)
- Maíra Aguiar (vice president)
- Ellen Baake (secretary)
- Bob Planqué (treasurer)
- Luděk Berec
- Sílvia Cuadrado
- Susanne Ditlevsen
- Torbjörn Lundh
- Anna Marciniak-Czochra

Andrea, Susanne, Torbjörn and Anna will end their term on the board by December 31, 2020.

Maíra, Ellen, Bob, Luděk and Sílvia will stay on until December 31, 2023.

The Reinhart-Heinrich Doctoral Thesis Award 2019

The winner of the ESMTB Reinhart-Heinrich Doctoral Thesis Award for 2019 is **Lisa Maria Kreusser**, for the thesis **Anisotropic nonlinear PDE models and dynamical systems in biology**. The award will be formally given in a ceremony at the ECMTB conference in Heidelberg in 2021. The awarding committee made the following statement: *The thesis by Lisa Maria Kreusser is very comprehensive and voluminous. [...] In summary, Kreussers thesis is very beautiful work, especially on the maths side, and is outstanding both in quality and quantity. Each of the two parts would have been excellent PhD theses on their own. The dissertation is appealing by its mathematical depth, exact and detailed presentation, and the biological applications and interpretation.* She did her PhD at the Department of Applied Mathematics and Theoretical Physics (DAMTP) and at the Cambridge Centre for Analysis (CCA), within the University of Cambridge, UK, under the supervision of Professor Peter A. Markowich and Professor Carola-Bibiane Schönlieb. We congratulate her for her excellent and exciting work! First, she presents herself, and then follows an extended abstract of the thesis.

Lisa Maria Kreusser Personal statement

Since my undergraduate studies at the University of Kaiserslautern, Germany, I have been very interested in partial differential equations due to their wide range of applications in biology, physics, engineering, and socio-economics. This was further enhanced by research projects I have been involved in at the Fraunhofer Institute for Industrial Mathematics ITWM and at Imperial College London. My research internship at Imperial College not only sparked my curiosity in interacting particle models which are prevalent in biological applications, but also convinced me to move to the UK for my PhD. I completed my PhD at the Department of Applied Mathematics and Theoretical Physics at the University of Cambridge in 2019.

During my PhD, supervised by Prof. Peter Markowich and Prof. Carola-Bibiane Schönlieb, I have worked on mathematical models with diverse biological applications, including the simulation of fingerprint patterns and the simulation of biological transport networks such as leaf venation or blood circulation systems. Since October 2019, I have been a Nevile Junior Research Fellow at Magdalene College, Cambridge. This independent research fellowship allows me to build my own research programme in the field of partial differential equations in biology and data science.

The research area of mathematical biology fascinates me because it is a highly interdisciplinary area where I can work at the intersection of significant mathematical problems and fundamental questions in biology. Driven by my desire to pursue biological applications in interaction with biologists, I investigate new and challenging mathematical models. For this research, I use a wide range of mathematical tools including mathematical modelling, numerical analysis, scientific computing and analysis of partial differential equations. This work gives new insights into the properties of the models and results in a better understanding of the underlying biological processes such as biological pattern formation.

Thesis summary: 'Anisotropic nonlinear PDE models and dynamical systems in biology' by Lisa Maria Kreusser

Overview The recent, rapid advances in modern biology heavily rely on fundamental mathematical techniques and, in particular, on partial differential equations, an essential tool for the mathematical modelling of biological, socio-economic and physical processes. The thesis deals with the analysis and numerical simulation of anisotropic nonlinear PDEs and dynamical systems in biology. It is divided into two parts:

- Part I is motivated by the simulation of fingerprint patterns and deals with a class of anisotropic interaction equations, based on the work in [1, 2, 3, 4, 11].
- Part II focuses on mathematical models for biological transportation networks describing living systems such as leaf venation in plants, blood circulatory systems, and neural networks, and is based on the research in [5, 6, 7, 12].

Through mathematical analysis and computer simulations, we have gained new insights into the qualitative properties of the underlying mathematical models which have resulted in a better understanding of complex phenomena in biology such as biological pattern formation. Equally important, these new and challenging PDE models have led to intra-disciplinary research, involving modelling, PDE theory, dynamical systems, graph theory and numerical simulations. This research has opened up a whole new range of fascinating mathematical problems, which we have studied by developing new mathematical tools.

Simulation of fingerprint patterns

In Part I of the thesis, we focused on modelling fingerprint patterns which is not only of great interest in the biological community, but also in forensic science and increasingly in biometric applications where large fingerprint databases are required for developing, validating and comparing the performance of fingerprint identification algorithms. Besides, similar models have proven to be very useful for modelling swarming in nature, including flocks of birds or colonies of bacteria/cells, and have received significant attention in the scientific community recently due to their great practical relevance in biological applications.

One of the key features of many of these models is the social communication between individuals at different scales, i.e. each individual can interact not only with its neighbours but also with individuals further away. This can be described by short- and long-range interactions. An example of this class of models is the Kücken-Champod model [13] for describing the formation of fingerprint patterns.

The development of fingerprints can be described by three phases [13]. In the first phase, growth forces in the epidermis and shrinkage of volar pad create compressive mechanical stress, modelled by Kücken and Newell [14, 15]. The second phase consists of the rearrangement of Merkel cells from a random configuration into parallel ridges along the lines of smallest compressive stress, cf. Figure 1. This phase can be regarded as the actual pattern forming process and was first modelled by Kücken and Champod [13]. In the third phase, the primary ridges are induced by the Merkel cells.

Since the first phase of the fingerprint devel-

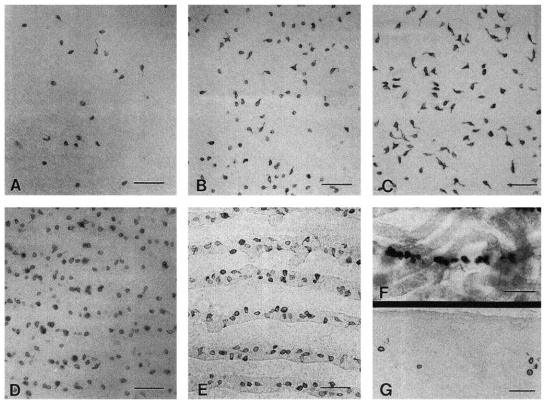


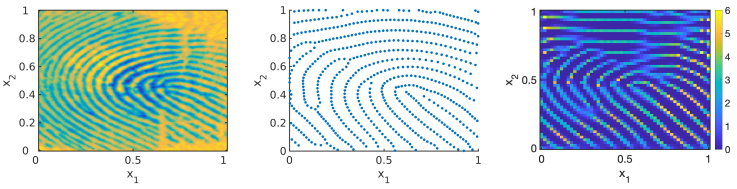
Figure 1: Development of Merkel cell distribution by Kim and Holbrook: Merkel cells appear at about the 7th week of pregnancy, multiply and arrange in lines at about the 10th week. Figure from [10].

opment has already been successfully modelled [14, 15] and the third phase can easily be modelled based on the second phase, we focus on the second phase where the stress field from the first phase is assumed to be a given input. Mathematically, the formation of fingerprints can then be described as a large system of interacting Merkel cells [13], which align themselves according to certain interaction forces and form our fingerprint lines.

Part I of the thesis deals with a class of interacting particle models with anisotropic repulsive-attractive interaction forces motivated by anisotropic pattern formation in nature. In most existing models, the forces are isotropic and particle models lead to non-local aggregation PDEs with radially symmetric potentials. The central novelty in the models we consider is an anisotropy induced by an underlying tensor field, cf. Figure 2(A). This innovation does not only lead to the ability to describe real-world phenomena more accurately, but also renders their analysis significantly harder compared to their isotropic counterparts. Due to the non-existence of an interaction potential and a gradient flow formulation, much of the existing analytic theory does not apply to these anisotropic interaction models and new methods are required for studying these models rigorously.

We studied the role of anisotropic interaction in these biological models by considering both the particle model and its continuum counterpart. This allowed us to propose a bio-inspired model to simulate realistic fingerprint patterns, cf. Figure 2(B) for simulation results of the discrete model, featuring important properties of a biologically meaningful fingerprint development model. We also gave a rigorous proof of the stability of line patterns. Moreover, we investigated the role of nonlinear diffusion on the widening of line patterns both analytically and numerically, and simulated realistic fingerprint patterns efficiently with the continuum model, cf. Figure 2(C). In the following, we describe the results of Part I in more detail.

Anisotropic pattern formation [1]: A crucial step towards understanding anisotropic



(A) Anisotropy (B) Particle model (C) Mean-field model

Figure 2: Numerical simulation results for fingerprint patterns.

pattern formation in nature is to investigate the role of the anisotropy which can be characterised by one parameter in the model. We studied the variation of this parameter, describing the transition between the isotropic and the anisotropic model, analytically and numerically. We analysed the equilibria of the corresponding mean-field partial differential equation and investigated pattern formation numerically in two dimensions by studying the dependence of the parameters in the model on the resulting patterns.

Simulation of fingerprint patterns [4]: Evidence suggests that both the interaction of Merkel cells and the epidermal stress distribution play an important role in the formation of fingerprint patterns during pregnancy [9]. To model the formation of fingerprint patterns in a biologically meaningful way these patterns have to become stationary. For the creation of synthetic fingerprints it is also very desirable that rescaling the model parameters leads to rescaled distances between the stationary fingerprint ridges. Based on these observations, as well as the model introduced by Kcken and Champod [13] we proposed a new model for the formation of fingerprint patterns during pregnancy. In this anisotropic interaction model, the interaction forces not only depend on the distance vector between the cells and the model parameters, but additionally on an underlying tensor field, representing a stress field. This dependence on the tensor field leads to complex, anisotropic patterns. We studied the resulting stationary patterns both analytically and numerically. In particular, we showed that fingerprint patterns can be modelled as stationary

solutions for an appropriate choice of the underlying tensor field.

Stability analysis of line patterns [3]: Stable line patterns play a crucial role in the pattern formation of the anisotropic interaction model and are also important for the simulation of fingerprint patterns. For a given spatially homogeneous tensor field, we showed that there exists a preferred direction of straight lines, i.e. straight vertical lines can be stable for sufficiently many particles, while many other rotations of the straight lines are unstable steady states, both for a sufficiently large number of particles and in the continuum limit. For straight vertical lines we considered specific force coefficients for the stability analysis of steady states, showed that stability can be achieved for exponentially decaying force coefficients for a sufficiently large number of particles, and relate these results to the Kücken-Champod model for simulating fingerprint patterns. The mathematical analysis of the steady states is completed with numerical results.

Role of nonlinear diffusion on pattern formation [2]: For simulating fingerprint patterns with a finite width an additional nonlinear diffusion term can be considered in the mean-field model resulting in an anisotropic, nonlocal aggregation equation with nonlinear diffusion which does not possess a gradient flow structure. We studied the equilibria of this model by deriving equilibrium conditions for stationary line patterns which can be reformulated as the minimisers of a regularised energy functional if the underlying tensor field is spatially homogeneous. For this case, we showed the existence of energy minimisers, established Γ-convergence of the regularised energy functionals as the diffusion coefficient vanishes, and proved the convergence of minimisers of the regularised energy functional to minimisers of the non-regularised energy functional. Finally, we proved weak convergence of a numerical scheme for the numerical solution of the model with any underlying tensor field, and showed numerical results. This numerical scheme allowed us to simulate fingerprint patterns using the mean-field modelling approach. The resulting patterns are better than for the associated particle model. In particular, by rescaling the forces we could vary the distances between the fingerprint lines.

Formation of biological transport networks Part II of the thesis deals with transportation networks which are ubiquitous in living systems such as leaf venation in plants, blood circulatory systems, and neural networks. Understanding the development, function, and adaptation of biologic transportation networks has been of long-standing interest in the scientific community due to their complexity. Inspired by the complex biological phenomena, mathematical models and methods have recently been developed for adaptive transportation networks.

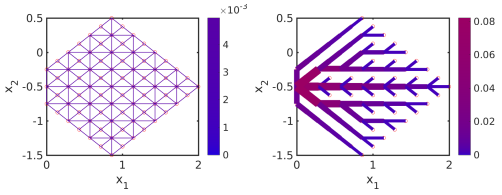
Mathematical modeling of transportation networks is traditionally based on discrete frameworks, in particular mathematical graph theory and discrete energy optimization, where the energy consumption of the network is minimized under the constraint of constant total material cost. However, networks and circulation systems in living organisms are typically subject to continuous adaptation, responding to various internal and external stimuli. For instance, for blood circulation systems it is well known that throughout the life of humans and animals, blood vessel systems are continuously adapting their structures to meet the changing metabolic demand of the tissue. In particular, it has been observed in experiments that blood vessels can sense the wall shear stress and adapt their diameters according to it. Consequently, dynamic models are required for modelling biological transport networks accurately.

Motivated by this observation, a new discrete dynamic modelling approach on a graph has recently been introduced by Hu and Cai [8] to describe the formation of biological transport networks. The main mathematical interest of this dynamical model stems from the highly unusual coupling of a system of ODEs whose solution is defined on the edges of a graph to a linear system on the nodes of the graph. In particular, the linear system is only solvable under certain conditions and due to the coupled defining equations on both nodes and edges of the graph

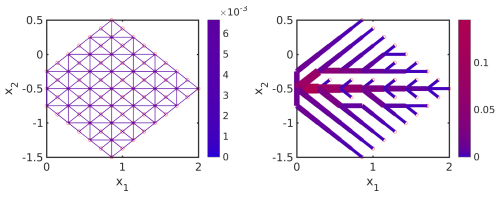
it is not clear under which assumptions a limit model can be derived.

The aim of Part II is to get a better understanding of the Hu-Cai model [8] for generic biological transport networks and adapt it to the cellular context for leaf venation. Using methods from various fields within mathematics, we investigated the global existence of solutions of the microscopic and the associated macroscopic models, which can be written as the unusual coupling of a linear system and a system of ordinary differential equations on a graph and its continuum counterpart. Moreover, we proved the rigorous limit between the microscopic and macroscopic model for the two-dimensional regular setting which required the formal derivation of an appropriate macroscopic model. These analytical results were complemented by numerical simulations of the discrete model (cf. Figure 3) illustrating the convergence to steady states, their non-uniqueness as well as their dependence on initial data and model parameters. Based on this model, we proposed an adapted model in the cellular context for leaf venation, investigated the model analytically and showed numerically that it can produce branching vein patterns (cf. Figure 4). In the following, we discuss our results in more detail.

