Mathematisches Forschungsinstitut Oberwolfach

Report No. 43/2018

DOI: 10.4171/OWR/2018/43

Differential Equations arising from Organising Principles in Biology

Organised by
Jose Antonio Carrillo, London
Alexander Lorz, Thuwal/Paris
Anna Marciniak-Czochra, Heidelberg
Benoît Perthame, Paris

23 September – 29 September 2018

Abstract. This workshop brought together experts in modeling and analysis of organising principles of multiscale biological systems such as cell assemblies, tissues and populations. We focused on questions arising in systems biology and medicine which are related to emergence, function and control of spatial and inter-individual heterogeneity in population dynamics. There were three main areas represented of differential equation models in mathematical biology. The first area involved the mathematical description of structured populations. The second area concerned invasion, pattern formation and collective dynamics. The third area treated the evolution and adaptation of populations, following the Darwinian paradigm. These problems led to differential equations, which frequently are non-trivial extensions of classical problems. The examples included but were not limited to transport-type equations with nonlocal boundary conditions, mixed ODE-reaction-diffusion models, nonlocal diffusion and cross-diffusion problems or kinetic equations.

Mathematics Subject Classification (2010): 92-XX; 35Q92 (primary); 37N25; 65M99 (secondary).

Introduction by the Organisers

Despite the immense progresses made over the last decades in mathematical biology, the multifaceted nature of biological processes still represents an enormous challenge for mathematical modeling. Technological advances lead to generation of massive data sets, which can then be used to improve the accuracy of modeling. This, in turn, contributes to a better understanding of the underlying complex biological processes. As a result, sophisticated mathematical methods have become

crucial for addressing the key questions and paradigms in diverse biological systems and for making predictions of the effects of system perturbations. In addition to providing an insight into the design principles of individual biological systems, mathematical modeling also allows comparative analyses across divergent systems and species, even in cases when direct molecular analogies are limited, such as when contrasting plants and animals.

This workshop brought together experts in modeling and analysis of organising principles of multiscale biological systems such as cell assemblies, tissues and populations. We focused on specific questions arising in systems biology and medicine and related to emergence, function and control of spatial and inter-individual heterogeneity in population dynamics. There were three main areas represented of differential equation models in mathematical biology. The first area involved the mathematical description and effective dynamics of structured populations. The second area concerned problems of control of the heterogeneity and synchronisation principles. The third area treated the evolution and adaptation of systems, following the Darwinian paradigm. This includes emergence and structure of the heterogeneity with their mathematical formulation using the selection-mutation models. These areas are intertwined and stimulated each other. They have contributed to progress in the fields of partial differential equations, asymptotic and multiscale analysis, singular perturbation methods, instability analysis, gradient flows, kinetic modelling, mean-field limits, cellular automata, hydrodynamic closures, entropy methods, semigroup theory and functional analytic methods.

One of the major aims of the workshop was an extensive exchange of ideas and techniques between experts from modeling and analysis of different self-organisation and structure formation mechanisms, as the corresponding mathematical problems are often tightly connected. This was very well accomplished as we corroborated with our colleagues that the activity level of information exchange during the workshop was quite high. We now elaborate a bit more in each of the subareas in which we focused during this workshop.

A.- Structured population dynamics: A typical feature of mathematical models based on biology is that multiple structuring variables appear, which are not only the spatial coordinates. Model equations typically describe the time dynamics of a population density $n(t, x)$ where x may represent a physiological, genetic or other characteristic of the individuals. The structure variables may be multidimensional, which leads to significant mathematical difficulties in model analysis and simulation, and often requires model reduction. Another challenge is understanding the difference between discrete and continuous structures, their impact and the choice of appropriate modeling approach.

A typical class of examples fitting into this area are the size-structured models and coagulation-fragmentation equations. They arise for instance in description of the dynamics of cluster growth, such as protein polymerization or in description of size distributions in bacterial populations. Structured population models also play an important role in mathematical epidemiology. Difficulties arise in linking the

dynamics in the environment to the within-host dynamics and accounting for processes taking place on very different time scales. Indeed, epidemiological processes run on a time scale of months or weeks, symptoms and infectiousness onset occur in few days, whereas the infection process at cellular level is usually completed within few hours from viral entry. Innovative modeling approachea accounting for the function of the immune system lead to new types of equations. The PDE for immune cell population couples a continuous transport process describing gradual decay of the immune status with jumps in the opposite direction modeling boosting of the immune system. Such reversible processes, often coupling continuous and jump-discontinuous transitions, appear also in cancer modeling due to the plasticity of cancer cells or in the modeling of tissue regeneration, *e.g.* when it is needed to take into account transitions between active and quiescent stem cells.

Another large class of structured population models appears in computational neuroscience. For instance voltage and conductance are typical structured variables in models of neural networks such as the integrate-and-fire neuron models. Among the different modeling approaches, the mean-field theory has proven to play a crucial part in investigating neural networks' dynamics. This leads to a formulation of population dynamics in terms of the Fokker-Planck type equations. However, the Fokker-Planck equations arising are far from standard since they frequently have atypical boundary conditions or stiff right-hand sides to take into account the firing and relaxation of neurons beyond voltage threshold values. The nonlinearity enters through the drift caused by the flux of neurons at the firing voltage. This nonlinearity and the firing mechanism are main challenges in the mathematical analysis of these models. There are clearly two future directions in this field that need to be addressed. On the one hand finding periodic solutions to some of the models will clarify the questions of synchronization in neuron models. Regularizing some of these models based on the biological observations including time delays and relaxation may lead to existence proofs of the sustained oscillations. There are other models which involve relaxation times and more classical structured population models such as age-structured equations. These connections should also be explored further. Spatial versions of the models with neurons labeled according to their location in the cortex constitute another interesting direction where interaction with groups working in synchronization might be interesting.

B.- Invasion, pattern formation and collective dynamics: At a certain scale, the spatial-temporal dynamics of biological populations can be modelled by a reaction-diffusion equation

$$\partial_t u - a_{i,j}(x,t)\partial_{ij} u - b_i(x,t)\partial_i u = f(x,u).$$

In case of constant coefficients, these equation have interesting particular solutions, so-called travelling waves. Their level-sets move at constant speed and can be interpreted as an invasion front. Showing existence of traveling waves when the coefficients depend on (x,t) and characterising their speed are challenging mathematical problems.

In case of systems of reaction-diffusion equations or their shadow type limits leading to equations with nonlocal terms, the lack of maximum principle leads to a complex dynamics. Different diffusion rates or nonlocal terms may lead to diffusion-driven instability (Turing mechanism) and emergence of asymptotically stable spatially heterogenous patterns (Turing patterns), while a lack of diffusion in a subsystem may induce formation of non-Turing patterns in the form of asymptotic spikes or transition layers with jump-discontinuities. Such systems arise from modeling of interactions between cellular processes and diffusing signaling factors. They proved to be very different from the classical reaction-diffusion models. Since stationary solutions for the non-diffusing variables are discontinuous, linearised stability analysis cannot be directly applied. Another problem encountered is that of existence of an infinite number of solutions with changing connecting point. Such problems and models are important in developmental biology. Moreover, there are crosslinks to the models of tumour growth and invasion of surrounding tissue.

Another well-established discipline, which generates interesting nonlinear mathematical problems is spatial ecology. This research is usually interdisciplinary and involves a variety of approaches, ranging from model analysis to field work. It is of immense practical importance, since it involves modeling of movements of populations and their interaction, under changing environmental conditions. Examples include invasion of aquatic species under pressure from ocean warming. Mathematically, it includes systems of nonlinear differential equations, which may or may not involve structure. Behaviors of interest include extinctions, periodicity and chaotic beahavior.

By including velocity as a structure variable, we arrive at models for populations structured by position and velocity. They can be used to explain self-organized dynamics of agents and their tendency to align. Dynamics of such systems are governed solely by interactions among individuals or agents, with the tendency to adjust to their environmental averages. This, in turn, leads to the formation of clusters, such as colonies of ants, flocks of birds, parties of people, *rendezvous* in mobile networks, and so forth. A natural question which arises in this context is when and how clusters emerge through the self-alignment of agents, and what types of rules of engagement influence the formation of such clusters. Of particular interest are cases where the self-organized behavior tends to concentrate into a single cluster, reflecting a consensus of opinions, flocking of birds, fish, or cells, rendezvous of mobile agents, and, in general, concentration of other traits intrinsic to the dynamics.

This area has been particularly active in the last decade using models ranging from transport equations, kinetic equations, to parabolic Fokker-Planck equations such as the famous Keller-Segel system. The extremely rich qualitative behaviours, including clustering and concentration, has led to a variety of mathematical methods adapted to each particular situation, including gradient flows, entropy methods, and self-similar solutions. In addition to that, hierarchies of models are also crucial because of the many scales, from the individual to the population and

multiscale analysis plays an important role in this field. The tools connecting the different levels of description such as mean-field limits or closure assumptions will be explored and expanded in other directions such as cell polymerization and cell movement.

The case of cells within a tissue is particularly relevant for this field but also much more challenging. A major outcome of this workshop will be to orient a part of the community to this important challenge for medical science including topics such as tumor growth, tissue repair and cell adhesion. Several species interaction is another major topic of expansion with very interesting biological implications in organogenesis such as neural crest or lumen formation, or in developmental biology such as stripe patterns organization by pigment cells in zebra fish. Here models for cell adhesion or pattern formation may be stimulated by feedback from groups working in collective behavior of animals. Taking into account nonlocal cell-to-cell interactions may bring new concepts and insights into the tissue self-organisation and patterning.

Models closely related to those of swarming and chemotaxis cell movement that have been used for the activation/deactivation of actine-myosin polymers in cells to model their movement. Cytoskeleton dynamics are usually modelled by gradient flows of energies involving the cross linking of polymer fibers. The mathematical analysis and modelling of these phenomena has been recently tackled and the cross fertilization of these ideas with modern techniques in simulation/understanding of steepest descent settings and kinetic approaches will certainly lead to further advances.

C.- Dynamics of adaptation: Models for population dynamics are motivated, in part, by the desire to understand how species evolve. This fascinating research area aims to understand Evolution, which is one of the fundamental principles in nature. At the same time, it has promising applications, including a better understanding of the emergence of resistance to antibiotics, chemotherapy or insecticides.

To build a model of evolution that includes selection and mutations, we start with a population structured by a physiological characteristic $x \in \mathbb{R}^d$. We assume that this characteristic confers a fitness advantage, and directly influences the competitiveness of an individual in the population.

We refer to this characteristic as a phenotypic trait. The population density $n(t,x)$ provides the number of individuals with trait x at time t. The population density changes over time by a growth/death term selecting for the fittest trait and a mutation term, leading to the following equation

$$\partial_t n(t,x) = \overbrace{n(t,x)R\big(x,I(t)\big)}^{\text{growth/death}} + \overbrace{\Delta n(t,x)}^{\text{mutations}},$$

with the total number of individuals defined as

$$I(t) := \int_{\mathbb{R}^d} n(t,x)\,dx.$$

The trait changes due to mutations are given by the Laplace operator. The growth/death term R models competition for a common resource, such as food or nutrients. The availability of the common resource depends on the total number $I(t)$ of individuals. In particular, the net growth rate $R(x, I)$ can become negative for I large enough. A typical example is $R(x, I(t)) = p(x) - d(x)I(t)$, where $p(x)$ models proliferation and $d(x)I(t)$ death/competition for a common resource. The question "what is the selected trait?" corresponds to the long-time behaviour of the equation. A Gaussian-like concentration effect arises which leads to the so-called constrained Hamilton-Jacobi equations

$$\begin{cases} \frac{\partial}{\partial t} u = R\big(x, \bar{\rho}(t)\big) + |\nabla u|^2, \\ \max_x u(x,t) = 0, \end{cases}$$

The selection-mutation models can be further generalized to account for more realistic description of the mutation process, such as in case of genetic mutations which take place during DNA replication. Such description is based on integral operators or infinite systems of ordinary differential equations, which lead to new challenges in mathematical analysis. New biological insights into the mutation process may also suggest a new generation of models defined on a metric space reflecting geometry of the space of mutations.