ODE- and PDE-based modelling [6]: To get a better understanding about the dynamics

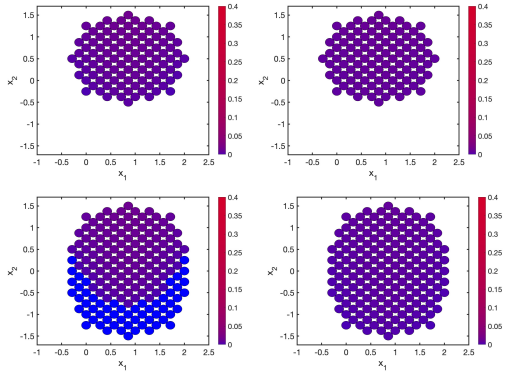


(A) Full graph

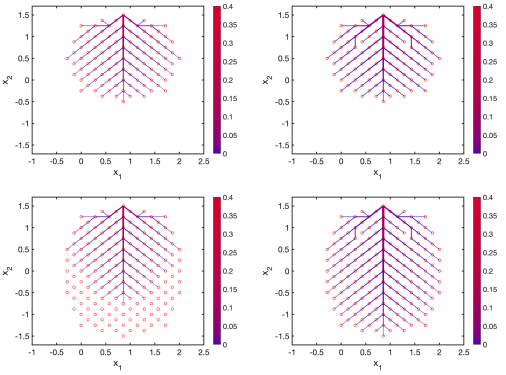


(B) Perturbed full graph

Figure 3: Steady states for full graph and perturbed full graph



(A) Auxin concentration



(B) Transport activity

Figure 4: Steady states for auxin concentration and transport activity for different background source strengths and different grid shapes (round, oval).

in the Hu-Cai model [8], we studied the global existence of solutions of a discrete (ODE based) model on a graph. We proposed an adaptation of this model so that a macroscopic (PDE based) system can be obtained as its formal continuum limit. We proved the global existence of weak solutions of the macroscopic PDE model. Finally, we presented results of numerical simulations of the discrete model, illustrating the convergence to steady states, their non-uniqueness as well as their dependence on initial data and model parameters.

Rigorous continuum limit [7]: For the analysis and simulation of complex dynamical systems in biology, it is often very useful to consider the associated continuum limit which may given additional insights about the biological transport and allows us to include additional modelling assumptions such as network growth.

This motivated our study of the rigorous limit of the discrete model. For the spatially two-dimensional rectangular setting we proved the rigorous continuum limit of the constrained energy functional as the number of nodes of the underlying graph tends to infinity and the edge lengths shrink to zero uniformly. The proof is based on reformulating the discrete energy functional as a sequence of integral functionals and proving their Γ-convergence towards the continuum energy functional.

Application to auxin transport in leaf venation [5]: The plant hormone auxin controls many aspects of the development of plants. One striking dynamical feature is the self-organisation of leaf venation patterns which is driven by high levels of auxin within vein cells. The auxin transport is mediated by specialised membrane-localised proteins. Many venation models have been based on polarly localised efflux-mediator proteins of the PIN family. We investigated a modelling framework for auxin transport with a positive feedback between auxin fluxes and transport capacities that are not necessarily polar, i.e. directional across a cell wall. Our approach is derived from a discrete graph-based model for biological transportation networks, where cells are represented by graph nodes and intercellular membranes by edges. The edges are not a-priori oriented and the direction of auxin flow is determined by its concentration gradient along the edge. We proved global existence of solutions to the model and the validity of Murray's law for its steady states. Moreover, we demonstrated with numerical simulations that the model is able connect an auxin source-sink pair with a mid-vein and that it can also produce branching vein patterns. A significant innovative aspect of our approach is that it allows the passage to a formal macroscopic limit which can be extended to include network growth. We also performed mathematical analysis of the macroscopic formulation, showing the global existence of weak solutions.

Conclusion In the thesis, we studied two complex PDE models arising in biological applications. Part I, motivated by the simulation of fingerprint patterns, is mainly based on four papers [1, 2, 3, 4] which are among the first works on the analysis of anisotropic interaction models. Using innovations on the modelling, analysis, and computational methods, this research on anisotropic interaction is a crucial step towards the accurate description of real-world phenomena. Part II is motivated by the formation of biological transport networks and is mainly based on three journal articles [5, 6, 7]. This research resulted in a better understanding of the Hu-Cai model for biological transport networks and its continuum counterpart, and led to an adapted model in the cellular context for leaf venation.

References

[1] M. Burger, B. Düring, L. M. Kreusser, P. A. Markowich, and C.-B. Schönlieb. Pattern formation of a nonlocal, anisotropic interaction model. *Math. Models Methods Appl. Sci.*, 28(03):409–451, 2018.

[2] J. A. Carrillo, B. Düring, L. M. Kreusser, and C.-B. Schönlieb. Equilibria of an anisotropic nonlocal interaction equation: Analysis and numerics. 2019.

[3] J. A. Carrillo, B. Düring, L. M. Kreusser, and C.-B. Schönlieb. Stability analysis of line patterns of an anisotropic interaction model. *SIAM J. Appl. Dyn. Syst.*, 18(4):1798–1845, 2019.

[4] B. Düring, C. Gottschlich, S. Huckemann, L. M. Kreusser, and C.-B. Schönlieb. An Anisotropic Interaction Model for Simulating Fingerprints. *J. Math. Bio.*, 78(7):2171–2206, 2019.

[5] J. Haskovec, H. Jnsson, L. M. Kreusser, and P. A. Markowich. Auxin transport model for leaf venation. *Proc. Roy. Soc. A*, 475(2231):20190015, 2019.

[6] J. Haskovec, L. M. Kreusser, and P. A. Markowich. ODE and PDE based modeling of biological transportation networks. *Comm. Math. Sci.*, 17(5):1235–1256, 2019.

[7] J. Haskovec, L. M. Kreusser, and P. A. Markowich. Rigorous Continuum Limit for the Discrete Network Formation Problem. *Comm. PDEs*, 44(11):1159–1185, 2019.

[8] D. Hu and D. Cai. Adaptation and Optimization of Biological Transport Networks. *Phys. Rev. Lett.*, 111:138701, 2013.

[9] M. K. Irmak. Multifunctional merkel cells: their roles in electromagnetic reception, fingerprint formation, reiki, epigenetic inheritance and hair form. *Med. Hypotheses*, 75:162–168, 2010.

[10] D.-K. Kim and K. A. Holbrook. The appearance, density, and distribution of merkel cells in human embryonic and fetal skin: Their relation to sweat gland and hair follicle development. *Journal of Investigative Dermatology*, 104(3):411–416, 1995.

[11] L. M. Kreusser. Analysis of Anisotropic Interaction Equations for Fingerprint Simulations. In *Proceedings in Applied Mathematics and Mechanics - 89th GAMM Annual Meeting*, 2018.

[12] L. M. Kreusser and P. A. Markowich. Discrete and continuum modeling of biological network formation. In *SIAM Workshop on Network Science (NS17)*, 2017.

[13] M. Kücken and C. Champod. Merkel cells and the individuality of friction ridge skin. *J. Theoret. Biol.*, 317:229–237, 2013.

[14] M. Kücken and A. Newell. A model for fingerprint formation. *Europhysics Letters*, 68:141–146, 2004.

[15] M. Kücken and A. Newell. Fingerprint formation. *J. Theoret. Biol.*, 235:71–83, 2005.

Modeling COVID-19: Challenges and results

By Maíra Aguiar

Weird times we are living in. While lots of technological, medical and scientific advances are generated in a short period of time, we are now fighting a pandemic, trying to stop the spread of a new virus that has not only killed thousands of people but has also crippled our economies as lockdowns were implemented.

In December 2019, a severe respiratory syndrome (COVID-19) caused by a new coronavirus (SARS-CoV-2), was identified in China and spread rapidly around the globe. COVID-19 was declared a pandemic by the World Health Organization (WHO) in March, 2020. As of this writing, about 25 million cases were confirmed with more than 830 thousand deaths - a global case fatality ratio (CFR) of approximately 3.5%.

COVID-19 symptoms can range from mild (or no symptoms) to severe illness, with signs and symptoms appearing between 2 to 14 days after exposure. With many asymptomatic individuals, everyone is at risk of getting COVID-19. SARS-CoV-2 infection results in disease severity and death according to a hierarchy of risks, with age and pre-existing health conditions enhancing disease severity [1]. If the young and "healthy" individuals are not severely affected, SARS-CoV-2 has put at a greater risk our beloved parents and grandparents. An effective vaccine would be the best way to prevent COVID-19 infections and while its development is ongoing, epidemiologists and public health workers are the frontline of this battle, fighting with well known public health surveillance strategies of testing, contact tracing and isolation of infected individuals.

While the global case fatality ratio (CFR), a measure that is often used to evaluate the severity of the epidemics, starts to decrease over time, there are too many unknowns about COVID-19 dynamics. Why do we observe so different CFR in different countries around the globe? Are there differences in population susceptibility to SARS-CoV-2 infection and how much would that affect the course of infection in the population? What is the influence of seasonality on COVID-19 transmission? Would it be enough to contain the epidemics, such as other Influenza Like Illnesses (ILIs), even when traveling restrictions start to be lifted and imported cases from the southern hemisphere would be likely to be detected? What is the proportion and the role of the mild and asymptomatic infected individuals? Are they transmitting more or less than the symptomatic severe infected? And to which extent the acquired immunity and its duration against SARS-CoV-2 will play a role in the so called herd immunity without vaccination? Too many open questions that scientists are trying to answer by laboratory experiments, field work and theoretical studies.

As the COVID-19 pandemic is unfolding, research on mathematical modeling became imperative and very influential, not only in understanding the epidemiology of COVID-19 but also in helping the national health systems to cope with the high demands of hospitalizations, for example, providing projections and predictions based on the available data. Used as a public health guiding tool to evaluate the impact of intervention measures, governments have already taken important decisions based on modeling results. The COVID-19 pandemic has resulted in an avalanche of epidemiological modeling papers [2, 3, 4, 5, 6, 7, 8], most of them using simple models such as the SIR (Susceptible-Infected- Recovered) or SEIR (Susceptible-Exposed-Infected- Recovered) in mechanistic or probabilistic frameworks to understand and predict the spread of the disease in a population. With valuable results, modeling the dynamics of COVID-19 is very challenging, as we still know very little about the disease. More complex models would be able to give more accurate projections about specific vari-

ables such as number of hospitalizations, intensive care units admissions (ICUs) and deaths, for example, over the course of the epidemics. However, to build useful models, good quality empirical data and its understanding, as well as a close collaboration among mathematical modelers, field and laboratory researchers as well as public health stakeholders are essential.

Here I present my experience, as part of the Basque Country Modeling Task Force (BMTF), in monitoring the development of the COVID-19 epidemic to assist the Basque Health Managers and the Basque Government during the lockdown lifting measures.

In March 2020, a multidisciplinary task force was created to assist the Basque Health managers and the Basque Government during the COVID-19 responses. BMTF is a modeling team, working on different approaches, including stochastic processes, statistical methods and artificial intelligence. The primary BMTF objectives were to describe the epidemic in terms of disease spreading and control in the Basque Country and to give projections on the national health system necessity during the increased population demand on hospital admissions. With a valid modeling framework, we now monitor disease transmission when the country lockdown was gradually lifted towards the so called "new normality".

We use stochastic SHARUCD-type models (susceptible (S), severe cases prone to hospitalization (H), mild, sub-clinical or asymptomatic (A), recovered (R), patients admitted to the intensive care units (U) and the recorded cumulative positive cases (C) which includes all new positive cases for each class of H, A, U, R, and deceased (D)) - an extension of the well known simple SIR model. Epidemiological data used to validate and parametrize the models are provided by the Basque Health Department and the Basque Health Service (Osakidetza), continually collected with specific inclusion.

In our first modeling attempt, disease severity was decided upon infection with a proportion η of infected individuals going to develop severe symptoms prone to hospitalization or $(1-\eta)$ to develop mild or no symptoms [9]. Mild

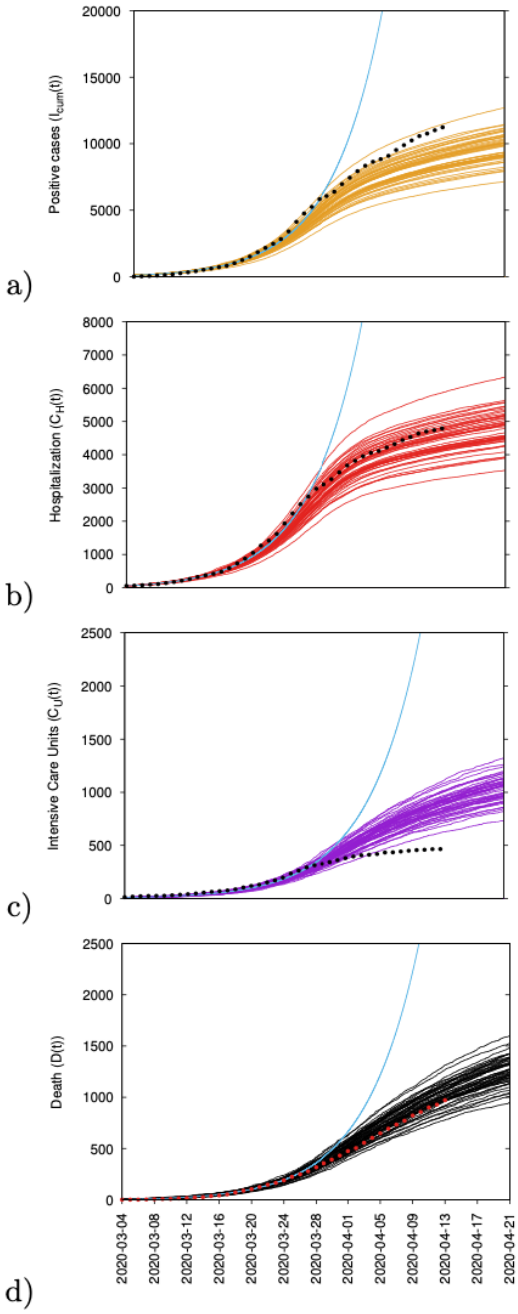


Figure 1: Ensemble of 200 stochastic realizations of the initial SHARUCD-model. Empirical data are plotted as black/red dots. In a) cumulative positive cases I_{cum}(t), in b) cumulative hospitalized cases C_H(t), in c) cumulative ICU admissions C_U(t) and in d) cumulative deceases cases D(t). The mean field solution without control is shown as a blue line.

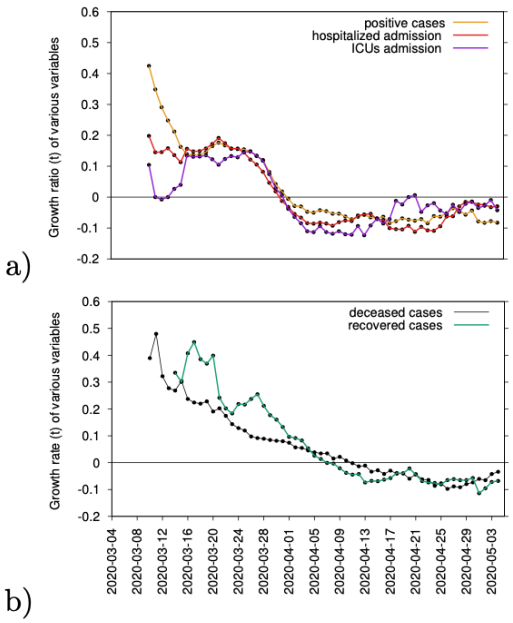


Figure 2: Growth rates estimations for various variables. In a) PCR positive cases (yellow), hospitalizations (red) and ICU admission cases (purple) and in b) growth rate for recovered (green) and deceased cases (black) notified in the Basque Country.

and asymptomatic individuals were assumed to transmit the disease more efficiently ($\phi\beta$, with $\phi > 1$) than the severe cases which would be first cases identified, at least at the beginning of the pandemic when testing capacity was low. In this approach, hospitalized cases could recover, die or go to ICU, i.e., ICU was considered a progression in severity of hospitalized cases. Parameter insecurities were calculated numerically with likelihood functions conditioned on the others and the data from all 5 model variables and fixed as the model was able to describe the disease incidence during the exponential phase of the outbreak. Partial lockdown implemented on March 16, 2020 was shown to decrease disease transmission in the Basque Country, with effects observed on March 27, 2020, well before the full lockdown on March 31, 2020.

The effect of the disease control measures was introduced using a standard sigmoid function which was able to describe well the gradual slowing down of the epidemic, see Fig. 1.

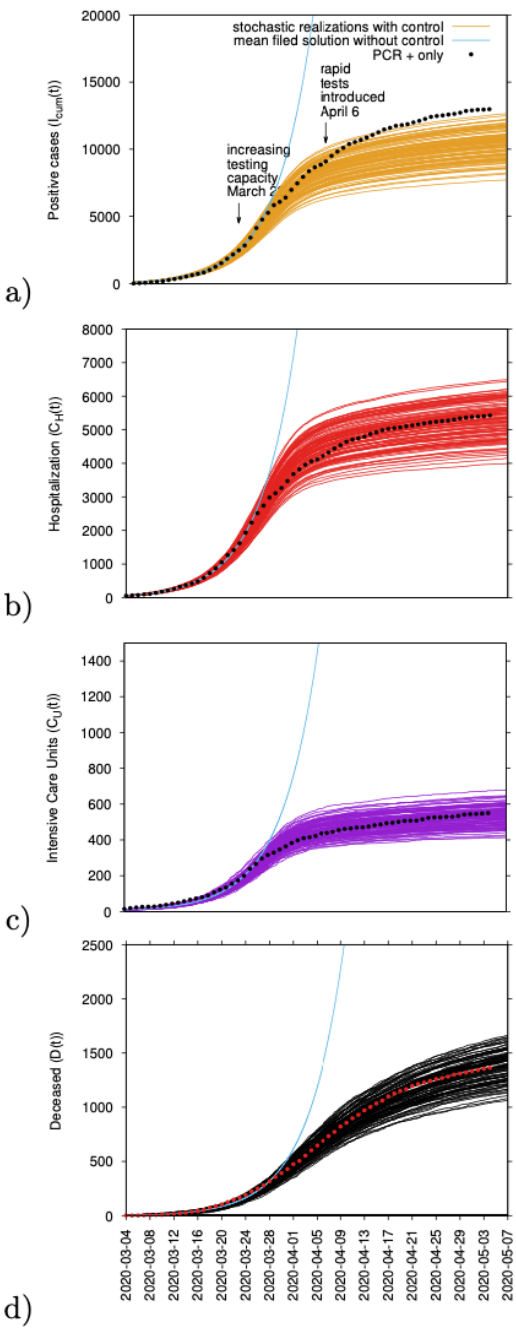


Figure 3: Ensemble of 200 stochastic realizations of the ICU refined SHARUCD-model. Empirical data are plotted as black/red dots. In a) cumulative positive cases I_{cum}(t), in b) cumulative hospitalized cases C_H(t), in c) cumulative ICU admissions C_U(t) and in d) cumulative deceases cases D(t). The mean field solution without control is shown as a blue line.

Analysis of the momentary reproduction ratio and momentary growth rates [10] have shown two groups of growth behaviour in response to the lockdown measures. Synchronization of the ICU admission cases with the cumulative tested positive cases and hospitalizations was observed, following the sigmoidal function behaviour, and the deceased and recovered cases showing a delay in response to the control measures of 8 to 10 days, see Fig. 2.

These findings have led to the first refinement of our model, with the transition into ICU admissions changed to a ratio, with infection causing from asymptomatic up to very severe cases. In good agreement, the refined model can now describe well the hospitalizations, the ICU admissions and the deceased cases (see Fig. 3), well matched within the median of the 200 stochastic realizations from the model [11]. Although the cumulative incidences for tested positive cases could only be described qualitatively, following the higher realizations range due to the increasing testing capacities in the Basque Country since March 22, 2020, we now work on further model refinements evaluating the role of seasonal effect, the "new normality"after lockdown lifting and the impact of imported cases and increase testing capacity (see Fig. 4).

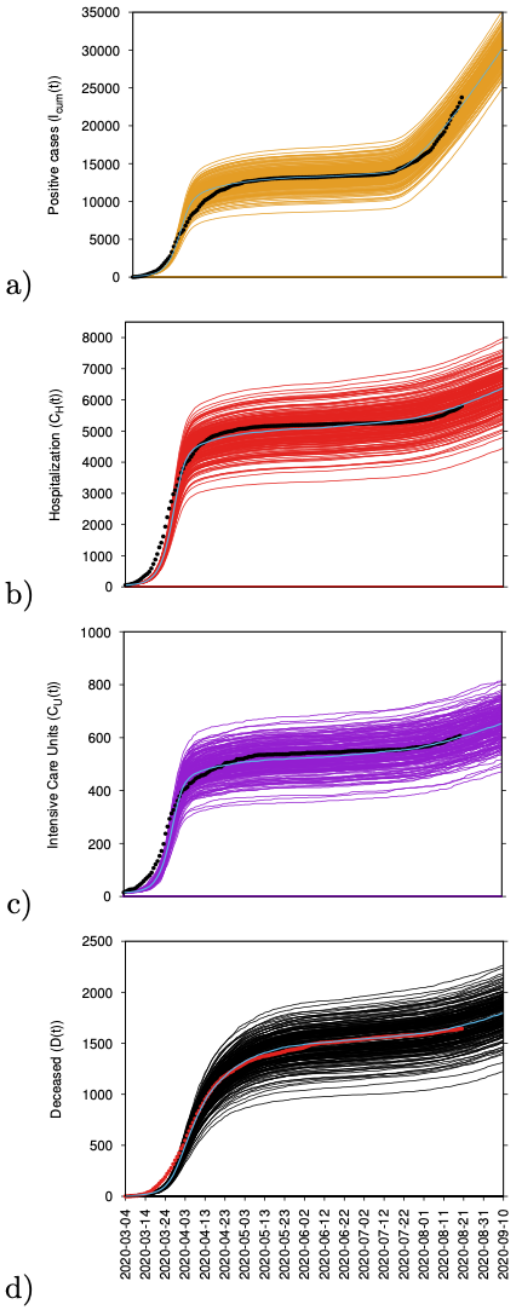


Figure 4: Ensemble of 200 stochastic realizations of the import and seasonality refined SHARUCD-model. Empirical data are plotted as black/red dots. In a) cumulative positive cases I_{cum}(t), in b) cumulative hospitalized cases C_H(t), in c) cumulative ICU admissions C_U(t) and in d) cumulative deceases cases D(t). The mean of the stochastic simulations is shown as a blue line. This is working in progress with a detailed analysis to be publicly available soon [11].

References

[1] M. Aguiar and N. Stollenwerk, 2020. Condition-specific mortality risk can explain differences in COVID-19 case fatality ratios around the globe. To appear in *Journal of Public Health*. https://doi.org/10.1016/j.puhe.2020.08.021

[2] R.M. Anderson, H. Heesterbeek, D. Klinkenberg, T.D. Hollingsworth. (2020). How will country-based mitigation measures influence the course of the COVID-19 epidemic? *The Lancet*. https://doi.org/10.1016/S0140-6736(20)30567-5

[3] Imperial College COVID-19 Response Team. March 30, 2020. Estimating the number of infections and the impact of non-pharmaceutical interventions on COVID-19 in 11 European countries. https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/report-13-europe-npi-impact/

[4] S.M. Kissler et al. (2020). Projecting the transmission dynamics of SARS-CoV-2 through the postpan-

demic period. *Science* 14 Apr 2020:eabb5793 DOI: 10.1126/science.abb5793

[5] C. Anastassopoulou, L. Russo, A. Tsakris, C. Siettos (2020). Data-based analysis, modelling and forecasting of the COVID-19 outbreak. *PLoS One*, 15, e0230405.

[6] K.B. Blyuss, Y.N. Kyrychko. (2020). Effects of latency and age structure on the dynamics and containment of COVID-19. *Preprint* https://doi.org/10.1101/2020.04.25. 20079848

[7] J. Michaud, J. Kates, L. Levitt (2020). COVID-19 Models: Can They Tell Us What We Want to Know? https://www.kff.org/coronavirus-policy-watch/covid-19-models/

[8] G. Giordano et al. (2020). Modelling the COVID-19 epidemic and implementation of population-wide interventions in Italy. *Nature Medicine*. https://doi.org/10.1038/s41591-020-0883-7

[9] M. Aguiar, E. Millán Ortuondo, J. Bidaurrazaga Van-Dierdonck, J. Mar, N. Stollenwerk (2020). Modeling COVID 19 in the Basque Country: from introduction to control measure response. To appear in Nature Scientific Reports. *Available as a preprint:* https:// doi.org/10.1101/2020.05.10.20086504

[10] M. Aguiar, J.B. Van-Dierdonck, N. Stollenwerk (2020). Reproduction ratio and growth rates: Measures for an unfolding pandemic. *PLoS ONE*, 15(7): e0236620. https://doi.org/10.1371/journal.pone.0236620

[11] *Epidemiological SHARUCD model*. https://wp.bcamath.org/news/en/epidemiological-sharucd-model/

ESMTB Thematic panels

The field of mathematical biology continues to grow, and ESMTB has therefore decided to foster interactions in subgroups, where society members can meet and interact within more focused areas. Membership to the societys thematic panels is open to all members. New thematic panels may be formed by petition to the ESMTB Board at any time.

Guidelines for the establishment and operation of ESMTB thematic panels

The ESMTB welcomes the fostering of specialised interest groups among its members, groups to be henceforth designated as *thematic panels* (name subject to discussion) to inspire, advance and promote activities within the scope of ESMTB. Thematic panels are organised within a certain theme and are hosted by a chair. The following guidelines shall apply to their establishment and operation.

1. Groups of at least 20 members may apply for the establishment of a thematic panel with the ESMTB board. Applications should be sent to the ESMTB secretary and be signed by the founding chair of the panel. A short description of the scope and scientific interests must be provided.
2. Affiliation to such panels is free of charge and open to all interested members, who may join in at any time. Membership in the panel ends with the end of membership in ESMTB.
3. The panel members will manage the operation of the panel on a democratic basis; in particular, they nominate (or elect) the chair in regular intervals. The chair is the representative of the panel and serves as the contact person for the ESMTB board. When the chair changes, the secretary of ESMTB should be informed as soon as possible.
4. ESMTB may financially sponsor (if budget is available) the activities of the panels, upon request by the panel's representative.
5. ESMTB expects each panel to produce periodic summary documentation reporting on the activities of the panel and indicating likely directions of development in the research area covered by the panel.
6. The ESMTB secretary is charged with facilitating panel operations and briefly reporting to the board on current developments.
7. ESMTB will host on the society's webpage, in the Newsletter, the Communications, and social media news related to the activities of the thematic panels, as provided by the panel representatives.
8. Thematic groups and their members consent the ESMTB to store and process their names and contact data.

Perspectives in Mathematical and Theoretical Biology

The series "Perspectives in Mathematical and Theoretical Biology" is published as a separate section in the Journal of Mathematical Biology, the official journal of the society. ESMTB invites its members and colleagues to contribute short Perspectives on topical issues in mathematical and theoretical biology to be published in the Journal of Mathematical Biology.

Perspectives highlight emerging fields and novel developments of wide interest. They are short contributions to highlight topical issues, emerging fields, fundamentally new approaches, and exciting novel developments in mathematical and theoretical biology, which are of interest for the diverse membership of ESMTB and the wide readership of the Journal of Mathematical Biology. Contributions should concentrate on current awareness and promising future directions: The aim is to draw attention and incite interest rather than to provide comprehensive reviews. Perspectives can express personal viewpoints and can voice the author's opinion in debated issues. For more information, see `https://esmtb.org/Perspectives`.

The contributions are peer reviewed. Perspectives are to be submitted via the Editorial Manager system of the Journal of Mathematical Biology, `https://www.editorialmanager.com/jomb/`.

The following is a preprint of a contribution by Elisenda Feliu published in Journal of Mathematical Biology, 80, 1159–1161, 2020.

On the role of algebra in models in molecular biology

By Elisenda Feliu[1]*, Department of Mathematical Sciences, University of Copenhagen,* `efeliu@math.ku.dk`

Classical reference books in mathematical biology, e.g. [7], illustrate how, in its origins, this once emerging field essentially relied on small models, and their thorough analysis employed a suit of advanced techniques from dynamical systems theory. It was often feasible to pursue such analysis without fixing the value of model parameters, thereby obtaining a full picture of the possible behaviors of the model. In many cases, the purpose of the model was to provide a qualitative understanding of a phenomenon, which not necessarily needed to fit exactly with observational data.

As models have become larger and more complex, and with the increasing availability of data, in particular in molecular biology, a standard approach to analyze mathematical models has been to first gain some insight about suitable parameter values, for example via estimation or extrapolating from related species, and then employ numerical methods to simulate the models. In this way, a precise description of the system of interest could be obtained. A problem arises when parameters are unidentifiable, or cannot be determined with the desired precision, or when we need to take into account that parameter values typically fluctuate, are specific to the individual, and depend on the environment. Then we are back to the original problem of understanding the model in a larger region of the parameter space. As the complexity of the models forbid detailed hands-on analyses, model inspection is often achieved through a combination of parameter sampling and numerical simulation.

Parallel to this development, some theories have centered around systems of ordinary differential equations that model the concentra-

[1]EF acknowledges funding from the Independent Research Fund of Denmark.

tion of species in an interaction network in time. Although these models are typically associated with chemical and biochemical reactions, the formalism fits as well models in ecology, like the Lotka-Volterra model, or in epidemiology: All these have in common that the interactions among entities drive the changes of the system.

The origin of these theories goes mainly back to the 70'ies and 80'ies, with, to name a few, the work of Feinberg, Horn and Jackson leading to what is known as Chemical Reaction Network Theory (CRNT) [6]; Vol'pert [8]; and Clarke, leading to Stoichiometric Network Analysis [2]. Common to these theories is the search for easy-to-apply methods concerning dynamics, by relying on the structure of the interaction network and assumptions about the rates of the interactions. This has lead to simple (but powerful) theorems on number of steady states and their stability, to give some examples.

These theories are at one end of the spectrum of the level of abstraction of mathematical models. At the left end of the spectrum we find models that are fitted to real data and provide detailed quantitative information of a specific system under study; and at the right end of the spectrum, we find general theories aimed at studying classes of models that share some particularities and their qualitative properties. Moving from left to right we go from models whose goal is to represent reality in detail, to models seeking to identify underlying principles. Although at first sight one might think that the left region of the spectrum is the one that really matters in practical scenarios, a throughout qualitative analysis of families of models can be valuable to guide experimental design, to support conclusions of fitted models, and can be helpful in synthetic biology. Furthermore, it is advantageous, and at the core of mathematics, to rely on general theories when studying specific models.

Algebra and Interaction Networks

In recent years, these old theories about interaction networks from the 70'ies, mainly CRNT, have been revised and further developed under the umbrella of computational algebra and algebraic geometry. The reason behind this, is that models arising from interaction networks typically involve polynomials and rational functions (quotients of polynomials). Prominent examples are the mass-action assumption, yielding polynomial differential equations, or Michaelis-Menten type kinetics, yielding models with rational functions. In this case, the steady states of a model are the solutions to a system of polynomial equations, which is the object of computational algebra and algebraic geometry. Furthermore, computational algebra is well suited to systems with unspecified parameters, after choosing the right coefficient field. It can for example find relations that hold for all parameter values at steady state, or find descriptions of the steady states by means of a simple parametrization. However, two main drawbacks prevent these methods to stand out: the high computational cost, and the fact that the restriction of the steady states to positive values causes nice results from the theory of polynomial equations to fail. For example, any real polynomial of degree n has exactly n complex roots counted with multiplicity, but only some generic upper bounds can be given for the number of real and positive real roots.