Another direction of further developments of selection-mutation models is related to coupled systems of equations accounting for a competition and cooperation among different populations. For systems, the classical approach to prove long-time behaviour is not feasible. Difficulty of the analysis is caused by the specific nonlinearities in the model, which do not allow for component-wise estimates. Entropy methods work only in some cases due to the lack of a rich class of entropies. We need, therefore, novel approaches to establish long-time behaviour for these coupled systems.

Final Outcome and Participants: The organizers were very positively surprised by the great thrive and enthusiasm that the conference produced in the international mathematical biology community based on PDE models. It has been several years that there were no conferences in the subject in Oberwolfach. This occasion, in the framework of the Year of Mathematical Biology 2018 organized by the EMS and the ESMTB, has served to structure a community of researchers with common goals and clear agendas in the use of mathematical modelling based on differential equations in the increasingly important area of Mathematical Biology. This is one of the most positive outcome of the meeting.

We had plenty of excellent talks given by senior and junior speakers with a high percentage of female and young participants. We had the participation of biologists and physicists interested in the mathematical modelling based on differential equations, this is essential for an interdisciplinary area to be able to overcome barriers and setting a common language of interaction. We made use of the Simons Program for Visiting Professors and the US Junior Oberwolfach fellows for Shigeru Kondo and Alexandria Volkening respectively.

The quality of the mathematical techniques used in the talks was very high and diverse using techniques of upscaling, mean-field limits, stochastic processes, kinetic theory, statistical mechanics, probability theory, numerical analysis apart from the obvious ones in differential equations such as bifurcation theory, long time asymptotics, pattern formation, travelling waves, concentrations, entropies, modelling, numerical simulations, and qualitative behavior tools.

Acknowledgement: The MFO and the workshop organizers would like to thank the National Science Foundation for supporting the participation of junior researchers in the workshop by the grant DMS-1641185, "US Junior Oberwolfach Fellows". Moreover, the MFO and the workshop organizers would like to thank the Simons Foundation for supporting Shigeru Kondo in the "Simons Visiting Professors" program at the MFO.

Workshop: Differential Equations arising from Organising Principles in Biology

Table of Contents

Abstracts

Multi-scale models of deformation and embolization of blood clots under variable shear flow

Mark Alber

Thromboembolism, one of the leading causes of morbidity and mortality worldwide, is characterized by formation of obstructive intravascular clots (thrombi) and their mechanical breakage (embolization). A novel two-dimensional multi-phase computational model will be described that simulates active interactions between the main components of the clot, including platelets and fibrin. It can be used for studying the impact of various physiologically relevant blood shear flow conditions on deformation and embolization of a partially obstructive clot with variable permeability. Simulations provide new insights into mechanisms underlying clot stability and embolization that cannot be studied experimentally at this time. In particular, model simulations, calibrated using experimental intravital imaging of an established arteriolar clot, show that flow-induced changes in size, shape and internal structure of the clot are largely determined by two shear-dependent mechanisms: reversible attachment of platelets to the exterior of the clot and removal of large clot pieces [1]. Model simulations also predict that blood clots with higher permeability are more prone to embolization with enhanced disintegration under increasing shear rate. In contrast, less permeable clots are more resistant to rupture due to shear rate dependent clot stiffening originating from enhanced platelet adhesion and aggregation. Role of platelets-fibrin network mechanical interactions in determining shape of a clot will be also discussed and quantified using analysis of experimental data leading to calibration of the SCE model. These results can be used in future to predict risk of thromboembolism based on the data about composition, permeability and deformability of a clot under specific local haemodynamic conditions.

References

[1] S. Xu, Z. Xu, O.V. Kim R.I. Litvinov, J.W. Weisel and M. Alber, *Model predictions of deformation, embolization and permeability of partially obstructive blood clots under variable shear flow*, J. R. Soc. Interface **14**: 20170441 (2017) http://dx.doi.org/10.1098/rsif.2017.0441.

[2] O. V. Kim, R. I. Litvinov, M. S. Alber and J. W. Weisel, *Quantitative structural mechanobiology of platelet driven blood clot contraction*, Nature Communications **8**: 1274 (2017), DOI: 10.1038/s41467-017-00885-x.

The effect of environmental stochasticity on a class of nonlocal hyperbolic models for self-organised biological aggregations

Raluca Eftimie

The collective movement of animals occurs as a result of communication between the members of the community. However, inter-individual communication can be affected by the stochasticity of the environment, leading to changes in the perception of neighbours and subsequent changes in individual behaviour, which then influence the overall behaviour of the animal aggregations. To investigate the effect of noise on the overall behaviour of animals, we start with a class of nonlocal hyperbolic models for the collective movement of animals introduced in [1], which we then adapt to model the effect of noise on animal perception of their conspecifics and on their turning rates [2]. We show that for some parameters the increase in noise can lead to a sequence of transitions between different spatial and spatio-temporal patterns, and these transitions are quite similar to the transitions obtained when we perturb deterministically these parameters. Moreover, we show numerically the existence of multiple stable bifurcation branches (with different amplitudes) for the stationary pulses and rotating pulses.

References

[1] R. Eftimie, G. de Vries, M.A. Lewis, *Complex spatial group patterns result from different animal communication mechanisms*, Proc. Natl. Acad. Sci. USA **104**(7), 6974-6979.

[2] R. Eftimie, *The impact of environmental noise on animal communication: pattern formation in a class of deterministic and stochastic hyperbolic models for self organised biological aggregations*, Biomath **7**(1) (2018), Article ID 1807217.

Evolutionary stability of ideal free dispersal under spatial heterogeneity and time periodicity

Chris Cosner

(joint work with Robert Stephen Cantrell)

A population is said to have an ideal free distribution on a spatial region if all of its members can and do locate themselves in a way that optimizes their fitness, allowing for the effects of crowding. Dispersal strategies that can lead to ideal free distributions of populations using them have been shown to exist and to be evolutionarily stable in a number of modeling contexts in the case of habitats that vary in space but not in time. Those modeling contexts include reaction-diffusion-advection models and the analogous models using discrete diffusion or nonlocal dispersal described by integro-differential equations. Furthermore, in the case of reaction-diffusion-advection models and their nonlocal analogues in temporally constant, there are strategies that allow populations to achieve an ideal free distribution by using only local information about environmental quality and/or gradients. This talk will present recent results showing that for reaction-diffusion-advection models for time-periodic environments with spatially varying resource levels, where the total level of resources in the environment remains fixed but

the spatial distribution of resources varies seasonally, there are strategies that allow populations to achieve an ideal free distribution. Furthermore, those strategies are evolutionarily stable, where evolutionary stability is defined in terms of pairwise invasability analysis. However, achieving an ideal free distribution in a time-periodic environment requires the use of nonlocal information about the environment such as might be derived from experience and memory, social learning, or genetic programming.

References

[1] R. S. Cantrell and C. Cosner, *Evolutionary stability of ideal free dispersal under spatial heterogeneity and time periodicity*, Mathematical Biosciences, in press.

Renewal equations arising from bookkeeping principles in population biology

Odo Diekmann

Renewal equations provide a general and flexible formalism for structured population models. The key idea is to start a clock when an event (birth, infection, jump, ...) happens and to use the state of an individual immediately after the event, together with the time on that clock, for bookkeeping purposes. In our formulation below we always speak about 'birth'. The renewal equation expresses the rate at which at time t newborns enter the population with a certain state-at-birth, in terms of contributions of individuals born at time t-a, for any positive age a and any feasible state-at-birth. The population state (a measure on the state space of the individuals), is given by an explicit expression in terms of the history of the birth rate. For given constant environmental condition E, the basic reproduction number R_0 and the Malthusian parameter r are defined. The sign of $R_0 - 1$ equals the sign of r. When individuals interact via feedback to the environment, the equation $R_0(E) = 1$ is part of the characterization of steady states. As a concrete example I discussed waning and boosting of immunity [1]. Moreover, I speculated about deriving Keller-Segel type aggregation models from renewal equations. Then I discussed dynamical systems aspects in the spirit of [2], so by considering renewal equations as delay equations, i.e., as rules for extending a function of time towards the future on the basis of the (assumed to be) known past. I showed how generation expansion (i.e., successive approximation) leads to a constructive definition of the extension for a given history. A dynamical system is defined by updating the history, i.e., by translation along the extended function. The choice of the space of histories is a subtle issue. Ideally, one would like to have a space such that translation is continuous and the rule for extension is represented by a bounded operator. As such spaces don't seem to exist, one either needs to work with two related spaces, like in sun-star calculus, see [2], or to sacrifice strong continuity, see [3]. Concerning numerical bifurcation analysis via pseudospectral approximation see [4]. As a closing remark I mentioned that Feller (in the chapter on Jump Processes in the second volume of his treatise on

Probability Theory and Its Applications) first formulates a renewal equation and then derives the Kolmogorov backward and forward equation from the renewal equation and that, in my opinion, it is a good idea to formulate models in terms of these Kolmogorov equations when diffusion guarantees that derivatives do indeed exist, but that when these Kolmogorov equations are first order PDE with nonlocal terms, one can better formulate the model in terms of the renewal equation.

References

[1] O. Diekmann, W.F. de Graaf, M.E.E. Kretzschmar, P.F. Teunis, *Waning and boosting: on the dynamics of immune status* J. Math. Biol. https://link.springer.com/article/10.1007/s00285-018-1239-5

[2] O. Diekmann, Ph. Getto, M. Gyllenberg, *Stability and bifurcation analysis of Volterra functional equations in the light of suns and stars*, SIAM Journal of Mathematical Analysis **39** (2007) 1023–1069.

[3] O. Diekmann, S.M. Verduyn Lunel *Twin semigroups and delay equations* (in preparation)

[4] D. Breda, O. Diekmann, D. Liessi, F. Scarabel, *Numerical bifurcation analysis of a nonlinear renewal equation*, Electronic Journal of Qualitative Theory of Differential Equations (2016) 65 : 1–24 doi: 10.14232/ejqtde.2016.1.65

Nonlinear partial differential equations modelling evolutionary dynamics of cancer cell populations

Tommaso Lorenzi

We consider a well-mixed population of cancer cells structured by the expression level of a gene which is linked both to the cell proliferation rate and to the cellular level of cytotoxic-drug resistance. Cells inside the population proliferate or die, compete for limited resources, and undergo phenotype variations due to spontaneous epimutations – *i.e.* heritable changes in gene expression that leave the sequence of bases in the DNA unaltered. Furthermore, a cytotoxic drug can be present, which acts by increasing the death rate of cancer cells.

We represent the expression level of the gene under consideration by a continuous variable $y \in \mathbb{R}_+$. We assume that there is a level of expression y^H which endows cells with the highest level of cytotoxic-drug resistance and a level of expression $y^L < y^H$ which gives to the cells the highest proliferation rate when the drug is not present. We model the phenotypic state of each cell in the population by means of the rescaled variable $x \in \mathbb{R}$ with

$$x = \frac{y - y^L}{y^H - y^L},$$

so that the state $x = 1$ corresponds to the highest level of cytotoxic-drug resistance, whereas the state $x = 0$ corresponds to the highest proliferation rate in the absence of the drug.

At any time $t \in \mathbb{R}_+$, we describe the cell population density (*i.e.* the phenotypic distribution of cells at time t) by means of the function $n(x, t) \geq 0$ and we use the function $u(t) \geq 0$ to model the (rescaled) dose of the cytotoxic drug. Moreover,

we compute the total number of cells (*i.e.* the population size) $\rho(t)$ and the cell mean phenotypic state $\mu(t)$, respectively, as:

$$\rho(t) = \int_{\mathbb{R}} n(x,t)\,\mathrm{d}x \quad \text{and} \quad \mu(t) = \frac{1}{\rho(t)} \int_{\mathbb{R}} x\, n(x,t)\,\mathrm{d}x. \tag{1}$$

The evolution of the population density function n is governed by the following nonlocal parabolic equation:

$$\partial_t n = \underbrace{R\big(x,\rho(t),u(t)\big)\, n}_{\text{proliferation/death}} + \underbrace{\beta\, \partial^2_{xx} n,}_{\substack{\text{spontaneous}\\ \text{epimutations}}} \qquad (x,t) \in \mathbb{R}_+ \times \mathbb{R}. \tag{2}$$

In equation (2), the diffusion term models the effects of spontaneous epimutations, which occur at rate $\beta > 0$ and are assumed to cause infinitesimally small phenotypic modifications. The reaction term takes into account the effects of cell proliferation, natural death, competition for resources and the cytotoxic action of the drug. The functional $R\big(x,\rho(t),u(t)\big)$ represents the fitness of cancer cells in the phenotypic state x under the environmental conditions determined by the population size $\rho(t)$ and the drug dose $u(t)$. We make use of the following definition for the fitness functional:

$$R\big(x,\rho(t),u(t)\big) = p(x) - d\,\rho(t) - k(x,u(t)). \tag{3}$$

In the definition given by equation (3), the term $p(x)$ is a smooth function that stands for the net proliferation rate of cancer cells (*i.e.* the difference between the rate of cell division and the rate of natural death) in the phenotypic state x, while the term $k(x,u)$ is a smooth function that models the rate of death caused by the cytotoxic drug. Moreover, the saturating term $d\,\rho(t)$ translates to mathematical terms the idea that higher total numbers of cells correspond to less available resources in the system, and thus to more intense intrapopulation competition. The parameter $d > 0$ models the rate of cell death due to intrapopulation competition. Since the phenotypic state $x = 1$ corresponds to the highest level of cytotoxic-drug resistance, we assume k to be a strictly convex function of x with minimum in $x = 1$. Furthermore, because the death rate of cancer cells will increase as the concentration of the cytotoxic drug increases, we let k be an increasing function of u. On the other hand, to take into account the fact that the phenotypic state $x = 0$ corresponds to the highest level of proliferative potential when $u \equiv 0$, we assume that p is a strictly concave function with maximum in $x = 0$.

We study the long-time behaviour of the solution to equation (2). The results of our analysis clarify the conditions for the successful adaptation of cancer cells faced with environmental changes. Furthermore, our asymptotic results demonstrate that the same cell population exposed to different concentrations of the same cytotoxic drug can take different evolutionary trajectories, which culminate in the selection of phenotypic variants characterised by different levels of drug tolerance. This suggests that the response of cancer cells to cytotoxic agents is more complex than a simple binary outcome – *i.e.* extinction of sensitive cells and selection of highly resistant cells. Also, our mathematical results formalise the idea that

the use of cytotoxic agents at high doses can act as a double-edged sword by promoting the outgrowth of drug resistant cellular clones. Overall, our theoretical work offers a formal basis for the development of anti-cancer therapeutic protocols that go beyond the 'maximum-tolerated-dose paradigm', as they may be more effective than traditional protocols at keeping the size of cancer cell populations under control while avoiding the expansion of drug tolerant clones.

References

[1] A. Lorz, T. Lorenzi, M.E. Hochberg, J. Clairambault, B. Perthame, *Populational adaptive evolution, chemotherapeutic resistance and multiple anti-cancer therapies*, ESAIM Math. Model. Numer. Anal. **47** (2013), 377–399.

[2] T. Lorenzi, R.H. Chisholm, J. Clairambault, *Tracking the evolution of cancer cell populations through the mathematical lens of phenotype-structured equations*, Biol. Direct **11** (2016), 1–17.

[3] L. Almeida, P. Bagnerini, G. Fabrini, B.D. Hughes, T. Lorenzi, *Evolution of cancer cell populations under cytotoxic therapy and treatment optimisation: insight from a phenotype-structured model*, Submitted

The interactions of singular patterns & the process of desertification

Arjen Doelman

Singular patterns appear in multi-scale systems. These systems exhibit the rich behavior of general systems, their singular nature provides a structure by which this may be understood. Moreover, many natural phenomena are modeled by such systems. A central theme of the talk was the strong cross-fertilization between applications and the development of mathematical theory. Unravelling the nature of patterns exhibited by specific chemical or ecological models goes hand in hand with uncovering novel generic destabilization mechanisms as the Hopf dance. Understanding realistic patterns requires analytical descriptions of deformations, bifurcations and annihilation of interacting localized structures – from an ecological point of view preferably under varying (climatological) circumstances: desertification can be seen, better: should be seen, as the coarsening process of a multi-pulse pattern induced by slowly varying parameters (that ends in the trivial 'bare soil' state). By this point of view, the mathematical theory of singular pulse interactions may explain why desertification sometimes is a sudden catastrophic event, while it is a gradual process in other situations.

Two attempts to promote the fusion of experiment and theory in the study of skin pattern formation

Shigeru Kondo

The reaction-diffusion model presented by Alan Turing has recently been supported by experimental data and accepted by most biologists. However, scientists have recognized shortcomings when the model is used as the working hypothesis in biological experiments. In this lecture, I will introduce two of my attempts to use the Turing model for research more effectively.

The first attempt is for the case where the detailed elementary process is not yet understood in the experimental system. There are many mathematical models with the same pattern forming ability as the reaction diffusion system, which are based on functions of different cells and molecules. Therefore, if cytologic factors involved in pattern formation have not been elucidated, researchers do not know which one to choose. In such case, I propose to use a variant of Turing model in which the interactions are not represented by partial differential equations, but rather by the shape of an activation-inhibition kernel(KT model). Simulation of the KT model with kernels of various shapes showed that it can generate all standard variations of the stable 2D patterns (spot, stripes and network), as well as some complex patterns that are difficult to generate with conventional mathematical models. The KT model can be used even when the detailed mechanism is poorly known, as the interaction kernel can often be detected by a simple experiment and the KT model simulation can be performed based on that experimental data. These properties of the KT model complement the shortcomings of conventional models and will contribute to the understanding of biological pattern formation. The KT model simulator and the original paper can be found at: `http://www.fbs.osaka-u.ac.jp/labs/skondo/simulators/KernelPatternGeneraterGauss_Web/KernelPatternGeneraterGauss.html`.

The second attempt is to help the construction of detailed agent-based simulation model for the skin pattern formation (see Figure 1). Especially in case of zebrafish skin pattern formation, information about the cells and molecular pathways involved in the pattern formation is getting accumulated. To construct the agent based model, it is required to determine the values of many parameters using the result of experiment. However, in vivo experiment is not much quantitative or flexible. to solve this problem, we developed an easy and effective method with which one can randomize the placement of all pigment cell by only irradiating blue light. This method (1) is able to disarrange all three types of pigment cell as any time point during zebrafish development, (2) does not cause the death of pigment cells, (3) does not affect to the initial movement of pigment cells, and (4) normal pattern formation is resumed immediately after switching off the blue light. This method can be easily performed even by theoretical researchers without experience in molecular biology.

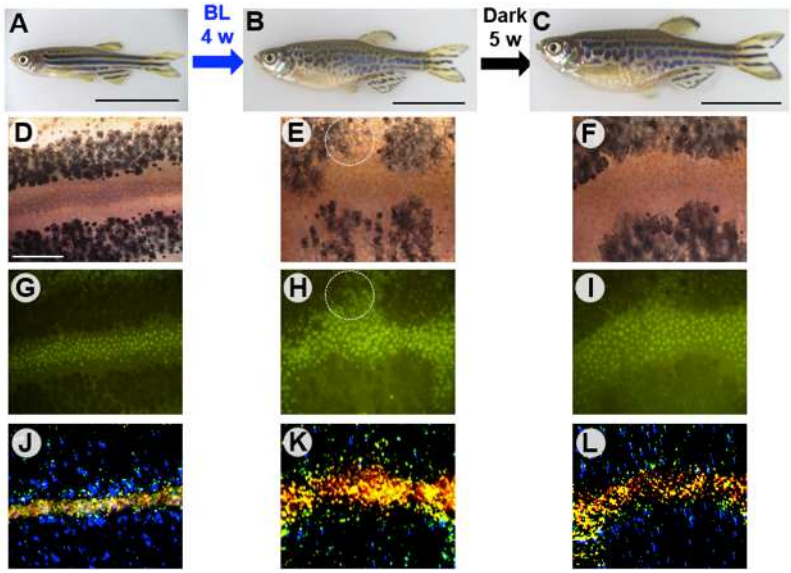

FIGURE 1. Forced melanophore movement resets the established stripe pattern. (A) mitfa:ChR2(C128S/D156A) transgenic fish was grown in the dark until 6.5 wpf. Well-established stripe pattern is shown. (B) The same transgenic fish were irradiated with blue light for 4 weeks. The stripe pattern was almost disrupted. (C) After regeneration in dark for 5 weeks, stripe pattern was regenerated but partially lost directionality. (D-F) Melanophores are shown in bright field images. (G-I) Green autofluorescence of xanthophores in fluorescence images. (J-L) Light reflection from iridophores in dark field images. Configurations of three types of pigment cells were rearranged after the blue light irradiation. Black scale bar, 10 mm. White scale bar, 500 μm.

References

[1] Shigeru Kondo, *An updated kernel-based Turing model for studying the mechanisms of biological pattern formation*, Journal of Theoretical Biology, **414**, 120–127 (2017).

Mathematic models of dynamic instabilities of microtubules and effect of antimicrotubule drugs

FLORENCE HUBERT

Microtubules (MTs) are protein filaments found in all eukaryotic cells which are crucial for many cellular processes including cell movement, cell differentiation, and cell division. Due to their role in cell division, they are often used as targets for chemotherapy drugs used in cancer treatment. Experimental studies of MT dynamics have played an important role in the development and administration of many novel cancer drugs, however, a complete description of MT dynamics is

lacking. Here, we propose new mathematical models for MT dynamics, that can be used to study the effects of chemotherapy drugs on MT dynamics.

References

[1] S. Honoré, F. Hubert, M. Tournus and D. White, *A growth-fragmentation approach for modeling microtubule dynamic instability* (submitted).

[2] D. White, S. Honoré and F. Hubert, *Exploring the effect of end-binding proteins and microtubule targeting chemotherapy drugs on microtubule dynamic instability*, Journal of Theoretical Biology, **429** (2017) 18–34.

[3] A. Barlukova, H. Gérard, S. Honoré, F. Hubert, D. White, *In silico modeling microtubule dynamic instability with new mathematical concept of GTP-hydrolysis and aging*, M2AN (2018).

[4] A. Barlukova, S. Honoré, F. Hubert, *Mathematical modeling of the microtubule dynamic instability: a new approch of GTP-tubulin hydrolysis*, Workshop on Multiscale and Hybrid Modelling in Cell and Cell Population Biology, **5** ITM Web of Conferences Ed. J. Clairambault and V. Volpert (2015).

How turtles get home

Kevin Painter

The green turtles of Ascension Island are renowned navigators, traversing thousands of kilometres of open ocean every 3-4 years and laying eggs on the same beaches from which they hatched. The question of which cues are used has fascinated researchers as far back as Darwin. I will use a biased random walk model to describe movements of this form and employ scaling techniques to derive the corresponding continuous and macroscopic model: an equation of drift/anisotropic diffusion form. This model is shown to have wide applicability in modelling movement paths, for example predicting the increased density distribution of wolves along seismic lines. Utilising ocean current data, we analyse the model and determine the critical swimming speeds and navigating strengths required for turtles to return to their island goal. As a prelude to the main talk, I present a tongue-in-cheek model to explain how academics self-organise into social cliques, aggregating their line of research into hot topics within their academic field.