Progress within this area has focused on solving these challenges by exploiting the fact that the polynomials under study arise from interaction networks. Through a close interplay with real algebraic geometry, this had lead to numerous strategies to count the number of positive steady states and even understand the parameter space in that respect [3]. More recently, similar ideas are being applied to study stability and bifurcations, as these, via the Routh-Hurwitz criterion, are also expressed in algebraic terms. In general, whenever the question of interest can be reduced to understanding the solutions to a system of polynomial equalities and inequalities, then computational algebra might well be the right theory to call.

Integrating the whole spectrum

Mathematical biology, and applied mathematics in general, is witnessing how theory traditionally belonging to the realm of pure mathe-

matics is finding its place in the study of mathematical models. This certainly applies to algebraic geometry, but also to other disciplines like topology. Despite the broad range of existing theories to analyze mathematical models in molecular biology from different perspectives, the preferred choice often involves numerical simulations combined with parameter inference or parameter sampling. This is presumably driven by the numerous existing tools that address this end of the spectrum, e.g. [1], while we lack proper dissemination and computational tools that cover the rest of the spectrum, and facilitate the access to users without a suitable mathematical background. With few exceptions [4, 5], the latter is partially a consequence of the notable challenges involved with providing easy-to-use black-box implementations of that end of the spectrum. But without these, much of the valuable theory currently being developed to analyze families of models at once, will remain a curiosity and its potential use in real applications will be overlooked.

As methods, tools and theories are constantly being developed to understand the overwhelmingly-complex systems of interacting elements, it would be desirable to have integrative platforms where users, these being experimental biologists or theoreticians, can dissect models at all possible levels.

References

[1] COPASI: Biochemical System Simulator. URL http://copasi.org/

[2] Clarke, B.L.: Stability of Complex Reaction Networks, *Advances in Chemical Physics*, vol. 43. John Wiley & Sons, Inc., Hoboken, NJ, USA (1980)

[3] Dickenstein, A.: Biochemical reaction networks: an invitation for algebraic geometers. In: Mathematical Congress of the Americas, *Contemp. Math.*, vol. 656, pp. 65–83. Amer. Math. Soc., Providence, RI (2016).

[4] Donnell, P., Banaji, M., Marginean, A., Pantea, C.: CoNtRol: an open source framework for the analysis of chemical reaction networks. Bioinformatics **30**(11), 1633–1634 (2014)

[5] Ellison, P., Feinberg, M., Ji, H., Knight, D.: Chemical reaction network toolbox, version 2.2. Available online at http://www.crnt.osu.edu/CRNTWin (2012)

[6] Feinberg, M.: Foundations of Chemical Reaction Network Theory, *Applied Mathematical Sciences*, vol. 202. Springer International Publishing (2019).

[7] Murray, J.D.: Mathematical Biology: I. An introduction, *Interdisciplinary Applied Mathematics*, vol. 17, third edn. Springer (2002)

[8] Vol'pert, A.I., Hudjaev, S.I.: Analysis in classes of discontinuous functions and equations of mathematical physics, *Mechanics: Analysis*, vol. 8. Springer Netherlands (1985)

Karl Peter Hadeler and the rise of Mathematical Biology

By Odo Diekmann

1. Introduction

During the opening session of the 2018 ECMTB in Lisbon, I presented a Tribute to K.P. Hadeler to commemorate the life (1936-2017) and work of a pioneer who has been instrumental in placing Mathematical Biology on the map of science. This text is, in essence, a written version of the tribute (with minor updates and additions).

2. Journals

Visionary scientists often start a new journal in order to promote their dreams. The Bulletin of Mathematical Biology was created as early as 1939 by Nicolas Rashevsky (under the name Bulletin of Mathematical Biophysics). In 1967 Richard Bellman (best known for developing Dynamic Programming) started Mathematical Biosciences. The Journal of Mathematical Biology was founded in 1974 by H.J. Bremermann, F.A. Dodge and K.P. Hadeler with the credo "The creation of this journal is a vote of confidence in the future of mathematical biology". From 1976 on, K.P. Hadeler and S.A. Levin served as Managing Editors and they managed in such a way that the journal became the predominant medium for publication of papers introducing high level mathematical methodology to tackle biologically motivated problems. For many PhD students and postdocs in the last quarter of the previous century, the journal, together with the Springer Lecture Notes in Biomathematics, of which S.A. Levin was the Managing Editor, defined the landscape in which they had to find their way.

3. Oberwolfach Meetings

Every week of every year there is a math meeting at the Mathematisches Forschungsinstitut Oberwolfach (`https://www.mfo.de/`) in Germany's Black Forest. If a sub-field of mathematics has a certain prestige, there is, very likely, an Oberwolfach meeting devoted to the topic at (ir)regular intervals.

K.P. Hadeler at the Bauer-Jacobs-Kolloquium Erlangen, Oberwolfach, 1988.
Oberwolfach Photo Collection

Under the title "Mathematische Modelle in der Biologie" meetings were held in the years listed below, with the listed persons as the organizers:

1971 W. Bühler, J. Gani

1975 K.P. Hadeler, W. Jäger, H. Werner

1978 K.P. Hadeler, W. Jäger, S.A. Levin

1981 K.P. Hadeler, W. Jäger

1984 K.P. Hadeler, W. Jäger

1987 K.P. Hadeler, W. Jäger

1990 W. Alt, K.P. Hadeler, U. an der Heiden

1993 K.P. Hadeler, P.K. Maini, L.A. Segel

1996 W. Alt, O. Diekmann

1999 O. Diekmann, K.P. Hadeler

2003 W. Alt, O. Diekmann, D.A. Rand

2009 E. DiBenedetto, B. Perthame, A. Stevens

The Mathematisches Forschungsinstitut Oberwolfach (MFO, Oberwolfach Research Institute for Mathematics, `https://www.mfo.de/`).

After a long gap, a meeting on "Differential equations arising from organizing principles in biology" took place in September 2018. It was organized by J.A. Carrillo, A. Lorz, A. Marciniak-Czochra and B. Perthame.

In 1989 K. Dietz, K.P. Hadeler and H.W. Hethcote organized a meeting on "Mathematical Models for Infectious Diseases" and in 1995 this was repeated, with H.R. Thieme replacing H.W. Hethcote. Then there was a name switch to "Design and analysis of infectious disease data" with at first N. Becker, K. Dietz and N. Keiding as organizers and later M. Eichner, M.E. Halloran and Ph. O'Neill, and meetings in 1999, 2004, 2009, 2013 and 2018.

The 1978 meeting was the first I attended and, without exaggeration, I can say that it opened my eyes. In a double way. First, I became aware of the richness of the subject (for instance, by a 16 mm movie that Günther Gerisch brought from Basel; in those days, it took some effort of the staff to make the projector work, but once that was accomplished, the miracle of Dicty's self-organization was shown in glorious black and white detail). Second, it proved that authors of papers did really exist and were human beings one could talk to (in Oberwolfach I met for the first time Simon Levin, Lee Segel, Hans Othmer, John Rinzel, Michael Mackey, Masayasu Mimura, Art Winfree, Don Ludwig and many others).

A practitioner of Mathematical Biology aims to act as a trait d'union between the two pillars "Mathematics" and "Biology" and hence risks to be pulled apart by opposing forces. To see how others deal with certain dilemmas helps to keep courage. The Oberwolfach meetings did help a lot in this respect, they showed paragons in action.

Specialization is as unavoidable in math bio as it is in other fields of science. But to get truly new ideas, one needs to look beyond one's 'comfort' zone. The Oberwolfach meetings offered a very comfortable and stimulating way to do exactly that. Moreover, they were instrumental in catalyzing contacts beyond geographical/continental borders. So I (and, I am sure, many others from my generation) am most grateful to Karl Hadeler and Willi Jäger for being for so many years the driving force of these Oberwolfach meetings!

4. ESMTB

In June 1988, KP (as Karl was often nicknamed) and Wolfgang Alt produced and distributed the first Biomathematics Newsletter in order to catalyze the formation of a European community of researchers active in this relatively new area. A little later, Enzo Capasso and Jacques Demongeot took the initiative for the First European Conference on Mathematics Applied to Biology and Medicine, which took place in l'Alpes d'Huez in 1991. During this meeting the ESMTB was formed. The first board consisted of Jim Murray (president), Vin-

cenzo Capasso, Jacques Demongeot, Karl Peter Hadeler and Willi Jäger. The list of presidents so far is:

1991-1993 James D. Murray
1994-1996 Karl Peter Hadeler
1997-1999 Jacques Demongeot
2000-2002 Vincenzo Capasso
2003-2005 Mats Gyllenberg
2006-2008 Wolfgang Alt
2009-2011 Carlos Braumann
2012-2014 Andrea Pugliese
2015-2017 Roeland Merks
2018-2020 Andrea de Gaetano

5. A first conclusion

A journal, series of meetings, a newsletter and a society, these formed the outfit of the scientific youngster 'Mathematical Biology'. And for sure KP Hadeler was among the designers, the trend setters, the shining examples, ...

6. Research

After doing a double 'master' in biology and mathematics, KP followed his heart and chose to do a PhD in mathematics under Lothar Collatz (yes, indeed, the one of the conjecture, see `https://en.wikipedia.org/wiki/Collatz_conjecture`). His first two papers, in 1964, were written in Russian (!) which he learned while staying a year in Moscow, and the next twenty or so in German. They were devoted to Operator Theory, Spectral Theory, Linear Algebra and Numerical Analysis. See [5] for a recent account of how some of this work relates to population dynamical models.

KP was an omnivore with very broad interests (let me mention, incidentally, that KP had an encyclopedic knowledge based on an exceptional memory; he had a staggering knowledge of languages, history, geography, field biology and many other subjects). Much of his subsequent work deals, in some way, with Dynamical Systems Arising in Biology. A non-complete list of bio topics: population genetics, spatial ecology, lateral inhibition, eco-epi interaction, demo-epi interaction, vaccination, core group, vector transmitted, animal orientation, mimicry, plasmids, cardiovascular function, proteasomal cleavage, quiescence. A non-complete list of math topics: travelling fronts, (neutral) delay equations, backward bifurcation, cross diffusion, parameter identification. A bit more physical: nonlinear Schrödinger, cellular automata (his book [4] with Johannes Müller appeared in 2017), granular matter. For sure KP was a multi-methodologist (by which I mean the mathematical version of what in music is called a multi-instrumentalist). Major topics:

- macroparasite load as a structuring variable (with Klaus Dietz, see [1] for a survey)
- hyperbolic submodels for movement (correlated random walks, reaction-telegraph/transport equations, see [3])
- pair formation in STD context; homogeneous differential equations (see [5])
- the impact of quiescence (diapause, temporary change of either behaviour, physiology or habitat, see [3])

7. Teaching

In 1971 the Universität Tübingen appointed KP Hadeler at the Lehrstuhl für Biomathematik in the Biology Department and in 1973 this appointment was extended to the Mathematics Department, making him a trait d'union in a very literal sense. (With the earlier noted side effect of being subject to opposing forces.) In 1974 Hadeler's text book Mathematik für Biologen was published as one of the Heidelberger Taschenbücher by Springer.

In the 1979 CIME Summerschool 'Mathematics of Biology' in Cortona, organized by Mimmo Iannelli, Hadeler lectured about 'Diffusion Equations in Biology' (the other lecturers were K.L. Cooke, J.M. Cushing, S. Hastings, F.C. Hoppensteadt and S-O Londen, so various forms of delay equations received ample attention). Many years later, in 1997, and in a different part of Italy (Martina

Franca in Puglia) Hadeler lectured about 'Reaction Transport Systems in Biological Modelling' during the CIME school 'Mathematics Inspired by Biology' organized by V. Capasso and myself (the other lecturers were R. Durrett, P.K. Maini, H.L. Smith and myself). Somewhere in between there has been a DMV (Deutsche Mathematiker-Vereinigung) Seminar in the small town Blaubeuren near Ulm with lectures on mathematical methods for the study of biological systems by KP Hadeler, Horst Thieme and myself. And there must have been many more such schools in which Hadeler gave a series of lectures...

Remarkably, after his Tübingen retirement KP Hadeler rejuvenated and moved part-time to the new world for a second youth as Research Professor at Arizona State University in Phoenix during the period 2005-2011. The material of many of his lectures (at both the School of Life Sciences and the School of Mathematical and Statistical Sciences) is collected in his book [3] 'Topics in Mathematical Biology' that appeared in 2017 in the Springer Series 'Lecture Notes on Mathematical Modelling in the Life Sciences'. During his time at ASU, Hadeler very actively assisted Carlos Castillo-Chavez in the sympathetic endeavour of providing research opportunities for underrepresented groups.

My impression is that KP Hadeler was a warm mentor for his many students, often like a father figure (thus, perhaps, promoting the puberal urge for independence and freedom in some?). He had more than 30 students and of these, Mirjam Kretzschmar, Johannes Müller, Thomas Hillen, Christina Kuttler and Frithjof Lutscher are presently most active in math bio research.

8. Conclusion

While once a naturalist observed and classified, the present day naturalist urges the government to protect an endangered species. Likewise a theoretical biologist once aspired to uncover the mechanisms underlying a certain phenomenon, while the present day theoretical biologist advises the government about Covid-19 control. The world has changed. But we build on what has been achieved by the predecessors.

KP Hadeler has been instrumental in building up Mathematical Biology

- both organizationally and regarding content
- especially in Europe
- especially at the math side
- notably by pointing the way to young talent

He was a very versatile researcher, a prolific writer and a master in inventing clever tricks that made hopeless looking problems suddenly amenable to analysis. His stimulating influence and his charming personality are sorely missed by his many old friends. Hopefully this short note informs the younger among us about the pioneer that helped shape the world in which they now live, work and move on.

PS

- Please also see the special issue [2].
- It is a pleasure to thank Enzo Capasso for helping out with ESMTB history reconstruction, Klaus Dietz for providing information about the later Oberwolfach meetings on infectious disease epidemiology and Susanne Ditlevsen for editorial and text editing help!

References

[1] Dietz, K. (2018) The epidemiological models of Karl-Peter Hadeler. *Infectious Disease Modelling*, 3: 171–175.

[2] Eds. Diekmann, O., Dietz, K., Hillen, T., Thieme, H.R. (2018) In memory of Karl Hadeler. Special issue. *Journal of Mathematical Biology*, Vol. 77, issue 6-7.

[3] Hadeler, K.-P. (2017) Topics in Mathematical Biology. Springer

[4] Hadeler, K.-P., Müller, J. (2017) Cellular Automata: Analysis and Applications. Springer

[5] Thieme, H.R., 2017. From homogeneous eigenvalue problems to two-sex population dynamics. *Journal of Mathematical Biology*, 75, 783–804.

Reports from 2019 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 member at the moment of submitting the application. The maximum amount of travel support per single application is currently 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 2019, nine travel grants were awarded, with total support of 1850 EUR.

The awardees are asked to write a brief report about the event. Here we present some of the reports. The original reports are slightly edited and shortened yet their spirit remains unchanged.

Yvonne Krumbeck: Mathematical Biology on the Mediterranean Conference (MBMC)
In September 2019, University of the Aegean hosted the first Mathematical Biology on the Mediterranean Conference (MBMC), located on the beautiful Greek island Samos. With great efforts by the organising committee, Stelios Xanthopoulos and Jean Clairambault, the conference has become a grand success and was received positively by the participants. Attendees from Universities of different countries created a culturally diverse atmosphere and encouraged exciting exchanges.