Fractional Diffusion in E.coli Chemotaxis

Min Tang

(joint work with Benoît Perthame, Weiran Sun)

Kinetic-transport equations that take into account the intra-cellular pathways are now considered as the correct description of bacterial chemotaxis by run and tumble. Recent mathematical studies have shown their interest and their relations to more standard models. For example when the adaptation is fast and the run-and-tumble processes are sensitive to the outside signal, kinetic-transport equation without intra-cellular information have been derived. Macroscopic equations of Keller- Segel type have been obtained using parabolic scaling as well.

Due to the randomness of receptor methylation or intra-cellular chemical reactions, noise occurs in the signaling pathways and affects the tumbling rate. Then, comes the question to understand the role of an internal noise on the behavior of the full population. Using a kinetic model for chemotaxis which includes biochemical pathway with noises, we show that under proper scaling and conditions on the tumbling frequency as well as the form of noise, fractional diffusion can arise in the macroscopic limits of the kinetic equation. This gives an explicit and rigorous explanation about how long jumps can be due to the internal noise of the bacteria.

References

[1] B. Perthame,W. R. Sun and M. Tang, The fractional diffusion limit of a kinetic model with biochemical pathway, Zeitschrift fur angewandte Mathematik und Physik, 69:67, June 2018.
[2] B. Perthame, M. Tang, N. Vauchelet, Derivation of the bacterial run-and-tumble kinetic equation from a model with biochemical pathway, Journal of Mathematical Biology, Vol. 73, No. 5, 1161-1178, November 2016.
[3] G. Si, M. Tang and X. Yang, A pathway-based mean-field model for E. coli chemotaxis: Mathematical derivation and its hyperbolic and parabolic limits, SIAM Multiscale Modeling and Simulation, Vol. 12, No. 2, 907-926, 2014.

A model of emergent blood capillary network

Pierre Degond

(joint work with P. Aceves-Sánchez, B. Aymard, D. Peurichard, P. Kennel, F. Plouraboué, A. Lorsignol, L. Casteilla)

We propose a new model for blood vessel formation. It relies on a hybrid approach featuring an agent-based model for the formation of new capillaries and a fluid model for blood and oxygen flows. Through the interactions between these three components a positive feedback takes place which triggers the formation of new capillary elements and in fine the creation of a network of branching capillaries. The topological and geometrical properties of this network are emergent properties as they are not encoded explicitly in the agents' interaction rules. This talk reports on [1] and is based on earlier work on ant trail network formation [2]

References

[1] P. Aceves-Sánchez, B. Aymard, D. Peurichard, P. Kennel, F. Plouraboué, A. Lorsignol, L. Casteilla, P. Degond, *A hybrid agent-based/continuum model of blood network formation*, in preparation.
[2] E. Boissard, P. Degond, S. Motsch, *Trail formation based on directed pheromone deposition*, J. Math. Biol., 66 (2013), pp. 1267-1301.

Singular limits for models of selection and mutations with heavy-tailed mutation distribution

Sepideh Mirrahimi

In this work [10] we are interested in the following selection-mutation model

$$\begin{cases} \partial_t n + (-\Delta)^\alpha n = n\, R(x, I), \\ n(x,0) = n^0(x), \ x \in \mathbb{R}, \end{cases} \tag{1}$$

with

$$I(t) = \int_{\mathbb{R}} n(t,x)dx.$$

Here, $\alpha \in (0,1)$ is given and the term $(-\Delta)^\alpha$ denotes the fractional Laplacian:

$$(-\Delta)^\alpha n(t,x) = \int_{h\in\mathbb{R}^d} [n(t,x) - n(t,x+h)] \frac{dh}{|h|^{d+2\alpha}}.$$

Equation (1) has been derived from a stochastic individual based model describing the evolutionary dynamics of a phenotypically structured population [7]. Here, t corresponds to time and x corresponds to a phenotypic trait. The function n represents the phenotypic density of a population. The term $I(t)$ corresponds to the total population size. The growth rate of the individuals is denoted by $R(x, I)$ which depends on the phenotypic trait and the total population size, taking into account in this way competition between the individuals. The fractional laplacian term models the mutations. The choice of a fractional laplacian rather than a classical laplacian or an integral kernel with thin tails, allows to take into account large mutation jumps with a high rate [7].

In this talk, we provide a nonstandard rescaling of (1) that leads to the concentration of the solution n as an evolving Dirac mass, corresponding to a dominant trait which varies with time. Such behavior can be described by a Hamilton-Jacobi equation.

This result extends an approach based on Hamilton-Jacobi equations with constraint that has been developed during the last decade for the study of quantitative genetics models, to the case of fat-tailed mutation kernels. There is a large literature on this approach which was first suggested by [3]. See for instance [11, 2, 8] where the basis of this approach for models from evolutionary biology were established. Note that this method has also been used to study the propagation phenomena in local reaction-diffusion equations (see for instance [5, 6, 4, 1]).

The possibility of big jumps in (1) changes drastically the behavior of the solutions and leads to much faster dynamics of the phenotypic density, comparing to a case with a classical diffusion. Therefore, a sginifcantly different rescaling must be used. Such rescaling is derived thanks to an analogy to the fractional Fisher-KPP equation and a suitable rescaling which allows to capture the exponential speed of propagation associated with such equation [9]. Another main difference

with previous results within this approach, is that the WKB transformation of the solution does not converge to a viscosity solution of a Hamilton-Jacobi equation but to a viscosity supersolution of such equation which is minimal in a certain class of supersolutions.

References

[1] G. Barles, L. C. Evans, and P. E. Souganidis. Wavefront propagation for reaction-diffusion systems of PDE. *Duke Math. J.*, 61(3):835–858, 1990.

[2] G. Barles, S. Mirrahimi, and B. Perthame. Concentration in Lotka-Volterra parabolic or integral equations: a general convergence result. *Methods Appl. Anal.*, 16(3):321–340, 2009.

[3] O. Diekmann, P.-E. Jabin, S. Mischler, and B. Perthame. The dynamics of adaptation: an illuminating example and a Hamilton-Jacobi approach. *Th. Pop. Biol.*, 67(4):257–271, 2005.

[4] L. C. Evans and P. E. Souganidis. A PDE approach to certain large deviation problems for systems of parabolic equations. *Ann. Inst. H. Poincare Anal. non lineaire*, 6:229–258, 1989.

[5] M. Freidlin. *Functional integration and partial differential equations*, volume 109 of *Annals of Mathematics Studies*. Princeton University Press, Princeton, NJ, 1985.

[6] M Freidlin. Limit theorems for large deviations and reaction-diffusion equations. *The Annals of Probability*, 13(3):639–675, 08 1985.

[7] B. Jourdain, S. Méléard, and W. A. Woyczynski. Lévy flights in evolutionary ecology. *Journal of Mathematical Biology*, 65(4):677–707, 2012.

[8] A. Lorz, S. Mirrahimi, and B. Perthame. Dirac mass dynamics in multidimensional nonlocal parabolic equations. *Comm. Partial Differential Equations*, 36(6):1071–1098, 2011.

[9] S. Méléard and S. Mirrahimi. Singular limits for reaction-diffusion equations with fractional Laplacian and local or nonlocal nonlinearity. *Comm. Partial Differential Equations*, 40(5):957–993, 2015.

[10] S. Mirrahimi. Singular limits for models of selection and mutations with heavy-tailed mutation distribution. *Preprint*.

[11] B. Perthame and G. Barles. Dirac concentrations in Lotka-Volterra parabolic PDEs. *Indiana Univ. Math. J.*, 57(7):3275–3301, 2008.

Lineage tracking in hematopoiesis: the role of self-renewal and generational aging in clonal extinction and resurrection

Tom Chou

(joint work with Song Xu, Renaud Dessalles, Sanggu Kin, Irvin Chen)

In recent experiments, individually tagged hematopoietic stem cells (HSCs) were autologously transplanted into rhesus macaques and peripheral blood cells sampled over fourteen years. Peripheral blood samples were sequenced quantified. Analysis of clone sizes using a rescaled neutral growth model indicated rapid equilibration of clone size distributions after transplantation. Besides a heterogeneous clone size distribution, the data revealed large temporal variations of individual clone populations that included occasional extinctions and resurrections.

We developed hybrid stochastic-deterministic birth-death-immigration (BDI) models to address these long-term experiment. The stochastic BDI models were developed in both the cell count and clone count representations. Analytic steady-state distributions of the multispecies process were derived in the presence of

carrying capacity interactions [1, 2]. Rather than counting the numbers of cells n_i in species i, we use the the clone count variable

$$c_k = \sum_{i=1}^{\infty} \mathbb{1}(n_i, k), \tag{1}$$

representing the number of clones represented by k cells. A mean-field equation for the expected clone counts $\langle c_k(t) \rangle$ was derived. After sampling from this population (corresponding to a small blood sample from the animals), the expected clone counts were compared with experimental data. After rescaling and renormalizing the data, we find that the underlying process had reached a stationary state. Fitting our model to the data allowed us to estimate the total number of active stems cells $\sim 10^3 - 10^4$ and their differentiation rate $\alpha \sim 1/\text{month}$ [3].

We then reverted back to the cell count representation to analyze the large temporal fluctuations in the individual clones. A stochastic model describing HSC self-renewal was used to determine the population of each stem cell clone. This population then feeds the progenitor cell pool through differentiation. Progenitor cells were assumed to carry a finite proliferative potential corresponding to L generations of replication. This limited amplification following each differentiation event allowed us to generate the highly variable clone populations, resulting in temporal extinctions and resurrections of individual clones. Within this mechanistic picture, we use the data to infer estimates for the total HSC differentiation rate and a consistent maximum number of progenitor cell divisions. By developing a statistical measure for the number of extinctions seen in an experiment, we find a least-squares fit of $L^* \approx 24$.

References

[1] Renaud Dessalles, Maria R. D'Orsogna, and Tom Chou, *Exact steady-state distributions of multispecies birth-death-immigration processes: effects of mutations and carrying capacity on diversity*, arXiv:1806.00105, In Press: Journal of Statistical Physics, (2018).

[2] Song Xu and Tom Chou, *Immigration-induced phase transition in a regulated multispecies birth-death process*, Journal of Physics A: Mathematical and Theoretical, **51**, 425602, (2018).

[3] Sidhartha Goyal, Sanggu Kim, Irvin Chen, and Tom Chou, *Mechanisms of blood homeostasis: lineage tracking and a neutral model of cell populations in rhesus macaques*, BMC Biology, **13**, 85, (2015).

[4] Song Xu, Sanggu Kim, Irvin Chen, and Tom Chou, *Modeling large fluctuations of thousands of clones during hematopoiesis: the role of stem cell self-renewal and bursty progenitor dynamics in rhesus macaque*, bioRxiv 343160, In Press: PLoS Computational Biology, (2018).

Free Boundary PDE Models of Active Gels

Leonid Berlyand

We consider free boundary PDE models of active gels that arise in the studies of motility of eukaryotic cells. Our goal is to capture mathematically the key biological phenomena such as steady motion with no external stimuli, spontaneous breaking of symmetry, and rotation.

We first review our past work on phase field models [1] and then present recent work on the two types of the free boundary models : curvature driven motion [2] and a generalized Hele-Show flow for nonlinear PDEs [3].

In the analysis of the above models our focus is on proving existence of the traveling wave solutions that are the signature of the cell motility. We also study breaking of symmetry by proving existence of non-radial steady states. Bifurcation of traveling waves from steady states is established via the Schauder's fixed point theorem for the phase field model and the Leray-Schauder degree theory and Crandal-Rabinowitz theorem for the free boundary problem models. These are joint works with V. Rybalko (ILTPE, Kharkiv, Ukraine, J. Fuhrman (PSU & Mainz, Germany)

References

[1] L. Berlyand, M. Potomkin, and V. Rybalko "Sharp interface limit in a phase field model of cell motility" (with), *Network and Heterogeneous Media*, Vol. 12, Number 4, pp. 551-590 (2017)

[2] L. Berlyand, J. Fuhrmann, and V. Rybalko "Bifurcation of traveling waves in a Keller-Segel type free boundary model of cell motility" *Communications in Mathematical Sciences*, V.16, No 3, pp. 735-762 (2018).

[3] L. Berlyand, and V. Rybalko, preprint, 2018.

A bulk–surface reaction–diffusion system for driven cell polarization

Matthias Röger

(joint work with B. Niethammer, J. J. L. Velázquez)

The polarization of a biological cell, for example characterized by a heterogenous distribution of certain proteins, is key to many functions. We study here a simple polarization module with two types of a certain protein on the cell surface, which are either in an active or in an inactive state. We denote the first surface concentration as u and the second as v. Furthermore the inactive proteins can move to the interior of the cell and vice versa, we denote the corresponding concentration by w. We are interested in the response to a given signal, in the form of a concentration c of a certain chemical messenger on the surface.

This setup leads to a system of bulk diffusion and surface reaction–diffusion equations. The coupling is via a Robin-type boundary condition for w and a source term in the v equation. To give a more precise formulation let a open, bounded set $\Omega \subset \mathbb{R}^3$ with smooth boundary $\Gamma := \partial\Omega$ describe the cell interior and

cell surface. We then consider the following system.

$$\partial_t u = \Delta u + cv - \frac{a_4 u}{1+u} \qquad \text{on } \Gamma \times (0,T) \tag{1}$$

$$\partial_t v = \Delta v - cv + \frac{a_4 u}{1+u} - a_5 v + a_6 w \qquad \text{on } \Gamma \times (0,T) \tag{2}$$

$$\partial_t w = D\Delta w \qquad \text{in } \Omega \times (0,T) \tag{3}$$

$$-D\frac{\partial w}{\partial n} = -a_5 v + a_6 w \qquad \text{on } \Gamma \times (0,T). \tag{4}$$

For the parameters we assume $a_3, a_4, a_5, a_6 > 0$, $D \geq 1$ and for the messenger concentration that $c\colon \Gamma \to \mathbb{R}_+$ is continuous and strictly positive. With some abuse of notation Δu and Δv denote the Laplace-Beltrami operator on the surface Γ, while Δw is the usual Laplacian.

Solutions satisfy the mass conservation property

$$\int_\Omega w(x,t)\,dx + \int_\Gamma (u(y,t) + v(y,t))\,d\mathcal{H}^2(y) \;=\; M \quad \text{ for all } t \geq 0.$$

Our goal is to study for given $c = c(x)$ stationary states of (1)-(4) in certain parameter regimes and to examine when polarization patterns appear.

We start our analysis by showing that for given initial data there exists a unique solution of the system (1)-(4). We also deduce uniform bounds that only depend on the parameter and the total mass, but not on the initial conditions. Together with a smoothing property for positive times this allow to prove the existence of stationary states by a fixed point argument.

Our main results then concern the following rescaled stationary system

$$0 = \Delta u_\varepsilon + cv_\varepsilon - \frac{a_4 u_\varepsilon}{\varepsilon + u_\varepsilon} \qquad \text{on } \partial\Omega \times (0,T) \tag{5}$$

$$0 = \varepsilon\Delta v_\varepsilon - cv_\varepsilon + \frac{a_4 u_\varepsilon}{\varepsilon + u_\varepsilon} - a_5 v_\varepsilon + a_6 w_\varepsilon \qquad \text{on } \partial\Omega \times (0,T) \tag{6}$$

$$0 = D\Delta w_\varepsilon \qquad \text{in } \Omega \times (0,T) \tag{7}$$

$$-D\frac{\partial w_\varepsilon}{\partial n} = -a_5 v_\varepsilon + a_6 w_\varepsilon \qquad \text{on } \partial\Omega \times (0,T), \tag{8}$$

with the property

$$\int_\Gamma (u_\varepsilon + \varepsilon v_\varepsilon) + \int_B \varepsilon w_\varepsilon = m.$$

From a mathematical point of view, the most remarkable feature is the convergence to a generalized obstacle problem. Responsible for this feature is the presence of the Michaelis-Menten reaction term, see [1] for a corresponding result for a standard reaction–diffusion system.

Theorem. *Consider a sequence $(w_\varepsilon, u_\varepsilon, v_\varepsilon)$ of solutions to (5)-(8) with total mass m. Then there exists a subsequence $\varepsilon \to 0$ and nonnegative functions (w, u, v) such that*

$$u_\varepsilon \rightharpoonup u \quad \text{in } H^2(\Gamma)\,, \qquad v_\varepsilon \rightharpoonup v \quad \text{in } L^2(\Gamma)\,, \qquad w_\varepsilon \rightharpoonup w \quad \text{in } H^1(\Omega)\,.$$

Moreover there exists $\xi \in L^\infty(\Gamma)$ *with* $0 \le \xi \le 1$ *such that*

$$0 = \Delta u + cv - a_4\xi \qquad \text{on } \Gamma, \tag{9}$$

$$0 = -cv + a_4\xi - a_5 v + a_6 w \qquad \text{on } \Gamma, \tag{10}$$

$$0 = D\Delta w \qquad \text{in } \Omega, \tag{11}$$

$$-D\frac{\partial w}{\partial n} = -a_5 v + a_6 w \qquad \text{on } \Gamma \tag{12}$$

and such that $u\xi = u$ *and* $\int_\Gamma u = m$ *hold. Moreover,* w, u *and* v *are all nonnegative,* $u \in W^{2,p}(\Gamma)$, $w \in W^{2-\frac{1}{p},p}(\Omega)$ *for any* $1 \le p < \infty$, *and* $v \in L^\infty(\Gamma)$.

In the following we restrict ourselves to a spherical cell shape, i.e. $\Omega = B(0,1)$. We then can reformulate the problem (9)-(12) as a generalized obstacle problem that involves the Dirichlet to Neumann operator N.

Proposition. *Let* $\ell = \frac{a_6}{D}$ *and define*

$$g(x) = \frac{c(x)}{c(x) + a_5} \in (0,1)\,, \qquad x \in \Gamma\,,$$

Then (u, v, w, ξ) *satisfies* (9)-(12) *if and only if* (u, ξ, α), $\alpha \in \mathbb{R}$, *is a solution of*

$$0 = \Delta u - a_4(1-g)\xi + \alpha g - g\ell\big(N(u) + u - \bar{u}\big)\,, \qquad u \ge 0\,, \tag{13}$$

$$u\xi = u \text{ almost everywhere on } \Gamma\,, \qquad 0 \le \xi \le 1, \tag{14}$$

and if

$$w = \frac{1}{a_6}\Big(\alpha - \ell\big(N(u) + u - \bar{u}\big)\Big), \qquad v = \frac{1}{a_5}(1-g)(a_6 w + a_4\xi).$$

Observe that we obtain by integration over Γ that

$$\alpha = \frac{1}{\int_\Gamma g}\int_\Gamma \Big(a_4(1-g)\xi + \ell g\big(N(u) + u - \bar{u}\big)\Big).$$

One important property of the generalized obstacle problem is the following monotonicity property.

Proposition. *Let* (u_1, ξ_1, α_1), (u_2, ξ_2, α_2) *be two solutions of* (13), (14) *with* $\alpha_1 < \alpha_2$. *Then* $u_1 \le u_2$. *If* $\alpha_1 = \alpha_2$ *then* $u_1 - u_2 = const.$.

It follows that for any $m > 0$ there exists exactly one solution (u, ξ, α) of (13), (14) with $\int_\Gamma u = m$. Moreover, the map $m \mapsto \alpha$ is monotone.

We finally turn to a characterization of polarization in terms of the limit problem. We therefore characterize a concentration u as a polarized state if both the set $\{u = 0\}$ and the set $\{u > 0\}$ have positive measure. The final outcome of our analysis is a threshold for the occurrence of polarized states in terms of a certain critical mass. To identify this value we first prove that there exists a unique value α_* for which

$$0 = \Delta u - a_4(1-g) + \alpha_* g - g\ell\big(N(u) + u - \bar{u}\big)$$

can be solved. Moreover, there exists a unique solution u_* with

$$\min_\Gamma u_* = 0.$$

We then define the critical mass as

$$m_* := \int_\Gamma u_*.$$

The following theorem now characterizes the onset of polarized states.

Theorem. *For $m > 0$ consider the solution (u, ξ, α) of (13), (14). If $m > m_*$ we have that $u > 0$ in Γ and $\alpha = \alpha_*$. Moreover $u = u_* + (m - m_*)|\Gamma|$. If $m < m_*$ we have $|\{u = 0\}| > 0$ and $\alpha < \alpha_*$.*

For details and additional results for a slightly extended system we refer to our forthcoming work [2].

References

[1] C.-M. Brauner and B. Nicolaenko, *Regularization and bounded penalization in free boundary problems*, Theory and applications of singular perturbations (Oberwolfach, 1981), **942** (1982) of *Lecture Notes in Math.*, 19–42.

[2] B. Niethammer, J. J. L. Velázquez, Matthias Röger, *A bulk–surface reaction–diffusion system for cell polarization*, in preparation.

Two-way coupling of growth and diffusion: Developmental PDEs

Nastassia Pouradier Duteil

Among the main actors of development are morphogens, signaling molecules that diffuse in the developing organism and act on cells to produce local responses. One specific example of morphogens is Gurken, whose distribution during *Drosophila* oogenesis (*i.e.* egg formation) is related to the morphology of the fully grown egg. In collaboration with the developmental biology laboratory of CCIB (Rutgers-Camden), we developed a model in the aim of explaining the spatiotemporal distribution of Gurken, taking into account mechanisms such as diffusion of Gurken on the surface of the oocyte, growth of the oocyte, and multiple reactions (binding to receptors, negative feedbacks etc.). Via numerical simulations, we are able to compare experimental and simulated perturbations of the system [3]. This provides a useful tool for biologists to predict numerically the outcome of perturbations and to guide future experiments. The model will be used to explore the mechanisms responsible for the diversity of Gurken distributions observed in other *Drosophila* species.

In this applied model, we took into account the effect of growth on the morphogen diffusion via the time-evolving Laplace-Beltrami operator, but the growth itself was prescribed a priori by a known vector field. However, by definition, morphogens are susceptible to act on the organism to influence growth. In other words, there is a complete coupling between the diffusion of the signal and the evolution of the surface on which it diffuses. We introduce a general mathematical model

to investigate such coupling [1]. The surface of the growing cell is represented by a compact Riemannian manifold $M_t \subset \mathbb{R}^d$, that varies in time as the result of a deformation given by a transport equation. The morphogen is represented by a probability measure $\mu_t \in P(M_t)$, diffusing on the manifold via a diffusion equation. Hence the Developmental PDE (DPDE) is written as:

$$\partial_t \mu_t = \nabla \cdot (v[\mu_t]\mu_t) + \Delta_t \mu_t, \tag{1}$$

where $\nabla\cdot$ denotes the divergence of $\mathbb{R}^d$, Δ_t represents the time-evolving Laplace-Beltrami operator of the manifold M_t and $v : P_c(\mathbb{R}^d) \to \mathrm{Lip}(\mathbb{R}^d, \mathbb{R}^d)$ is a function from the space of compact probability measures in $\mathbb{R}^d$ to Lipschitz vector fields of $\mathbb{R}^d$. We show the existence of a solution to the DPDE (1) by taking the limit of an operator-splitting scheme in which we do alternate steps of transport and diffusion. As a first step towards understanding what shapes of the manifold can be attained from an initial configuration, we explore the non-commutativity of the growth (manifold change in time) and the diffusion operator (on the manifold itself). A newly defined concept of Lie bracket between the diffusion (2nd order operator) and growth (1st order operator) is able to capture such non-commutativity and thus provide new shapes towards which the manifold may evolve. We illustrate the non-commutativity of these two operators via numerical simulations. Lastly, we introduce a toy problem in which we explore the controlability of a one-dimensional manifold by the source of the signal diffusing on it (see [2]).