The conference was split into 1 week of a summer school and a 1-week long workshop, where participants could attend either one or both events. During the first week, 5 lectures covered a range of topics in mathematical biology. The lecturers, Benoît Perthame, Nicolas Vauchelet, James Sneyd, José Antonio Carrillo and Nikolaos Sfakianakis addressed mathematical models and methods for evolutionary and bio-chemical dynamics, cell kinetics, collective motion and many more. For me personally, the lecture on an epidemiological model for the spread of Wolbachia bacteria in mosquito populations held by Vauchelet was the most insightful lecture. A well-balanced mix of lectures made the summer school accessible for those who are more mathematically as well as more biologically oriented students. It offered many opportunities to ask and discuss questions and exchange knowledge of different expertise.

The workshop during the second week added more interesting talks by researchers from various fields of mathematical biology. Among all, Mats Gyllenberg, Charalambos Makridakis, Anna Marciniak-Czochra, Luigi Preziosi and Christian Schmeiser have been invited as keynote speakers. Up to 45-min long presentations offered a great opportunity - especially for PhD students - to speak more in depth and have longer discussions about the research.

Unfortunately, there was only a small number of participants who presented a poster. Thus, the sessions to view and discuss them was rather short. Nonetheless, attendees had many opportunities to gather in small groups and discuss their research in more depth.

Excursion days were organised to explore the island Samos and learn more about its history and culture, including the life of the famous mathematician Pythagoras. First, we visited the archaeological site of the ancient temple of Hera, followed by a stop

at the museum in Pythagoreio. After that, we were offered to taste the sweet wine from Samos and learn about its production at the wine museum. The location of the conference close to the sea, beautiful hiking areas and delicious local food made the overall experience even more enjoyable.

To conclude, interdisciplinary gatherings like MBMC always offer a pleasant opportunity for researchers from various fields to meet and exchange their knowledge. The diversity of participants helped to reinforce the network of those interested in mathematical biology. After the great success of this conference, I hope that other Universities will follow up and soon host the next of this series.

Diana-Patricia Danciu: Mathematical Biology on the Mediterranean Conference (MBMC) I attended the MBMC, held between 1-14 September 2019 at the University of the Aegean, Karlovasi on the Greek island of Samos, the island of Pythagoras. The first week of the event consisted of a summer school, with lectures on various topics in mathematical biology presented by renowned professors in the field. The lecturers taught complementary subjects inspired by their own research: Attractive-repulsive mathematical models in collective motion by José Antonio Carrillo, Models of adaptive dynamics in mathematical biology and their analysis by Benoît Perthame, Mathematical problems in evolutionary theory and associated numerical questions by Nikolaos Sfakianakis, Topics in mathematical physiology by James Sneyd and Control of vector-borne diseases and their epidemics by Nicolas Vauchelet. Not only did I learn something from each lecture, but I also had the possibility to further discuss the topics with the lecturers. Working with compartmental models myself, I found the lectures by Nicolas Vauchelet particularly interesting and helpful, and it was very rewarding to see once again the power of relatively simple deterministic models when applied to specific biological systems: in this case, modelling the dynamics of disease-carrying mosquito populations and the techniques used for preventing the spread of the disease. On the other hand, the lectures by James Sneyd were very entertaining, and even though there were no similarities to my projects, I enjoyed not only learning about the mathematical methods used and about the importance of calcium in living organism, but also about the importance of having a goal, a question to answer when starting to develop a mathematical model a concept which I have been supporting, as well. The lectures by Nikos Sfakianakis taught me, among others, about certain optimization techniques, and were very inspiring, showing how certain mechanisms from physics can explain evolution, for example how one can use the brachistochrone problem to explain limb regeneration in salamanders.

In the second week of the event, we took part in a workshop hosting talks on various advanced topics in mathematical biology, presented by researchers at various stages of their career. The plenary talks, in particular, were very interesting, offering a general overview of methods in applied mathematics used in understanding various biological aspects. From among the other talks, I found those by Emeric Bouin, Diane Peurichard and Nikolaos Kavallaris particularly interesting, once again discovering the impact that relatively simple mathematical models can have in explaining biological mechanisms. I also had the opportunity to present the work I did during my doctoral studies and my talk was well received, with many follow-up questions from interested persons. One participant told me she would like to find out more details, as she could use some methods that I presented for her own project.

During the two weeks I had the possibility to interact with fellow researchers and made many new friends, extending my network of scientific connections. It was extremely rewarding to learn about their projects and the various methods that they use, thus paving the way towards possible future collaborations. I usually find it difficult to do networking in big conferences, but during these two weeks I had no such problems, as the MBMC event nicely facilitated and encouraged the interactions through the good organization.

In conclusion, I consider that participating in this event was very rewarding, having had the opportunity to learn many new things, to make a lot of new connections, even friends, and to get ideas for possible future research topics.

Lin Wang: Croucher Summer Course on Computational Genomics of Viral Evolution and Epidemiology This summer school introduced mathematical and computational concepts, methods and analytical tools for dealing with genomic sequencing data, which are very important in pathogen surveillance, clinical diagnosis, treatment, vaccination, risk assessment, disease prevention, etc. The school had three modules: Phylogenetic Inference (PI) Module, Evolutionary Hypothesis Testing (EHT) Module, and Next Generation Sequencing (NGS) Analytics Module. PI module focused on

the sequence alignments and maximum likelihood methods for building phylogenetic trees, EHT module focused on the likelihood and Bayesian inference (e.g. coalescent theory, phylogenetics, phylodynamics, phylogeographic analyses), and NGS module covered more complex analysis of full genomes and huge datasets of pathogens with a focus on Next Generation Sequencing data.

I attended the EHT Module led by Professor Philippe Lemey and Professor Marc Suchard. This module not only provided a comprehensive overview of the Bayesian inference and hypothesis testing theory, but also instructed their computational implementation, e.g. BEAST, HyPhy, SpreaD3, ggTree. I also attended several lectures about the alignment algorithms, transcriptomics, RNASeq, metagenomics, molecular adaptation, large-scale visualization offered by the other modules. These lectures have been highly relevant to my studies in the evolution and transmission of arboviruses such as dengue.

During the summer school, I presented a poster 'Characterizing the dynamics underlying global spread of epidemics'. The co-director, Professor Anne-Mieke Vandamme, mentioned that all poster abstracts will be published as a special issue by the journal 'Virus Evolution' (https://academic.oup.com/ve). I discussed with several course instructors about collaborations on combining molecular evolution, phylogenetic and epidemic dynamics together for jointly estimating virus evolution and epidemic transmission.

In sum, "Croucher Summer Course on Computational Genomics of Viral Evolution and Epidemiology" was very informative and provideed an excellent opportunity for connecting with experts in the fields of mathematical modelling, infectious disease dynamics, molecular epidemiology, genomic analysis, evolution, phylogenetics and phylodynamics. I very much appreciate the ESMTB to support my attendance of the Croucher Summer Course on Computational Genomics of Viral Evolution and Epidemiology.

Chakib Jerry: Mathematical Models in Ecology and Evolution (MEEE) The conference was divided into several working sessions. Each session was distinguished by a field of applied mathematics. I attended several plenary lectures and presentations during various sessions where I was able to enrich my scientific culture especially on the different fields of applications of mathematics such as epidemiology, evolution, decision-making, ecology, population and ecosystems dynamics as well as emerging trends such as population genetics and game theory.

This conference gave me the opportunity to meet several researchers including Johann Bauer, Dibyendu Sekhar Mandal, Katherine Heath and Katerina Stankova who are interested in my field of application and other areas for possible scientific collaborations that will help me in my research and preparation of my authorisation.

During the session "Epidemiology I", I presented my work entitled "Simple cancer model as controlled switched system" in which we investigated a simple mathematical population model of Proliferative/Quiescent cells interactions where chemotherapy treatment was considered as a control variable. The feature thing in this work is that the control variable is not considered continuous by time but piecewise-continuous which is introduced in our work by an impulsive control. This kind of control is motivated by the fact that chemotherapy is not applied continuously (day by day treatment) but piece wisely continuous (a break between two chemotherapy applications). Furthermore, we study an optimal control problem to find the best strategy to minimise the size of tumor cell which mean maximising health state of the treated person. We discuss also numerical results for chemotherapy regimens.

Several researchers and specialists attended my presentation and at the end of it numbers of relevant questions were asked mainly about tools used to study the model, perspectives of my work and the degree of experimentation with the results obtained.

I hope that my contribution to this conference, as well as the many discussions held with several researchers, will be able to contribute to possible collaboration, in particular with Dibyendu Sekhar Mandal, Katherine Heath and Katerina Stankova. I hope that our Moulay Ismail University will made more effort to give opportunities to different professors and researchers to distinguish themselves in the international scientific world.

Lukas Eigentler: Mathematical Models in Ecology and Evolution (MEEE) I have been awarded a travel scholarship from the ESMTB to partially fund my travel to and attendance of the 7th edition of Mathematical Models in Ecology and Evolution (MMEE 2019), which took place in Lyon from 16th July 2019 to 19th July 2019.

The meeting was the latest of a series of biennial workshops that brings together theoretical ecologists, theoretical biologists and mathematical

biologists to discuss their advances in the modelling of problems arising in ecology and evolution. The conference consisted of five plenary talks by Joanna Masel (Arizona), Florence Debarre (Sorbonne), Thomas Hansen (Oslo), Jeremy Draghi (New York) and Thomas Lenormand (Montpellier); a public lecture by Steven Frank (UC Irvine); ten minisymposia; 16 parallel sessions of contributed talks; and a poster session.

I actively participated in the meeting by contributing my talk Metastability as a coexistence mechanisms in a model for dryland vegetation patterns in one of the parallel sessions. The talk emerged to be the foundation for many fruitful discussions afterwards, including some suggestions for further work that may well prove to be useful in the future.

In general, the event provided me with a good networking opportunity, allowing me to discuss my work with fellow researchers and learning about their recent advances. The conference organisers also provided a large poster with one column to which anyone looking for postdoc positions could add their names and a short description of their work, while a second column was being used by senior researchers to list any open postdoc positions. I believe that this was a fantastic idea and may well provide a good reference point as I am in the process of funding a postdoc position.

Further, the conference allowed me to broaden my knowledge across different topics in mathematical biology since presentations covered a wide area of topics, some of which were completely new to me. It was of particular interest to learn how similar methods (including methods closely related to those used in my research) can be applied to a wide range of different problems in ecology and biology.

I would like to kindly thank the ESMTB for the award of this travel scholarship which enabled my participation at the conference.

Simon Syga: Annual Conference of the Society for Mathematical Biology (SMB) I attended the Annual Conference of the Society for Mathematical Biology (SMB) in Montreal, Canada, from July 21 to July 26, 2019 and was supported by the ESMTB. I presented a poster titled A new lattice-gas cellular automaton model explains plasticity in breast cancer invasion, that summarized a model that is part of a joint publication with Peter Friedl, Nijmegen, which is currently in preparation. For the outstanding poster, I was awarded a poster prize. Besides the ECMTB, SMB is one of the biggest and most important conferences on mathematical biology, which allowed me to get in touch with many researchers of his field working outside of Europe.

Aleksandra Plochocka: Annual Conference of the Society for Mathematical Biology (SMB) I would like to thank the ESMTB for awarding me a travel scholarship to attend the Annual Meeting of the Society for Mathematical Biology (SMB) in Montreal, Canada between the 21st and 26th of July 20191. The SMB 2019 meeting was the largest SMB gathering of researchers in Mathematical Biology since its foundation with over 360 attendees. A plethora of research topics meant that many of the plenary talks were given by individuals in research areas unfamiliar to me. This provided a great opportunity to get a glimpse at the cutting edge work in other fields. The highlights of these talks for me included Lindin Wahl (bottlenecks in influenza), Arthur Sherman (reversing vs. preventing type 2 diabetes) and Nick Monk (philosophical discussion of teaching in mathematical biology). Aside from this, the meeting included seminar on "how to get a tenure track position", interactive discussion of presenting research in short digestible formats and a women's lunch which discussed the unconscious bias in academia and how to overcome it.

Personally, since I am starting a postdoc in New York in October I found this meeting to be particularly apt for me since it enabled me to meet many academics from North America. Through giving a talk at the mini-symposium on intracellular transport I was able to meet many academics whose research formed the basis of my PhD thesis literature review. It was exciting to discuss my research in detail with academics such as Eric Cytrynbaum and Adam Hendricks. Various mini-symposium's captured my interests, with two highlights including the 'Mathematical modeling of normal and abnormal tissue growth and development' and 'Multiscale modeling of cytoskeleton-mediated cellular transport and aggregation'. SMB provided a great atmosphere to meet both new and familiar academics in an stimulating environment. SMB 2019 was a truly rewarding experience, thank you.

Models, data and statistics - why is it so difficult?

By Susanne Ditlevsen and Torbjörn Lundh

For a mathematical modeller these corona times have been extraordinary. Never has there been so much public interest in scientific research, where mathematical models and their predictions play a prominent role. Scientists are constantly being interviewed in public media, and researchers that have been working their entire lives outside the spotlight has suddenly become well-known media darlings. The public is allowed to peek into the messy engine room of scientific development; hypotheses, theories, analyses are presented before there has been any time to peer-review, and they are being criticised, updated and improved upon in public, as more data are arriving and more knowledge is obtained. This is usually happening behind the scenes, until a consensus has been reached. Now we lay the rails while the train is running, and this might be confusing and seem like researchers do not know what they are doing if you are not used to the scientific process.

What is a good model? And what is it good for?

An essential tool used by epidemiologists to describe the development of an infectious disease in a population and evaluate the effectiveness of various countermeasures is the use of mathematical models of various kinds. Models have thus become very important when expert knowledge is communicated to decision-makers and policies are formulated and justified.

How this should be done is not entirely clear, and many questions have been discussed during the corona crisis. Should we rely on the experts' knowledge or on forecasts from models? But what if different models provide varying forecasts? Which model should be used and how reliable are they really?

There are two extreme positions. One can argue that complex models should function as a direct basis for decision-making, so that predictions are "objective" and not based on gut feelings. One could also argue that the subject matter experts' knowledge should dominate, because they will have the best intuition and experiences with such problems. However, we believe that those two positions should not be opposed, but rather go hand in hand and complement each other. Let's look at some characteristics of scientific models that are often taken for granted by researchers but rarely discussed in the media [1].

Mathematical models, consisting of equations describing various variables, is just one type of models out of all types of scientific models. When a medical doctor describes how the virus enters a human cell through attachment to the ACE_2 receptor, then it is also a model, albeit a verbal or conceptual one. To fully describe how the virus interacts with human cells would require quantum mechanical explanations, which would be accurate, but not very informative. The different scales at which these model variants operate make it possible for researchers to isolate and zoom in on certain phenomena of interest.

A famous quote usually attributed to the statistician George Box says that "all models are wrong, but some are useful". The point is that models are tools for specific purposes, and these purposes are often of a practical nature. The usefulness of a model does not only depend on how well it describes the real world. In fact, that they work at all is exactly due to the fact that they are simplifications of a complicated reality. For example, the simplest models for how a disease is spreading simply describes the number of infected, ignoring all geographical and socioeconomical information. It will provide a rough estimate, but will be less sensitive to misspecifications of the many unknown parameters that invariably are needed in a more complex and specialised model, and might therefore, in a world of uncertainty, pro-

vide more robust estimates than more realistic models.