References

[1] U. Boscain, B. Piccoli, N. Pouradier Duteil, F. Rossi, *Developmental Partial Differential Equations*, Proceedings of the 2015 IEEE 54th Annual Conference on Decision and Control.

[2] B. Piccoli, N. Pouradier Duteil, F. Rossi, N. Yakoby, *Control of reaction-diffusion equations on time-evolving manifolds*, Proceedings of the 2016 IEEE 55th Annual Conference on Decision and Control.

[3] B. Piccoli, N. Pouradier Duteil, N. Revaitis and N. Yakoby, *Modeling the spatiotemporal dynamics of EGFR activation in the follicular epithelium* (in preparation).

Predator-prey model with competition: the emergence of territoriality

Henri Berestycki

(joint work with Alessandro Zilio)

In this talk, I report on a series of joint works with Alessandro Zilio (University Paris-Diderot), dealing with systems of predators interacting with a single prey.

With a view to shed light on the question of territoriality formation, we introduce a system describing several hostile packs interacting with each other and with a single prey. This leads us to consider the set of classical non-negative solutions $\mathbf{v} = (\mathbf{w}, u)$ of the following system of elliptic semilinear equations in a bounded

smooth domain $\Omega \subset \mathbb{R}^n$,

$$(1) \qquad \begin{cases} -d\Delta w_i = \left(-\omega + ku - \beta \sum_{j \neq i} w_j\right) w_i & \text{in } \Omega \\ -D\Delta u = \left(\lambda - \mu u - k \sum_{i=1}^{N} w_i\right) u & \text{in } \Omega \\ \partial_\nu w_i = \partial_\nu u = 0 & \text{on } \partial\Omega. \end{cases}$$

Here we denote by $\mathbf{w} = (w_1, \ldots, w_N)$ the vector of predator densities. System (1) adapts to the present context the classical model of Lotka and Volterra for predators and prey [1]. In this model, the interaction of two population is represented by the product of their densities. We are especially interested in studying the case where competition between predators is very strong, that is, when $\beta \to \infty$.

This system models the interaction between a prey (spatially distributed as the density u) and N groups of competing ($\beta > 0$) predators (the densities w_i) in an environment $\Omega \subset \mathbb{R}^n$. We recently introduced this model in [2, 3] to describe the ecological impact of territorial behaviors for predatory animals. The aim was to shed light on the basic mechanisms from which territoriality emerges, and to understand what are the consequences of these behaviors at the scale of the environment and the total populations of predators and prey.

More specifically, we study the stationary states of the system given by (1), their stability and the bifurcation diagram. Then, we investigate the asymptotic properties of the system when the intensity of the competition becomes infinite. The main questions that we ask are: (i) under which conditions do the predators segregate in packs, (ii) how many packs does an environment sustain, (iii) what are the resulting shapes and sizes of territories and (iv) whether there is a benefit for the total population in hostility between the packs.

In [2] we discuss the model and its consequences from an ecological standpoint. There, we compare some of these outcomes with reported observations on territories formation, shape and size.

From a mathematical viewpoint, in [3] we have shown existence and uniqueness results of the parabolic version of (1), explored the asymptotic limit when the competition β is very large, and we have obtained results about the existence of non-constant stationary solutions in the special case of $N = 2$ groups of predators. Then, in [4] we have shown that the solutions of (1) are uniformly bounded in Hölder norm, independently of the value of β and N. It is worth emphasizing that the derivation of estimates independent of the number N of components is a novel features of these works. This has allowed us to strengthen our conclusion about the asymptotic limit of large competition that we derived in [3]. We use these precise estimates to derive new results about the structure of the solution set when either β is small or N is large [5].

We show in particular that the number N of different packs that an environment can sustain is a priori bounded in terms of the various biological parameters in system (1). We also prove that in some parameter regimes, the total population of predators increases when there is segregation ($\beta > 0, N \geq 2$) even though the

hostility between packs leads to a depletion of predators. This gives a quantitative basis to the favorable effect of the creation of *buffer zones* that comes with territoriality.

Ackowledgments. This work has been supported by the ERC Advanced Grant 2013 No. 321186 ReaDi – Reaction-Diffusion Equations, Propagation and Modelling, held by Henri Berestycki while Alessandro Zilio was a Post-Doctoral Fellow of the research grant. This work was also partially supported by the French National Research Agency (ANR), within project NONLOCAL ANR-14-CE25-0013

References

[1] Vito Volterra. Variations and fluctuations of the number of individuals in animal species living together. *Journal du Cons. Int. Explor. Mer*, 3:5–51, 1928.
[2] Henri Berestycki and Alessandro Zilio. Predators-prey models with competition: the emergence of territoriality. *The American Naturalist (to appear)*, 2018.
[3] Henri Berestycki and Alessandro Zilio. Predators–prey models with competition, Part I: Existence, bifurcation and qualitative properties. *Commun. Contemp. Math.*, 20(7):1850010, 53, 2018.
[4] Henri Berestycki and Alessandro Zilio. Predators-prey models with competition Part II: uniform regularity estimates. *In preparation.*
[5] Henri Berestycki and Alessandro Zilio. Predators-prey models with competition Part III: classification of solutions and rigidity of the model. *In preparation.*

Relative entropy method for the growth-fragmentation equation with measure data

Piotr Gwiazda
(joint work with Tomasz Debiec, Marie Doumic, Emil Wiedemann)

The aim of this study is to generalise recent results of on entropy methods for measure solutions of the renewal equation to other classes of structured population problems. Specifically, we develop a generalised relative entropy inequality for the growth-fragmentation equation and prove asymptotic convergence to a steady-state solution, even when the initial datum is only a non-negative measure.

References

[1] P. Gwiazda and E. Wiedemann. *Generalized entropy method for the renewal equation with measure data.* Commun. Math. Sci., (2016) 577–586. M. Muster, *Computing certain invariants of topological spaces of dimension three*, Topology **32** (1990), 100–120.
[2] Tomasz Debiec, Marie Doumic, P. Gwiazda and E. Wiedemann., *Relative entropy method for the growth-fragmentation equation with measure data*, accepted SIAM J. Math. Anal.

Nonlinear noisy leaky integrate and fire models for neural networks

María J. Cáceres
(joint work with José A. Carrillo, Benoit Perthame, Pierre Roux, Delphine Salort, Ricarda Schneider)

We analyse nonlinear noisy leaky integrate and fire (NNLIF) models, which describe the activity of neural networks by means of the membrane potential. These models are based on nonlinear systems of PDEs of Fokker-Planck type. We study the wide range of phenomena that appear in this kind of models: blow-up, asynchronous/synchronous solutions, instability/stability of the steady states ...

This talk is based on works in collaboration with Carrillo, Perthame, Roux, Schneider and Salort [2, 3, 5, 6, 4].

In [6] we study the NNLIF system presented in [1]:

$$\begin{cases} \frac{\partial \rho_I}{\partial t}(v,t) + \frac{\partial}{\partial v}[h^I(v, N_E(t-D_E^I), N_I(t-D_I^I))\rho_I(v,t)] - a_I(N_E(t-D_E^I), N_I(t-D_I^I))\frac{\partial^2 \rho_I}{\partial v^2}(v,t) \\ \qquad\qquad = M_I(t)\delta(v-V_R), \\ \frac{\partial \rho_E}{\partial t}(v,t) + \frac{\partial}{\partial v}[h^E(v, N_E(t-D_E^E), N_I(t-D_I^E))\rho_E(v,t)] - a_E(N_E(t-D_E^E), N_I(t-D_I^E))\frac{\partial^2 \rho_E}{\partial v^2}(v,t) \\ \qquad\qquad = M_E(t)\delta(v-V_R). \end{cases} \tag{1}$$

This study was possible because we analysed some simplified versions of the model previously in [2, 3, 5]. The probability densities $\rho_\alpha(t,v)$ describe the limiting probability of a neuron of the excitatory population ($\alpha = E$) or of the inhibitory one ($\alpha = I$), with a membrane potential v at time t, when the total number of neurons of the network, n, goes to infinity. Moreover, for each population, $R_\alpha(t)$ represent the limiting proportion of neurons that do not respond to stimuli. The drift and diffusion coefficients are given by $h^\alpha(v, N_E, N_I) = -v + b_E^\alpha N_E - b_I^\alpha N_I + (b_E^\alpha - b_E^E)v_{E,ext}$ and $a_\alpha(N_E, N_I) = d_E^\alpha v_{E,ext} + d_E^\alpha N_E + d_I^\alpha N_I$, respectively, and are delayed in terms of the synaptic delays D_E^α and D_I^α. The rest of parameters (d_E^α, d_I^α, $v_{E,ext}$, b_E^α and b_I^α), are non negative constants. The main parameters of the model are the connectivities of the network b_E^α and b_I^α and the synaptic delay D_E^E. The coupling of the system (1) is given by the mean firing rates N_α, which obey to

$$N_\alpha(t) = -a_\alpha\left(N_E(t), N_I(t)\right)\frac{\partial \rho_\alpha}{\partial v}(V_F, t) \geq 0 \quad \alpha = E, I,$$

and, therefore the model is nonlinear.

The right hand sides in (1) describe the fact that when neurons reach the threshold potential V_F, they emit a spike over the network, reset their membrane potential to the reset value V_R and remain some time in a refractory period τ_α, (see [1, 3] for different choices of $M_\alpha(t)$). The system (1) is completed with two ODEs for $R_\alpha(t)$, the limiting probabilities to find a neuron from population α in the refractory state,

$$\frac{dR_\alpha(t)}{dt} = N_\alpha(t) - M_\alpha(t), \quad \forall \alpha = E, I, \tag{2}$$

Dirichlet boundary conditions: $\rho_\alpha(-\infty, t) = 0$ and $\rho_\alpha(V_F, t) = 0$, and initial data: $R_\alpha(0) = R_\alpha^0 \geq 0$ and $\rho_\alpha(v, 0) = \rho_\alpha^0(v) \geq 0$, $\alpha = E, I$.

First, we prove that the NNLIF model presents the blow up phenomenon: If $D_E^E = 0$ the system can blow-up in finite time in two case:

- For initial data fixed and $b_E^E > 0$ large enough.
- For $b_E^E > 0$ fixed, when the initial datum is concentrated enough around V_F.

This phenomenon was first analysed in the simpler models studied in [2, 3, 5], and it was also described at a microscopic level in [10, 9]. In [7] some existence results were proven for the simplest NNLIF model, where only one population of neurons is considered (in average excitatory or inhibitory) and where neither synaptic delays nor refractory periods were taken into account. The authors showed a criterium to determine the maximum time of existence: the solutions exist for every time for which the firing rate does not diverge. Therefore, the maximum time of existence is $T^* := Sup\{t \geq 0 : N(t) < \infty\}$. In the average inhibitory case, where the solutions do not blow up, $T^* = \infty$, while for the average excitatory case $T^* < \infty$, because blow up was proved in [2]. Recently, in [4], we have proved the global existence of solutions in the case where a synaptic delay between excitatory neurons is taken into account. In other words, $D_E^E > 0$ avoids the blow-up. Moreover, in [6], we show numerically that the remaining delays do not avoid the blow-up phenomenon.

Studing the number and shape of steady states is a complicated issue. In a few words we can say that, in terms of the values of the parameters, with refractory states there is always an odd number of steady states, while without refractory states there are some values of the parameters for which the model has an even number of steady states, and in other case there is an odd number of them. Some interesting situations are:

- If b_E^E is small enough then there is a unique stationary solution.
- If b_E^E is large enough and there are not refractory states, then there are no steady states.

In [2] we studied the long time behaviour of the simplest NNLIF model in the linear case ($b = 0$) and proved the exponential convergence to the unique steady state, by means of the entropy method. Then, in [8] this results was extended for the non linear case but with $|b|$ small, where there is a unique steady state. Recently, in [5, 6, 4] we have proved the exponential convergence of the solutions to the unique steady states of the more general NNLIF models.

Numerically we have found periodic solutions in the general NNLIF system, where all the phenomena of the network are included in the model (two populations of neurons: excitatory and inhibitory, synaptic delays and refractory periods) [6]. We do not observe periodic solutions if the synaptic delays and the refractory periods are not taken into account. In this simpler situation, we find periodic solutions only if we consider a modification of the model (see [3]), where randomness

is included on the firing potential V_F, instead of a fixed value of the threshold potential. In this case the model does not present blow-up and there are strong controls on the firing rate (or total activity of the network) $N(t)$.

The properties of the solutions of the NNLIF models, which we proved analytically or showed numerically, can be related to neurophysiological phenomena. For instance, the blow-up can be interpreted as a synchronization of a part of the network, maybe associated with epilepsy. The presence of several steady states, with multi-stable phenomena, could be related, for example, to visual perception and decision making. And periodic or oscillatory states are also related to neurophysiological phenomena, for instance those observed during cortical processing.

Finally, we point out several open problems, the analytical study of:

- The stability of the models when there is more than one stationary solution.
- Criteria to have oscillatory states.
- A more general notion of solution that allows to continue after blow-up.
- Relations with other PDE models which describe the activity of the networks at the level of the membrane potential.

References

[1] N. Brunel, *Dynamics of sparsely connected networks of excitatory and inhibitory spiking networks*, J. Comp. Neurosci., **8** (2000), 183–208.

[2] M. J. Cáceres, J. A. Carrillo, and B. Perthame, *Analysis of nonlinear noisy integrate & fire neuron models: blow-up and steady states*, Journal of Mathematical Neuroscience, 1-7 (2011).

[3] M. J. Cáceres and B. Perthame, *Beyond blow-up in excitatory integrate and fire neuronal networks: refractory period and spontaneous activity*, Journal of theoretical Biology, *350* (2014), 81–89.

[4] M. J. Cáceres, P. Roux, D. Salort, and R. Schneider, *Global-in-time classical solutions and qualitative properties for the nnlif neuron model with synaptic delay*, arXiv preprint arXiv:1806.01934, (2018).

[5] M. J. Cáceres and R. Schneider, *Blow-up, steady states and long time behaviour of excitatory-inhibitory nonlinear neuron models*, Kinetic and Related Models, **10** (2017), 587–612.

[6] M. J. Cáceres and R. Schneider, *Analysis and a numerical solver for excitatory-inhibitory networks with delay and refractory periods*, ESAIM: M2AN, (2018).

[7] J. A. Carrillo, M. d. M. González, M. P. Gualdani, and M. E. Schonbek, *Classical solutions for a nonlinear Fokker-Planck equation arising in computational neuroscience*, Comm. in Partial Differential Equations, **38** (2013), 385–409.

[8] J. Carrillo, B. Perthame, D. Salort, and D. Smets, *Qualitative properties of solutions for the noisy integrate & fire model in computational neuroscience*, Nonlinearity, **25** (2015), 3365–3388.

[9] F. Delarue, J. Inglis, S. Rubenthaler, and E. Tanré, *Global solvability of a networked integrate-and-fire model of McKean-Vlasov type*, The Annals of Applied Probability, **25** (2015), 2096–2133.

[10] F. Delarue, J. Inglis, S. Rubenthaler, and E. Tanré, *Particle systems with a singular mean-field self-excitation. Application to neuronal networks*, Stochastic Processes and their Applications, **125** (2015), 2451–2492.

Ecological invasion in competition-diffusion systems when the exotic species is either very strong or very weak

Danielle Hilhorst
(joint work with L. Contento, M. Mimura)

Reaction-diffusion systems with a Lotka-Volterra-type reaction term, also known as competition-diffusion systems, have been used to investigate the dynamics of the competition among m ecological species for a limited resource necessary to their survival and growth. Notwithstanding their rather simple mathematical structure, such systems may display quite interesting behaviours. In particular, while for $m = 2$ no coexistence of the two species is usually possible, if $m \geq 3$ we may observe coexistence of all or a subset of the species, sensitively depending on the parameter values. Such coexistence can take the form of very complex spatio-temporal patterns and oscillations.

Unfortunately, at the moment there are no known tools for a complete analytical study of such systems for $m \geq 3$. This means that establishing general criteria for the occurrence of coexistence appears to be very hard. Instead we give some criteria for the non-coexistence of species, motivated by the ecological problem of the invasion of an ecosystem by an exotic species. We show that when the environment is very favorable to the invading species the invasion will always be successful and the native species will be driven to extinction. On the other hand, if the environment is not favorable enough, the invasion will always fail.

The understanding of the mechanisms behind the rich biodiversity observed in nature is a central problem in theoretical ecology. It is a generally accepted fact that when two or more species are competing for the same limited resources in a constant and homogeneous environment which is isolated from external influences, they cannot coexist and all but one species will become extinct; this is known as the *competitive-exclusion principle* and has been experimentally confirmed for cultures of microorganisms. However, in real ecosystems a high number of coexisting species is often observed also in places where resources are scarce. A famous example of this apparent contradiction with the principle is Hutchinson's paradox of the plankton: a high number of phytoplankton species are able to coexist, even if they all compete for the same resources. Traditionally theoretical ecologists have explained this biodiversity by observing that natural environments are inhomogeneous in space and/or time, so that the principle does not apply. Thus, even species which are competing for the same resource may coexist, each being dominant in a particular zone or season, without any equilibrium being reached.

Mathematical models for the competition between species can aid in the understanding of this problem. In the case where only two species are present, it has been shown that a reaction-diffusion system with Lotka-Volterra-like reaction terms (from here on called a *competition-diffusion system*) with constant parameters (i.e., modeling a homogeneous environment) always displays competitive exclusion if the space domain is convex. Non-convex domains may allow for stable coexistence equilibria in which the species segregate spatially, but this

can be interpreted ecologically as being due to immigration effects, a violation of the hypotheses of the competitive-exclusion principle. Another example of a mechanism which leads to coexistence is the addition of cross-diffusion; since this amounts to the species avoiding each other and nearly not competing, it is again a failure of the principle's hypotheses.

It has been recently shown that, when three or more species are considered, dynamical coexistence is possible even in convex homogeneous environments with only random dispersal. This is due to the effect of indirect competition between the species, under the form of the so-called *cyclic competition*. The competition-diffusion system in this case has the form

$$\begin{aligned} u_t &= D_u \Delta u + (r_1 - u - b_{12} v - b_{13} w)\, u, \\ v_t &= D_v \Delta v + (r_2 - v - b_{21} u - b_{23} w)\, v, \\ w_t &= D_w \Delta w + (r_3 - w - b_{31} u - b_{32} v)\, w. \end{aligned}$$

In particular, the following ecological situation is considered. An ecosystem which is inhabited by two native species u and v which are usually unable to coexist is invaded by a third, exotic species w from outside. The parameter r_3 represents the suitability of the new environment for the invader. Intuitively, if r_3 is very small the invasion should fail, while if r_3 is very large the two native species should be supplanted by w. Then, coexistence is possible only for intermediate values of r_3.

This line of reasoning can be extended to the general case in which we have m different competing species. Let us choose one species, which without loss of generality can always be thought to be the m-th one. If r_m, the intrinsic growth rate of the m-th species, is very large, then the m-th species will be able to invade an ecosystem occupied by the first $m-1$ species, completely replacing them.

If on the other hand r_m is very small, the invasion will not succeed and the m-th species will go extinct. Note that if $m > 3$ the remaining species may still be able to coexist. Then, coexistence of all species is possible only for intermediate values of r_m, when the invasion by the m-th species is successful but its strength is not sufficient to drive the native species to extinction.

We are mainly concerned with studying the dependence of the system's behavior on the parameter r_m. We will only consider the extreme cases in which such parameter is very large or very small. The intermediate value case, while very interesting since it allows for coexistence of all species, is much more challenging to study analytically and will not be considered here. We recall the basic properties of the solutions of the m-species competition-diffusion system. We first study the scalar case $m = 1$, i.e., the Fisher-KPP equation, and its limiting behavior. We then consider the case in which r_m is large and show that the first $m-1$ species become extinct. We study this case first as a singular limit problem, keeping the time interval fixed and letting r_m go to infinity, and then as a large-time problem, choosing r_m sufficiently large but finite and studying the behavior of the solutions as time tends to infinity. Finally, we study in a similar way the case where r_m is small and the m-th species disappears.

Mathematical modeling of the spread of Wolbachia for dengue control

Nicolas Vauchelet
(joint work with P.-A. Bliman, G. Nadin, M. Strugarek, J. Zubelli)

Bacteria Wolbachia has gain a lot of attention since scientists discover that infected mosquitoes with this bacteria cease to transmit some disease like dengue, chikungunya and Zika. Moreover, this bacteria is maternally transmitted from mother to offsprings. Then a strategy of control of dengue transmission consists in releasing Wolbachia infected mosquitoes in the aim to replace to natural population of mosquitoes by infected mosquitoes. In this work, we are concerned with the spatial spread of Wolbachia infected mosquitoes into a host population. We focus on the following questions: How the spatial repartition of the releases will influence the spread of the bacteria into the population ? Once the spread is initiated, is it possible that environmental characteristics stop the spread ?

In order to answer to these questions, we introduce a simple competition reaction-diffusion model for two species : Wolbachia-infected mosquitoes and Wolbachia-free mosquitoes. We first reduce this model to a simple scalar reaction-diffusion equation thanks to an asymptotics analysis [3]. The limiting system is a bistable scalar reaction-diffusion equation for the fraction of infected mosquitoes for which we know the existence of traveling waves. Thanks to this simple model, we are able to state sufficient conditions on the initial release to initiate the spatial spread of Wolbachia-infected mosquitoes [4]. We also look for an active control in time of the release [1]. Finally, we study the effect of heterogeneities on the environment which may block the propagation [2].

References

[1] P.-A. Bliman, N. Vauchelet, *Establishing traveling wave in bistable reaction-diffusion system by feedback*, IEEE Control System Letter, July 2017, vol 1, issue 1, pp 62–67.
[2] G. Nadin, M. Strugarek, N. Vauchelet, *Hindrances to bistable front propagation: application to Wolbachia invasion*, J. Math. Biol. **76** (2018) no 6, 1489–1533.
[3] M. Strugarek, N Vauchelet, *Reduction to a single closed equation for 2 by 2 reaction-dffusion systems of Lotka-Volterra type*, SIAM J. Appl. Math. **76** (2016), no 5, 2060–2080.
[4] M. Strugarek, N. Vauchelet, J. P. Zubelli, *Quantifying the survival uncertainty of Wolbachia-infected mosquitoes in a spatial model*, Math. Biosci. Eng. **15** (2018), no 4, 961–991.

Coupled bulk-surface free boundary problems from a model for receptor-ligand dynamics

Chandrasekhar Venkataraman
(joint work with Charles M. Elliott, Thomas Ranner)

Let Γ be a smooth, compact closed n-dimensional hypersurface contained in a domain $D \subset \mathbb{R}^{n+1}$, $n = 1, 2$. The surface Γ separates a domain D into an interior domain I and an exterior domain Ω. We will denote by $\partial_0\Omega$ the outer boundary of Ω, i.e., the boundary ∂D. We will assume that this boundary is Lipschitz. We

consider the following problem: Find $u\colon \Omega \times [0,T] \to \mathbb{R}$ and $w\colon \Gamma \times [0,T] \to \mathbb{R}$ such that

$$\delta_\Omega \partial_t u - \Delta u = 0 \qquad \text{in } \Omega \tag{1a}$$

$$\nabla u \cdot \vec{\nu} = -\frac{1}{\delta_k} uw \qquad \text{on } \Gamma \tag{1b}$$

$$u = u_D \text{ or } \nabla u \cdot \vec{\nu}_\Omega = 0 \qquad \text{on } \partial_0\Omega \tag{1c}$$

$$\partial_t w - \delta_\Gamma \Delta_\Gamma w = \mu \nabla u \cdot \vec{\nu} \qquad \text{on } \Gamma \tag{1d}$$

$$u(\cdot,0) = u^0(\cdot) \qquad \text{in } \Omega \tag{1e}$$

$$w(\cdot,0) = w^0(\cdot) \qquad \text{on } \Gamma, \tag{1f}$$

where $\delta_\Omega, \delta_\Gamma, \delta_k > 0$ are given model parameters and the initial data are bounded, non-negative functions, i.e., $u^0 \in L^\infty(\Omega)$, $w^0 \in L^\infty(\Gamma)$ and $u^0, w^0 \geq 0$. In the above Δ_Γ denotes the Laplace-Beltrami operator on the surface Γ and Δ the usual Cartesian Laplacian in $\mathbb{R}^{n+1}$.