Simple or complex models?

We can compare a scientific model with a map. A 1:1 map that completely agrees with the landscape it intends to describe is useless as a map. Whether a given map is good or not depends on the problem it is trying to describe. If you need to find the quickest way to cross a city by car you need a different map than if you are a tourist searching for beautiful spots in the city centre or a good restaurant, or if you need to find a specific office in a large office building.

There is always (or should be!) some specific purpose or goal a model is trying to reach. Different researchers might have different goals, and thus, there will also be a large variety of models. In the case of the corona pandemic, there are very complex and detailed models with the purpose of understanding the underlying mechanisms, as well as more statistical models with the main focus of predicting number of infected or needs for healthcare measures such as hospital beds. This could be done by looking at the development of the pandemic in different countries, but without any or only very mild assumptions on the properties of the virus or the dynamics of the spread. These descriptions are not contradictory, on the contrary, they are parallel descriptions from different perspectives that could complement each other.

The point is that the models should not be looked upon as the truth, since they are always simplifying and idealising. Furthermore, more complex models are not automatically better. The models and their predictions should therefore be seen as supporting tools for political decisions, when results from different models are combined together with the empirical expert knowledge.

So how should decision makers relate to models and their predictions in the middle of the current crisis? There is no simple answer. Which models are needed for a given situation depends on various factors, but we believe that the best result is achieved when various models are used in parallel and the predictions, robustness and "understandability" are evaluated together with subject matter experts. Complex models may possibly explain more than simple models, but it is a risky business. Especially if uncertain model assumptions and simplifications are hidden or forgotten, or even being used for propaganda. Simpler models might provide a better overview, be statistically more robust because of the limited access to detailed data to validate the more complex models, but they might seem too arbitrary for non-experts.

Many data models that have been presented around the world to predict the spread of covid-19 have been very complex - despite the lack of validated data. These models are complex in the sense that they have many unknown parameters that are difficult to estimate or measure. Furthermore, the parameter values used are most often not the result of training and validation on a large and representative data base but are instead set manually, often without clearly justified support from empirical studies. Thus, one should be careful when interpreting the outputs of these models, especially with non-linear models where small parameter variations can cause large fluctuations in the model predictions.

Let's look at an example of a parameter appearing in many of the recent modelling attempts of the effect of societal measures to contain the epidemic. What is the effect of closing schools on the spread of the disease? School closure, of course, eliminates the risk of spreading infection in schools. However, it might increase the risk in the family. The total effect then depends on how you model the spread of infection in each environment. Assuming that pupils infect little or not at all in schools, the net effect is that the spread of infection can increase after a school closure. However, assuming the same spread of infection as in the family and leisure time, the spread of infection decreases significantly. Thus, depending on the model assumptions, the effect of a school closure can either be an increase or a decrease in the reproductive rate (that represents how many individuals an infected individual on average transmits the in-

fection to). It can also affect how the infection is spread between different age groups, such as the elderly. Is it the parents who look after the children, or grandma and grandpa?

How good are complex models compared to simple models at predicting reality? That depends to a large extend what we mean by "reality". If "reality" is the data that we have access to, this is often limited to time series of infected and deaths with no further information on details like who the subject was infected by, which, if any, symptoms there were, what contact patterns the subject had adopted, how many that person further infected etc. For such rough data, a simple model such as the soon 100-year-old SIR model [2] can reasonably well recreate the time series from most countries. However, this does not necessarily imply that it can predict future numbers well.

For a complex model to have predictive ability, it is required that its unknown parameter values are selected on the basis of reliable and sufficiently informative training data. In order to reduce the risk of over-adaptation to training data, separate validation data are also required against which the model can be evaluated before it is put into use.

In general, but especially in a situation where adequate training and validation data are not available, the simplest model describing available data is preferable. This principle is the well known Occam's razor, or the rule of parsimony. In addition, simple models are generally more transparent in terms of how parameter choices relate to outcomes, i.e. more understandable and can thus be better tools for thoughts and discussions. However, the need for data-supported parameter selection and validation remains, even for simple models.

To sum up: Models with higher complexity than what training and validation data can support should be used sparingly as a basis for decision-making.

What is statistics?

Mathematical models of biological phenomena only become really interesting when we can test the models against data. Statistics is a tool for translating what we can observe into knowledge about the world. Many things we want to know about the world cannot be observed directly. For example: How long does it take for a person being infected with the corona virus to develop symptoms? How does this vary from person to person? How many don't develop any symptoms, but nevertheless infect others? You can then collect data and use statistical tools to interpret data and get an estimate for the answer to the questions you have asked.

Not all questions are easy to answer. Here are some examples of things we can estimate from data that go from easy to harder.
Easy: How long does the virus stay alive on different surfaces and under given conditions? This can be tested in a laboratory under controlled conditions.
Medium: How many have been infected or are possibly immune? This requires far more testing, but if we have a test for antibodies it can in principle be done.
Difficult: How long time passes from getting the infection before symptoms appear, and when does the person become infectious? It requires that we can identify the exact time a person has been infected, when the symptoms appear, and in what time interval the person has been infectious. This has to be done for many people, since there is probably a great deal of variability from person to person, and this is also important to understand.

We need to collect data, to gain knowledge, and not base our inferences on guesswork and gut feelings. Frequently, our ideas about the world is coloured by our own most recent personal experience, or a quick look at some statistical table with no thorough analysis. However, it is tricky to translate data to knowledge about the world! For example, take the data on number of infected or deaths due to the corona virus in different countries that we are all googling in these times. These numbers cannot be directly compared, because countries calculate numbers differently, and even more importantly, have different strategies for testing for corona. So even though we have nice tables that looks very "ob-

jective", we can not use it without a deeper analysis.

Parameter sensitivity

As the amount of parameters and assumptions in a model grows, so does the requirement to validate these assumptions. Parameter values are most appropriately validated against data; and assumptions and results should be tested through the usual scientific review. When mathematical models are used to make socially important decisions, this requirement is even more important.

One should be aware about the uncertainty in the statistical estimates. The more data, the less uncertainty on estimates. Therefore, estimates are constantly updated because more and more data is being collected. This has to be done carefully, because if the data collection process is not accounted for in the models and data is analysed incorrectly, we get a biased result, that is, a systematically wrong result. If you then collect more and more data, you will get increasingly more accurately estimates of something wrong. This is particularly important in larger, non-linear complex models, where small perturbations in parameters can make huge effects on the model's output.

High quality data – to learn about the disease or to combat the disease?

Good estimates of model parameters are needed to make useful predictions – and for that we need statistics. And to do statistics, we need data. Not only that. We need good quality data. But what does good quality data mean in this context?

In many countries there are a lot of discussions about the best test strategy. Testing requires resources, and therefore decisions on whom to test have to be taken. However, there is almost exclusively focus on one aspect of it, namely, what is the best strategy to get as many as possible through the crisis by containing the infection and limit the number of deaths. This is a very important issue, but there is another issue that is only rarely discussed. That is the statistical issue: What is the best test strategy to gain the most insight into the disease? The golden standard is randomised trials, which is the best way to ensure reliable estimates of parameters of interest. In addition to testing individuals who have shown symptoms, we should in parallel test a randomly selected sample of the population, whether they have symptoms or not, while registering important background variables, such as gender, where they live, age, activity level, state of health, possible symptoms, etc. This is the only way we can obtain solid estimates for the disease-specific parameters. Preferably, everyone in the sample should be tested several times. It would provide a data material to much more reliably estimate how long it takes from infection to symptoms, how many have no symptoms but are still infected, the herd immunity level, the reproduction rate, etc. If the tested are selected not randomly, but because they have symptoms, or have specific functions like health care workers, this will not be a random sample and estimates will be biased. It is conceivable that they are more exposed to viruses, and therefore the immunity may develop differently. Moreover, the age distribution is probably different than in the general population. Furthermore, it cannot inform us about those infected without or with mild symptoms. So we have to do randomised trials in more than only a few countries.

We sum up this story by quoting Rutherford D. Rogers: "We are drowning in information and starving for knowledge".

References

[1] P. Gerlee and T. Lundh Scientific models: red atoms, white lies and black boxes in a yellow book, *Springer*, 2016.

[2] F. Brauer. Mathematical epidemiology: Past, present, and future. *Infectious Disease Modelling*, 2, 113–127, 2017.

Educational corner: Testing for antibodies, Bayes formula and the difficult conditional probabilities

By Susanne Ditlevsen

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!

An important unknown in the current corona-crisis is the so-called *dark figure*, the proportion of the population that have been infected with SARS-CoV-2, the virus that causes COVID-19, and therefore is assumed immune to the disease (which is another important unknown! We do not yet know whether the presence of antibodies means that you are immune to the coronavirus in the future; or if you are immune, how long it will last). Why is that so important? From a predictive point of view, this number is essential because predictions of future cases heavily depend on it - the larger the proportion of immune and not infectious in a population, the less spread of the disease. But also from a personal point of view, we would like to know if we are immune, and therefore do not risk neither to get sick, nor to infect others. However, it turns out that even if we can conduct reliable population studies that can reveal the dark figure, it is much more difficult to estimate exactly *who* are the individuals that are immune. This is due to a tricky and counter-intuitive effect when small probabilities are in play.

A COVID-19 antibody test, also known as a serology test, is a blood test that can detect if a person has antibodies to SARS-CoV-2, and therefore has had a COVID-19 infection. Many antibody tests are currently under development, and by now many good tests are available, where "good" means that they have a high *sensitivity* and a high *specificity*. Sensitivity is the probability of the test to correctly identify a person with antibodies, also known as the *true positive rate*. A highly sensitive test will identify most people who truly have antibodies, and only a small proportion of the people with antibodies will be missed by the test (*false negatives*). Specificity is the probability of the test to correctly identify a person without antibodies. This is known as the *true negative rate*. A highly specific test will identify most people who truly do not have antibodies, and only a small proportion of the people without antibodies will be identified as having antibodies by the test (*false positives*). By now, many tests are available with a sensitivity of nearly 100% and also a high specificity of around 95-99% [1]. With so high probabilities, we would indeed believe that we can trust the result of the test! However, let's see why that is not so.

The *positive predictive value* is the probability that people who have a positive test result truly have antibodies. This is *not* the same as the sensitivity, and this is why this is so tricky. To see this, let's define two events: A is the event that a person has antibodies, B is the event that a person has a positive test result. Then we have the following *conditional probabilities*

$$\text{Sensitivity } = P(B|A)$$

and

$$\text{Positive predictive value } = P(A|B)$$

where $P(A|B)$ denotes the probability that A is true *conditional* on B being true, and likewise for $P(B|A)$. These are not the same! It is the positive predictive value, we are interested in, when we get tested and want to know what the probability is that we are immune, given the test was positive. The positive predictive value depends on the *prevalence*, the proportion of the

population that have antibodies (the dark figure) at the time of the test, that is, the *marginal* probability,

$$\text{Prevalence } = P(A).$$

Bayes' theorem states that

$$P(A|B) = \frac{P(B|A)P(A)}{P(B)}$$

where we assume $P(B) > 0$. Thus, we see that these two conditional probabilities are only the same if $P(A) = P(B)$. This is only the case if the sensitivity and the specificity of the test are 100%, which is rarely (if ever!) the case for any test. Moreover, their ratio becomes quickly very small if the prevalence is low, as is the case for SARS-CoV-2 antibodies, at least in most places at this stage of the endemic, so the two conditional probabilities can be very different. Let's do the calculations. The probability $P(B)$ can be found by the law of total probabilities,

$$\begin{aligned} P(B) &= P(B|A)P(A) + P(B|\text{not}A)P(\text{not}A) \\ &= \text{sensitivity } \times \text{prevalence} + \\ &\quad (1 - \text{specificity }) \times (1 - \text{prevalence}). \end{aligned}$$

Thus, the lower the prevalence, the lower the predictive value! This means that COVID-19 antibody tests, even with high sensitivity and specificity, used in areas with low prevalence will have a lower positive predictive value than in an area with higher prevalence. The prevalence is probably strongly varying from area to area, but in many places, an estimate of 2-5% is likely not far from the truth at the time of writing. Let's assume a test with sensitivity of 100% and specificity of 98%, used in an area with prevalence of 2%. Then the positive predictive value is

$$P(A|B) = \frac{0.02}{0.02 + (1 - 0.98)(1 - 0.02)} = 0.5.$$

Even with such a good test, the chance of having had COVID-19 is only fifty-fifty if you test positive for antibodies!

The reason is that there are two unlikely events in play: the probability that you are immune (a small probability, given by the prevalence), and therefore will be tested positive (with a large probability, in the example above with probability one) – or the probability that you will be tested positive, even if you do not have antibodies (a small probability), but many people without antibodies will be tested (because the prevalence is small), and thus, the number of false positive will be large.

Why this is so counterintuitive is beautifully explained in the highly recommendable book by Nobel prize winner Daniel Kahneman [2], for example in chapter 14, where it is shown how we psychologically tend to forget or ignore base rates (the prevalence) in the light of further information (the outcome of the test).

A low positive predictive value will lead to more individuals with a false positive result, which is dangerous, since a positive test result most likely will make us more relaxed about maintaining cautious behaviours to not become infected or infect others. In this particular example, we can be sure we do not have antibodies if we get a negative result since the sensitivity is 100%, so there are no false negatives.

Note than even if it is difficult to identify the specific individuals that have antibodies, we can use the tests to obtain good estimates of the prevalence if we test many, since we can correct for the expected number of false positives and false negatives. Thus, reasonable population estimates are available, even if personal estimates are not.

References

[1] FDA U.S. Food & Drug Administration. EUA Authorized Serology Test Performance. `https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/eua-authorized-serology-test-performance`. Retrieved on September 9, 2020.

[2] D. Kahneman. (2020). Thinking, Fast and Slow. *Penguin Books*. 2011

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!

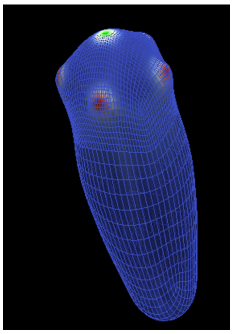
Applied Analysis and Modelling in Biosciences Group headed by Anna Marciniak-Czochra is located at the Institute of Applied Mathematics (IAM), Interdisciplinary Center of Scientific Computing (IWR) and BIOQUANT Center, Heidelberg University.

Research focus: The interdisciplinary expertise of the group lies in the areas of applied mathematics and mathematical and computational biosciences. Specifically, our field of focus is the dynamics of self-organisation and structure formation in developmental and regeneration processes and in cancer. The aim of our research is to develop and analyse mathematical models of the dynamics of structure formation in multicellular systems and to develop new mathematical methods of modelling of such complex processes. Accordingly, we collaborate closely with experimentalists and clinicians, and pursue mathematical problems arising in modelling of biological processes, both analytically and computationally.

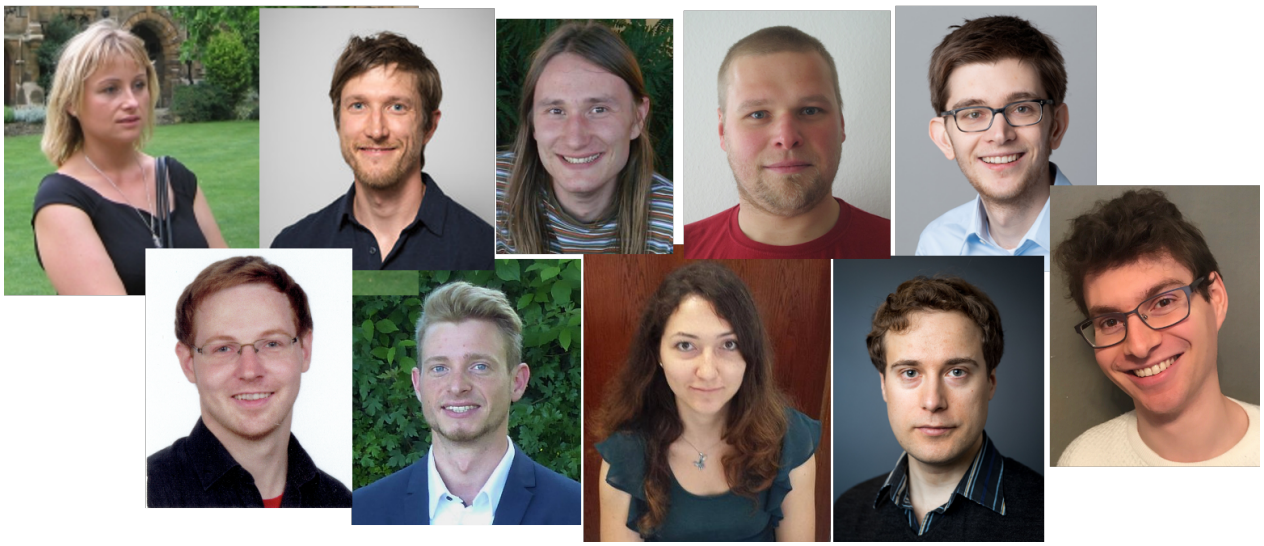
Mathematical areas of groups focus are partial differential equations, dynamical systems, and multiscale and singular perturbation analysis. Methods of mathematical analysis are used to formulate the models and to study the spatio-temporal behaviour of solutions, such as stability and dependence on characteristic scales, geometry, and sensitivity to initial data and key parameters. Our analytical research includes (1) analysis of pattern formation mechanisms in the systems of reaction-diffusion type; (2) analysis of nonlinear structured population models; linking continuous and discrete structures; (3) derivation of effective models from first-principles to describe transport of cells and molecules through heterogeneous media such as biological tissues. Particular attention is paid to methods of model upscaling and reduction.

Applications in biology and medicine: Mathematical models and methods developed by the group are applied to specific problems of developmental and cell biology, as listed further on.

(1) Pattern formation



The first area of focus is modeling, analysis and simulation of symmetry breaking and pattern formation in developmental biology. Together with the experimental group of Thomas Holstein (Center for Organismal Studies (COS), Heidelberg University), we investigate the role of different components of the complex spatio-temporal Wnt signaling in development and regeneration of the fresh water polyp Hydra. We focus on models coupling non-diffusive cellular processes with diffusing signaling factors, which we derived using homogenization techniques. Our results transcend the classical Turing theory. We investigate how the structure of nonlinearities determines model dynamics and lead to pattern formation phenomena. We explore multistability and hysteresis in signaling, diffusion-driven instability or interplay between the two mechanisms. We also investigate a new pattern-formation mechanism based on coupling of chemical signaling with tussue mechanics, described by 4th order PDEs. Numerical simulations of the mechano-chemical models show symmetry breaking and formation of patterns similar to those observed in experiments. Currently, we work on a new approach to model identification combining statistical methods of parameter estimation with singular perturbation analysis of the hypothetical mechanisms.



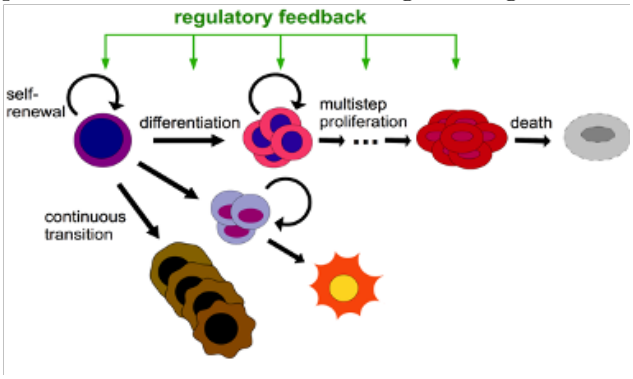
Applied Analysis and Modeling in Biosciences Group, August 2020: Anna Marciniak-Czochra. Moritz Mercker, Thomas Stiehl, Filip Klawe, Jooa Hooli, Chris Kowall, Johannes Kammerer, Diana-Patricia Danciu, Alexey Kazarnikov, Christian Düll.

---

(2) Stem cell dynamics in development, regeneration and cancer

The second, related, line of our studies is mathematical modeling, analysis, and simulation of dynamics of stem cell self-renewal, differentiation, and clonal evolution in different contexts. In close collaboration with developmental biologists (Lazaro Centanin and Jan Lohmann, COS, Heidelberg University), we established multiscale models of stem cell-initiated organogenesis. We built models of plant meristem development providing mechanistic understanding of meristem regulations and mutant phenotypes. Furthermore, we proposed models identifying functional heterogeneity of stem cells in development of the fish respiratory organ.

The role of intercellular heterogeneity is also the topic of our research in aging and regeneration in adult neurogenesis (collaboration with experimental labs of Ana Martin-Villalba, DKFZ, Heidelberg and Francois Guillemot, Francis Crick Institute, London). Integrating mathematical models with experimental data allows identifying stem cell properties that change with age to compensate reduction of the stem cell pool and to maintain life-long neurogenesis.



In a collaboration with hematologists (Anthony D. Ho, Carsten Müller-Tidow and Christoph Lutz, Heidelberg Medical Clinic), we develop multi-compartment and structured population models that allow explaining observations on regeneration processes in hematopoiesis, development of leukemia, clonal selection and resulting therapy resistance in blood cancers. The study reveals different scenarios of possible cancer initiation and provides qualitative hints to treatment strategies. The models, combined with clinical data, may serve as a tool of personalised (targeted) therapy and provide insight into healthy and leukemic stem

cell behavior in addition to molecular or biological classification of these cells.

Different areas of applications require diversified mathematical methods ranging from stochastic models to partial differential equations, integro-differential and ordinary differential equations. Development and comparison of different models often requires new mathematical and computational approaches and leads to new analytical results.

(3) Systems Medicine

We find it important to develop models that may contribute not only to a mechanistic understanding of the underlying processes but also to integration of this knowledge with experimental and patient data and providing a tool for patient stratification, risk prediction and treatment plannig. We focus on mathematical hematology projects, working on applications of mathematical models to acute myeloid leukemia and multiple myeloma (collaboration with Heidelberg Medical Clinic V). Our blood production models have been also applied to predict onset of sepsis and SIRS in intensive care patients. The latter is a collaboration with Mannheim University Clinic within the SCIDATOS Consortium (Scientific Computing For Improved Detection And Therapy of Sepsis).

During recent years our research has been supported by funding from ERC Starting Grant, German Research Council (DFG) through Research Collaborative Centers (SFB 873 and SFB 1324), Emmy Noether Program and Cluster Structures of the Excellence Strategy, Tschira Foundation and Humboldt Foundation, Federal Ministry of Education and Science (BMBF) and Heidelberg Academy of Sciences and Humanities.

More about our research, projects and publications can be found at `http://www.biostruct.uni-hd.de`.

Meeting Reports

The International Conference "Dynamical Systems Applied to Biology and Natural Sciences - DSABNS" is a well established international scientific event, organized every year since 2010, in February. The DSABNS conferences present both methods from the theory of dynamic systems, stochastic processes and statistical inference and practical applications to research topics in population dynamics, eco-epidemiology, epidemiology of infectious diseases, molecular and antigenic evolution and other fields in the natural sciences.

Without registration fee, this series of conferences favours the participation of researchers and students from different countries of the world in order to present their recent scientific results. The 11th DSABNS Conference was held in a friendly atmosphere at the Department of Economics and Management of the University of Trento, from 4 to 7 February 2020, with the participation of 168 researchers and students from 40 different countries.

The Conference programme (see `http://www.dsabns2020.maths.unitn.it/index.html`) included:

• 2 Public Lectures and 10 Plenary Talks:
- Maíra Aguiar, University of Trento, Trento, Italy & Basque Center For Applied Mathematics (BCAM), Bilbao, Spain
- Gianfranco Anfora, University of Trento, Trento, Italy
- Konstantin Blyuss, Universty of Sussex, Sussex, UK (online lecture)
- Susanne Ditlevsen, University of Copenhagen, Copenhagen, Denmark
- Bob W. Kooi, VUUniversity Amsterdam, Amsterdam, The Netherlands
- Bas Kooijman, VU University Amsterdam, Amsterdam, The Netherlands

- Anna Marciniak-Czochra, Heidelberg University, Heidelberg, Germany
- Roeland Merks, Leiden University, Leiden, The Netherlands
- Lucia Russo, Istituto di Ricerche sulla Combustione, Cnr, Naples, Italy
- Constantinos Siettos, University of Naples Federico II, Naples, Italy
- Hal Smith, Arizona State University, Tempe, AZ, USA
- Rebecca Tyson, University of British Columbia Okanagan, Vancouver, Canada

• 20 parallel sessions, each introduced by an Invited Speaker, followed by a total of 82 Contributed Talks.

• A Poster Session with 35 posters took place during the welcome cocktail and 4 prizes (consisting of a Diploma, a book and one year's membership to the ESMTB) were awarded to the best posters.

• A Book of Abstracts with ISBN: 978-989-98750-7-4 was published at the end of the event and is available to download at the conference website.

The Conference closed with a round table to discuss the Coronavirus epidemic (COVID-19), a great opportunity to update on the disease and the mathematical challenges concerning the current epidemiological scenario.



The Conference DSABNS 2020 received financial support from:
- European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement with No 792494 "COMPLEXDYNAMICS" Project
- European Society for Mathematical and Theoretical Biology (ESMTB)
- Basque Center for Applied Mathematics (BCAM)
- University of Trento
- Department of Mathematics of the University of Torino
- Gruppo Nazionale per l'Analisi Matematica, la Probabilità e le loro Applicazioni (GNAMPA-INdAM)
- SurvEthi project which is co-funded by the Autonomous Province of Trento and the Italian Agency for Development Cooperation

Local Organizers/Scientific committee:
- Maíra Aguiar, Università degli Studi di Trento, Italy & Basque Center for Applied Matehmatics (BCAM), Bilbao, Spain
- Giorgio Guzzetta, Fondazione Bruno Kessler, Italy
- Mattia Manica, Fondazione Edmund Mach, Italy
- Giovanni Marini, Fondazione Edmund Mach, Italy
- Valentina Marziano, Fondazione Bruno Kessler, Italy
- Piero Poletti, Fondazione Bruno Kessler, Italy
- Andrea Pugliese, Università degli Studi di Trento, Italy
- Roberto Rosà, Università degli Studi di Trento, Italy
- Mattia Sensi, Università degli Studi di Trento, Italy
- Filippo Trentini, Fondazione Bruno Kessler, Italy

International Organizers/Scientific committee:
- Carlos Braumann, Évora University, Portugal
- Mimmo Iannelli, Università degli Studi di Trento, Italy
- Bob Kooi, Vrije University Amsterdam, The Netherlands
- Nico Stollenwerk, Lisbon University, Portugal
- Ezio Venturino, Turin University, Italy

Science communication in (a time of) crisis

By Federica Bressan

Introduction

In normal times, science communication activities are generally associated with leisure and entertainment. We watch a documentary out of interest or curiosity, not for an immediate practical return. We visit a museum or a science fair for the same reason: we find pleasure in learning something new while having a good time. We don't do it out of fear or anxiety. There is nothing instrumental in a visit to the planetarium: we just enjoy doing it.

In a time of crisis, it is a different story. We do not want to be entertained. We do not watch a documentary because we enjoy it, we watch it because something is threatening our safety and we want to know more, so that we can plan for action. It is very instrumental. And we can experience fear and anxiety.

In a time of crisis, most people who do not work in science are not interested in the structure of a virus for the sake of being educated: they want to know, 'will it affect me?' They don't want to know how long the virus can survive on a given surface because it's an interesting fact, they want to know, 'if I touch the shopping cart, can I catch it?'

In a time of crisis, we only value the information that will help us plan for action. It is not the case that the global population has suddenly developed a keen interest in virology and epidemiology. People *need* this knowledge to know what to do in order to feel safe.

And this is a problem, because science does not tell us what to do [1]. Science informs our decisions, but it doesn't take them for us. In a time of crisis, we should look at politicians and policy makers, because they have the responsibility to devise our plan for action. Unfortunately, this pandemic has exposed some confusion about the attribution of roles and responsibilities.

Science is often expected to be a source of definitive truths, from which should derive a necessary code of conduct.

Much 'bad communication' is to be laid at the feet of this misconception about science. The problem is not 'how do we communicate better?', but what we communicate, to whom, and why. In a time of crisis, good science communication matters; but the best science in the world cannot make up for a lack of political leadership.

Science or communication

Since the beginning of the pandemic, mainstream media have been filled with technical language that people absorbed and brought to their everyday life. The use of some terms is not always accurate, and the expression 'herd immunity' deserves the grand prize.

The British Prime Minister Boris Johnson's first response to the epidemic, back in March of this year, was to allow "a significant part of the population to get coronavirus to build immunity against it in the long-run" [2]. This was called 'herd immunity strategy' and cost Johnson severe backlash. There was never much ambiguity on the meaning of the expression: the same source explains that it "refers to the state in which the majority of the population [...] has contracted and survived a disease, and is therefore immune to contracting and spreading it a second time." Herd immunity became synonym of 'no action to contain the virus' and 'let nature do its course'.

First of all, herd immunity is not a strategy: it is a desirable condition to achieve. There are two important things to say about herd immunity: (1) when herd immunity is achieved, it means that a sufficient percentage of the population is immune to the disease, and this minimises the risk that the rest of the population gets infected; (2) there are two ways to achieve this: by allowing the population to develop immunity by contracting the disease, or via vaccine. This is what the 'general public' should know about herd immunity. The details of how

the percentage is calculated etc. are for technicians.

Yet, the internet is covered with headlines that reinforce the understanding of herd immunity as 'let everybody get sick.' Some examples:
– CNN Health: *A herd immunity strategy to fight the pandemic can be 'dangerous,' experts say. Here's why* [3]
– Fox News: *Dr. Atlas blasts reports he backed 'herd immunity': 'I've never said that to the president'* [4]. In the text: "One of Donald Trump's top new medical advisers is urging the White House to embrace a "herd immunity" strategy to combat the coronavirus pandemic. Herd-immunity strategies entail allowing disease to spread through much of the population, thereby building natural immunity to the deadly, highly contagious virus" [4]
– The Washington Post: "One of President Trump's top medical advisers is urging the White House to embrace a controversial "herd immunity" strategy to combat the pandemic, which would entail allowing the coronavirus to spread through most of the population to quickly build resistance to the virus" [5]

Truth be told, the word 'herd' does not help. It does not suggest the idea that only *a percentage* of the population needs to be immune. And referred to human beings, it is a pejorative, thus misleading many into thinking that herd immunity is a bad thing (just like 'herd mentality' has a negative connotation).

Still, I cannot comprehend why this expression is so widely misused by the majority of the media, regardless of the political orientation. The misconception about herd immunity is well rooted. And what about the appointed medical advisor to the President of the United States that publicly defends himself from the 'accusation' of backing herd immunity? Even if we conceded that 'herd immunity' were short for 'herd immunity achieved by means of natural infection', which Dr. Atlas may well oppose, his response should not have been to distance himself from herd immunity altogether, but to emphasise that of course he wishes herd immunity be achieved, only via vaccine. It is really difficult to understand how these misunderstandings persist around public figures surrounded by assistants, consultants, teams of experts, without someone walking up to them and say sir, actually...

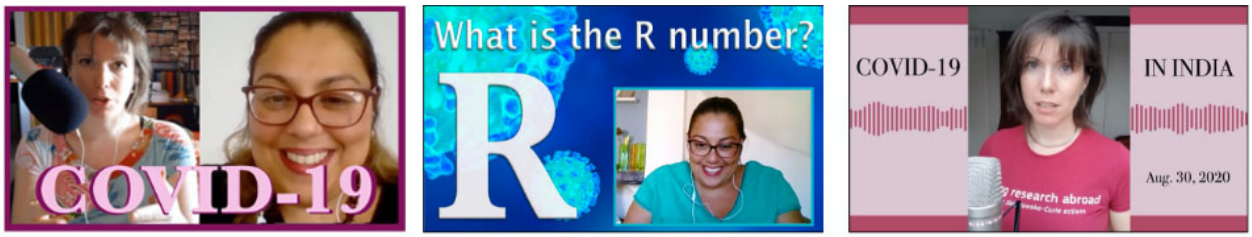
What is the role of scientists in this scenario? What accountability should they have when technical language is (mis)used by lay people, including news anchors? Does it mean that they miscommunicated in the first place, are they the source of the misunderstanding? Or it is outside their hands, and all they could do is jump in and rectify the information every time, probably coming across like pedantic school teachers? Whether this is bad science communication, misinformation, or an innocent misunderstanding, I am not sure.

Learning through communication

I was one of the people who believed that herd immunity was a bad thing. I didn't *'know for sure, but'* in doubt I would have probably abstained. In this sense, I am an excellent representative of the average member of the 'general public' (a rather unspecific definition). The media reinforced my belief, of course. One day I decided to reach out to Maíra Aguiar, biomathematician I connected with through the Marie Curie network. I wanted to pose her some questions, hoping she could clear my doubts.

In the light of the first part of this article, I think it is worth noting that I was not seeking answers instrumentally, in order to know *what to do*. Even if we are in the middle of a pandemic, I reached out to Maíra moved by curiosity. I was not afraid or anxious. I wasn't understanding the news, I could not form my own opinion, and it bothered me because I am a curious person and I want to understand. I was hoping that maybe I would understand alone over time, but the news were very repetitive, not really adding useful information.

I spoke with Maíra on the phone, and very early in the conversation I decided I wanted to do a public interview with her. I was receiving clear, convincing, exhaustive answers from her. I had the feeling that I was advancing my understanding, no longer lost in a fog of doubts–



(a) (b) (c)

Figure 1. Videos on COVID-19 I have produced since June 2020. Accessible on YouTube.

at last! I felt compelled to share this knowledge: if even CNN can accidentally misrepresent herd immunity, it is everybody's responsibility to speak up when they have good information. So, I decided to be that voice. Maíra brought her expertise, and I brought the questions and my platform. And this is how our first COVID-19 video came about (Fig. 1-a) [6].

Is our video science communication? Does it qualify as such? Like other trending expressions, 'science communication' is a blanket term. So, the answer is yes and no. But I like narrow definitions, so I would say no. This video marked the beginning of a beautiful friendship, and an ongoing conversation on how to spread good information about COVID-19, within the limits of the tools we have. Maíra has been very patient with me, answering all of my questions. But some questions raised more questions. Especially about the basic reproduction number, the implications of which I found somewhat difficult to follow. And this is how our second video came about: What is R (Fig. 1-b).

Conclusions

People need to be informed, and they have a right to accurate and complete information. But beyond the science and the knowledge that comes from it, the pandemic has a very concrete impact on people's lives, an impact that is very personal and very real. It touches us, it has changed the way we live.

People in different situations, and around the world, experience the pandemic in very different ways. The science is the same, but our experiences are not. That is why my third video on COVID-19 is not about plasma therapy or self-spreading vaccines, but about people. I was interested in exploring this virus through human eyes, and not only the eyes of science.

Living through this pandemic remains first and foremost a human experience, no matter how advanced our science can get.

So, I asked an Indian friend, and former public health official, to send me a voice message with an overview of the situation in her home country. Her response was heartfelt but sober, informed and accessible. I didn't know much about the social repercussions of the pandemic in India. I was caught off guard. Her message shook me. Again, I decided to use my platform to channel that story. I asked my friend if I could share her message, and this is how my third video on COVID came to be (Fig. 1-c). Is it science communication? No. But I am convinced that it serves a purpose. It helps us paint a more meaningful picture of the current situation, it increases our awareness of the pandemic as a social crisis, and altogether it better equips us to face the challenge.

Ultimately, people want to stay safe and meet on the other side of this as soon as possible. And probably forget about R numbers, or at least learn about them out of curiosity, and not because they feel that their lives depend on it. The science is necessary to get us there faster and better, but the social aspect of the pandemic is still the most important one. And everybody must do their part, as citizens, scientists, business owners, lay people, old and young, or we do not have the right to point our finger at science communication and say it is broken. Communication is a two way street.

References

[1] Federica Bressan, Sept. 4, 2020. The misunderstanding between science and society. https://www.linkedin.com/pulse/misunderstanding-between-science-society-federica-bressan/

[2] Tommy Hilton, March 15, 2020. The UK response to coronavirus: 'Herd immunity' and its risks explained. *Al Arabiya English*, https://english.alarabiya.net/en/features/2020/03/15/The-UK-response-to-coronavirus-Herd-immunity-and-its-risks-explained

[3] Jacqueline Howard, Sept. 1, 2020. A herd immunity strategy to fight the pandemic can be 'dangerous,' experts say. Here's why. *CNN Health*, https://edition.cnn.com/2020/09/01/health/herd-immunity-coronavirus-pandemic-explainer-wellness/index.html

[4] Angelica Stabile, Sept 1, 2020. Dr. Atlas blasts reports he backed 'herd immunity': 'I've never said that to the president'. *Fox News*, https://www.foxnews.com/politics/dr-atlas-denies-promoting-herd-immunity-coronavirus

[5] Yasmeen Abutaleb, Aug. 31, 2020. New Trump pandemic adviser pushes controversial 'herd immunity' strategy, worrying public health officials. *The Washington Post*, https://www.washingtonpost.com/politics/trump-coronavirus-scott-atlas-herd-immunity/2020/08/30/925e68fe-e93b-11ea-970a-64c73a1c2392_story.html

[6] Federica Bressan, Aug. 12, 2020. How an interview on COVID-19 made me think about science communication *The Marie Curie Alumni Associationo Blog*, https://medium.com/marie-curie-alumni/how-an-interview-on-covid-19-made-me-think-about-science-communication-22b0936e43bd

Federica Bressan, Stony Brook University, New York, e-mail: federica.bressan@stonybrook.edu is a researcher and science communicator. She hosts the podcast Technoculture and writes about science and society, see http://podcast.federicabressan.com.

Minutes of the ESMTB board meetings

Palermo, October 25, 2019

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

Time: 9:30–12:20, 13:30–17:30

- The informal decisions taken via email ballot since the Heidelberg meeting were unanimously approved. The list of informal decisions is attached to the minutes.
- News from JOMB: Helen Byrne has stepped back as editor of the Perspectives Section, Susanne Ditlevsen has been appointed as her successor by the Managing Editors. The role of the Perspectives editor is analogous to that of an associate editor or guest editor. The Perspectives are reviewed and remain under the scientific responsibility of the Managing Editor(s). A self-arxived version may appear on the ESMTB website and in the Communications (analogous to a preprint on arXiv).
- The Board discusses in detail the new draft of the Publishing Agreement with Springer and agrees on a number of changes to be made.
- ECMTB 2020:
  - ECMTB 2020 is an ESMTB endeavour financially, but SMB is an equal partner in all scientific issues. SMB may also give out its own prizes, or support plenary speakers. AdG and AMC will draft and circulate a MOU with the University of Heidelberg.
  - We plan for 9 plenary speakers, 1 free afternoon, no special homage. The General Assembly of ESMTB will take place on Thursday afternoon, separate from SMB. We may think of an additional joint meeting with SMB about more scientific issues. In one lunch break, we will provide the opportunity for a meeting with the editors of BMB; and similarly with those of JOMB (provided the Managing Editor(s) support the idea).
  - The previous agreement about the scientific board (1st tier) is in place. AdG will clarify with SMB the structure of scientific committee.

- ECMTB 2022: With 1 abstention, it is decided that an ECMTB conference will be held in Europe in 2022 (despite the possibility of a big international biomathematics convention coming up in the Far East the same year; the latter is not considered a substitute for a more 'regional' event in Europe, simply due to the distance). A suitable organiser and location must now be sought. MA will put together a list of minimum requirements for an ECMTB, to be communicated to potential organisers.
- ECMTB 2024: A call will be issued at ECMTB 2020 in Heidelberg.
- thematic groups: SMB has thematic subgroups and suggests to structure ECMTB along these themes. The themes of the SMB subgroups cover around half of the topics present in ESMTB; an extended list should be prepared.

  SMB (which has 1500 members) accepts a subgroup on request from at least 50 members; subgroups have at least 30 members and have their own board. In ESMTB, a subgroup in mathematical oncology could serve as a pilot project, so it is suggested that a corresponding subset of members applies for such a thematic group; the proposal should also specify how the group will be structured and organised.
- conference support rules, conference invoicing:
  - ESMTB membership solicited via conference fee: It is decided that, for meetings supported by ESMTB that have a registration fee, each participant gets a free one-year ESMTB membership upon registration. The event organisers are required to transfer to ESMTB 50 EUR for each registered participant to cover the membership fee. BP will redraft the conference support rules accordingly and add further clarifications.
  - administrative support for events: The possibility of registration and payment for conferences via ESMTB's Wild Apricot system is discussed in the case of conferences supported, but not run, by ESMTB. In this case, a board member has to serve as a formal administrator, in place of the genuine conference organiser. It is discussed whether problems related to payment of value added tax may arise from such a construction. BP will seek professional advice by an international tax consultant. If this problem can be resolved, a pilot project will be done.
- web page issues, emails, newsletter: BP will put together a list of responsibilites and administrative rights for the Board members. Currently, SC takes care of emails.
- financial report: BP delivers the financial report, which is discussed and approved. For ECMTB in Heidelberg, we aim at a marginal profit. A problem with Paypal payment is discussed: 80 percent of membership fees are payed this way, but currently we only have a French account because we are a French society. This is only a temporary solution; it would be desirable to have a German account linked to our French address, which requires an officer at large for handling bank transfers in France.
- prizes:
  - Reinhart Heinrich prize: The prize consists in the opportunity of a plenary talk at ECMTB and coverage of the corresponding expenses. The new procedures are approved as suggested and will be published on the web page. Helen Byrne and Mirjam Kretzschmar are elected as new members in the award committee, and Stefan Schuster is elected as new chair. Both elections are unanimous.
  - Ovide Arino prize: As with the Reinhart Heinrich prize, TL serves as contact person with board. The next step will be to set up the procedures.
- 8ECM in Portoroz (Slovenia), July 2020: We are given the opportunity to hold a society meeting there, but decide against it (too few of the board members will be there, and an even smaller proportion of the ESMTB members; also, a society meeting will take place in Heidelberg 2 months later).
- reciprocal memberships: So far, we have reciprocal memberships with SMB, SFBT etc., but not with EMS, although this would be desirable. SD will find out how this works with other EMS member societies, and work out a suggestion.
- board elections: The next board elections come up in September 2020. Application is open to all active members and will be solicited via a call to all members. EB will take care of the procedure. Candidates attending the ECMTB 2020 will have the opportunity to present themselves during the General Assembly. Those who will not be able to attend the meeting will have their description briefly presented by the Society Board.

E-vote decisions of the ESMTB board, March–July. 2020

- 29.04.19: Given that no one raised objections on the matter, the Board approves by majority the new ESMTB logo (blue butterfly, dark Lorenz). MA will proceed to distribute it in its definitive form.
- 29.04.19: After a brief e-mail discussion, the Board nominates Anna Marciniak (organizer), Maira Aguiar and Torbjorn Lundh as Organizer and ESMTB Principal Scientific Committee Members for ECMTB2020 Heidelberg, to be associated with two Principal Scientific Committee Members from SMB.
- 28.05.19: The ESMTB Board will henceforth use the list of email addresses of European biomathematicians, as it stands and as it will be progressively enriched by further gathering email addresses by consensus or by exploration of publicly accessible sources (public information), in order to send out emails inviting potential interested prospects to adhere to ESMTB initiatives, provided that in each message the option of deleting their names form the aforesaid list is clearly indicated to the prospects.
- 28.06.19: the Board entrusts the president to distribute invitations for joining ESMTB, using the newly prepared email list, the standard yearly rate covering, this time only, the two years 2019 and 2020.
- 16.01.20: The Board decides to grant 1 year of free ESMTB membership to 3-4 poster prize winnders of DSABNS 2020 (following a request by MA).
- 26.2.20: The Board decides to grant 1500 Euros each to the workshops 1) The Helsinki summer school on mathematical ecology and evolution 2020 2) Modelling in Ecology and Evolution Meeting, Lausanne, 2020 3) Interdisciplinary workshop on evolution and ecology (IWEE) Bath 2020
- 25.04.20: Unanimous decision taken for "ECMTB in Heidelberg shall be postponed by one year and take place if possible in August/September 2021"
- 07.05.20: In a zoom meeting, it is decided that ESMTB will support this year's online SMB meeting. MA and TL are designated as contacts. With 2 votes for, 1 vote against, and 5 abstentions, it is decided to vote in favour of ICIAM signing the MoU concerning the gender equality initiative STEM.
- 20.07.20: In a zoom meeting, we finalised the new version of the contract with Springer; planned the workflow for the elections in October 2020; and Toby reported on the preparations for the SMB eConference.

Ellen Baake
ESMTB Secretary

ECMTB 2021

The **12th European Conference on Mathematical and Theoretical Biology** has been postponed to 2021. **ECMTB 2021** will be held in **Heidelberg, Germany, from 30st August to 3th September 2021**. The conference will be hosted at Heidelberg University, in the campus located in the old town: Neue Universitt, Universittsplatz 1, 69117 Heidelberg.

We invite all researchers and students interested in Mathematical and Theoretical Biology and its applications to join us on this exciting scientific event! Previously accepted proposals for ECMTB2020 have been either shifted to the eSMB2020 virtual meeting, cancelled or postponed to ECMTB2021, as per request. The submission of proposals for new or updated 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 ECMTB2021, follow us on

Facebook @ecmtb2021
`https://www.facebook.com/ecmtb2021/`

and on

Twitter @ecmtb2021
`https://twitter.com/ecmtb2021`

Looking forward to seeing you in Heidelberg,

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

ESMTB
European Society for Mathematical and Theoretical Biology

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 2020 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 2021 issue of the European Communications in Mathematical and Theoretical Biology.
- Invitation to present a lecture at the forthcoming 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 2021.***

Only theses that have been accepted in 2020 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 2020

ESMTB
European Society for Mathematical and Theoretical Biology

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:
Bob Planqué, ESMTB treasurer
Department of Mathematics
Vrije Universiteit Amsterdam
r.planque@vu.nl