Problem (1) may be regarded as a basic model for receptor-ligand dynamics in cell biology, modelling the dynamics of mobile cell surface receptors, w reacting with a mobile bulk ligand, u. The model arises, after nondimensionalisation, as a large binding affinity reduction of a model including receptor-ligand complexes, in which we neglect the complexes. Taking biologically realistic parameter values for the characteristic scales used to nondimsionalise the model, motivates the consideration of the following three biologically relevant asymptotic limits

$$(1)\ \delta_k \to 0, \quad (2)\ \delta_\Gamma = \delta_k \to 0, \quad \text{and } (3)\ \delta_\Omega = \delta_\Gamma = \delta_k \to 0.$$

We prove the existence and uniqueness of a (weak) solution pair (u,w) to (1) together with rigorous convergence of (u,v), with $v = -w$ to weak solutions of three limiting bulk-surface free boundary problems in the biologically relevant limits above. The limiting problems correspond to interesting free boundary problems due to the complementarity nature of the fast reaction limit ($\delta_k \to 0$), i.e., in the limit one has

$$u \geq 0, \qquad w \geq 0, \qquad uw = 0 \qquad \text{on } \Gamma.$$

The details are given in [2], here we focus only on the case (3). The limiting problem corresponds to

Elliptic limit problem with dynamic boundary conditions ($\delta_\Omega = \delta_k = \delta_\Gamma \to 0$):

$$-\Delta \hat{u} = 0 \qquad \text{in } \Omega \times (0,T) \tag{2a}$$

$$\nabla \hat{u} \cdot \vec{\nu} + \partial_t \hat{v} = 0 \qquad \text{on } \Gamma \times (0,T) \tag{2b}$$

$$\hat{v} \in \beta(\hat{u}) \qquad \text{on } \Gamma \times (0,T) \tag{2c}$$

$$\hat{u} = u_D \qquad \text{on } \partial_0\Omega \times (0,T) \tag{2d}$$

$$\hat{v}(\cdot,0) = v^0(\cdot) \leq 0 \qquad \text{on } \Gamma, \tag{2e}$$

the complementarity is encoded in the constraint $v \in \beta(u)$ with β defined by

$$\beta(r) = \begin{cases} \emptyset & \text{if } r < 0 \\ [-\infty, 0] & \text{if } r = 0 \\ \{0\} & \text{if } r > 0. \end{cases}$$

We are further able to prove that the solution to (2) is unique. Moreover, we may write the problem as an abstract degenerate parabolic equation holding on the surface Γ which reveals the structure. Introducing a Dirichlet to Neumann (DtN) map $\mathcal{A}^0$ (see [2] for details), we may write problem (2) as follows.
Elliptic problem with dynamic boundary condition ($\delta_k = \delta_\Gamma = \delta_\Omega = 0$)

$$\partial_t \hat{v} + \mathcal{A}^0 \hat{u} + \nabla U_D \cdot \nu = 0 \qquad \text{in } L^2(0, T; H^{-1/2}(\Gamma)), \tag{3}$$

with $v \in \beta(u)$, $v^0 = -w^0$, and with U_D an extension associated with the boundary data for u. Written in this way, one sees that (3) may be thought of as a Hele-Shaw or steady one phase Stefan problem on the surface Γ with the operator $\mathcal{A}^0$ in place of the usual Laplacian. Interpreting the operator $\mathcal{A}^0$, as $(-\Delta_\Gamma)^{1/2}$ we may think of (3) as a surface Hele Shaw problem with the half-Laplacian in place of the usual Laplacian.

Following techniques employed for the resolution of the one-phase Stefan and Hele Shaw problems [3] we may integrate in time and reformulate (3), as an elliptic variational inequality of obstacle type. The obstacle problem lies on the surface Γ and time simply enters as a parameter, hence the problem may be solved at any given time independent of the values at other times leading to significant speed up in terms of computations.

References

[1] García-Peñarrubia P, Gálvez JJ and Gálvez J, *Mathematical modelling and computational study of two-dimensional and three-dimensional dynamics of receptor–ligand interactions in signalling response mechanisms*, Journal of Mathematical Biology **69**, 3, (2014), 553–582.

[2] C. M. Elliott, T. Ranner, and C. Venkataraman, *Coupled bulk-surface free boundary problems arising from a mathematical model of receptor-ligand dynamics*, SIAM Journal on Mathematical Analysis (2017).

[3] C. M. Elliott and V. Janovskỳ, *A variational inequality approach to Hele-Shaw flow with a moving boundary*, Proceedings of the Royal Society of Edinburgh: Section A Mathematics **88**, 1-2, (1981), 93–107.

A two species hyperbolic-parabolic model of tissue growth

Agnieszka Świerczewska-Gwiazda

(joint work with Piotr Gwiazda, Benoît Perthame)

Models of tissue growth are now well established, in particular in relation to their applications to cancer. They describe the dynamics of cells subject to motion resulting from a pressure gradient generated by the death and birth of cells, itself controlled primarily by pressure through contact inhibition. In the compressible regime we consider, when pressure results from the cell densities and when two

different populations of cells are considered, a specific difficulty arises from the hyperbolic character of the equation for each cell density, and to the parabolic aspect of the equation for the total cell density. For that reason, few a priori estimates are available and discontinuities may occur. Therefore the existence of solutions is a difficult problem.

In [4] we established the existence of weak solutions to the model with two cell populations which react similarly to the pressure in terms of their motion but undergo different growth/death rates:

$$\begin{cases} \partial_t n_1 - \operatorname{div}[n_1 \nabla p] = n_1 F_1(p) + n_2 G_1(p), \qquad x \in \mathbb{R}^d,\ t \geq 0, \\ \partial_t n_2 - \operatorname{div}[n_2 \nabla p] = n_1 F_2(p) + n_2 G_2(p), \end{cases}$$

with

$$n := n_1 + n_2, \qquad p = n^\gamma, \quad \gamma > 1.$$

We assume that there is a value $P_H > 0$ such that the smooth functions F_i, G_i, describing the division/death rates of cells, satisfy the properties

$$F(p) := F_1(p) + F_2(p) \leq 0, \qquad G(p) := G_1(p) + G_2(p) \leq 0, \qquad \forall p \geq P_H.$$

In opposition to the method used in the recent paper [2], our strategy is to ignore compactness on the cell densities and to prove strong compactness on the pressure gradient. We improve known results in two directions; we obtain new estimates, we treat higher dimension than one and we deal with singularities resulting from vacuum.

We have started to work on this problem during the visit of Benoit in Poland and continued during the visit of Piotr and myself in Paris. We have proposed a strategy to prove existence of weak solutions for this two species model of tumor invasion. It relies on the extension of the Aronson-Benilan ([1]) regularizing effect for porous media equations which provides estimates of the Laplacian of the pressure. The most important limitation so far is a combined condition on the two bulk growth terms which we assumed

$$\sup_{0 \leq p \leq P_H} \frac{|F(p) - G(p)|^2}{p^{1/\gamma}} \leq C_H.$$

and it is an open question to remove it.

A question which we have not handled is the strong compactness of n_i^ϵ in the stability result of the approximation process. The bounds on Δp are too weak for the L^1 theory of renormalized solutions (Di Perna - Lions) and are boarder line to apply the compactness theorems (Ambrosio, Bouchut and Crippa) which require that $D^2 p$ is a bounded measure.

The extension to more than two species, with the present strategy, requires combined conditions on the three growth terms which read, in the case of three species for instance, $c_1 F(p) + c_2 G(p) + c_3 H(p) \leq C p^{1/\gamma}$ whenever the nonnegative c_i satisfy $c_1 + c_2 + c_3 = 1$. Then, the analysis goes through without major changes.

An interesting question concerns an incompressible limit, $\gamma \to \infty$, which has attracted much attention recently because of its relation to congested traffic. Clearly

the bounds provided here are not enough to investigate this question. For the recent studies in one dimensional case see [3].

Another question is about different mobilities, where the parabolic aspects of the equation for $n = n_1 + n_2$ do not apply, see e.g. [5].

References

[1] D. G. Aronson and P. Bénilan. *Régularité des solutions de l'équation des milieux poreux dans* $\mathbf{R}^N$, C. R. Acad. Sci. Paris Sér. A-B, **288** (1979), A103–A105.

[2] J. A. Carrillo, S. Fagioli, F. Santambrogio, and M. Schmidtchen. *Splitting schemes & segregation in reaction-(cross-)diffusion systems*, arxiv:1711.05434, (2017).

[3] P. Degond, S. Hecht, and N. Vauchelet. *Incompressible limit of a continuum model of tissue growth for two cell populations*, arXiv:1809.05442 (2018).

[4] P. Gwiazda, B. Perthame, A. Świerczewska-Gwiazda *A two species hyperbolic-parabolic model of tissue growth*, arXiv:1809.01867, (2018)

[5] T. Lorenzi, A. Lorz, and B. Perthame. *On interfaces between cell populations with different mobilities*, *Kinet. Relat. Models*, **10** (2017), 299 – 311.

Two models of tumour growth with emergence of heterogeneity, in the framework of chemotherapies

Cécile Carrère

The resistance of tumours to chemotherapies is a main reason of treatment failure in classical protocols. We present here two models that exhibit how clonal heterogeneity can give rise to such resistance.

The first model is a competition-diffusion model, with two cell species (sensitive or resistant to the drug) invading an empty territory while competing with each other. The growth function for each species is logistic, with different growth factors and competition rates. Using successive sub- and super-solutions of the equation, the long time behaviour of the system is described for a large class of initial conditions. For a certain range of parameters, even if the resistant cells population is weaker than the sensitive cells population (i.e. it is replaced in each bounded interval), if its Fischer-KPP speed is faster, then it will invade the empty environment first, creating a growing ring of resistant cells around a slower growing core of sensitive cells[1].

In a second model, in a joint work with J.Clairambault, T.Lorenzi and G.Nadin, we investigate this problem in the framework of bet hedging. We define here bet hedging as the situation when, under stressful conditions, generalists may win against specialists. We define a PDE model of a population structured in epigenetic traits, with a diffusion corresponding to the epigenetic mutations and a competition accross the whole population[2]. We study the long time behaviour of the system under a time-periodic treatment. After proving the existance and attractivity of time-periodic solutions, we analyse the effect of different protocols on the mean final tumour size $\bar{\rho}$. We show that, for a fixed treatment dose to deliver during one time period, a constant dose minimizes $\bar{\rho}$. Moreover, under some hypothesis on the growth function and under bang-bang treatment protocols,

tumours with a higher mutation rate may become larger. This situation might cause problems for future treatments, as more plastic tumors might adapt faster to new drugs.

References

[1] Carrre, C. (2018). "Spreading speeds for a two-species competition-diffusion system". *Journal of Differential Equations*

[2] Lorenzi, T., Chisholm, R.H. and Clairambault, J. (2016). "Tracking the evolution of cancer cell populations through the mathematical lens of phenotype-structured equations", *Biology Direct*

Heterogeneity in epigenetic regulatory systems: Epigenetic plasticity in aging and cancer

Tomás Alarcón

Understanding the control of epigenetic regulation is key to explain and modify the aging process. Because histone-modifying enzymes are sensitive to shifts in availability of cofactors (e.g. metabolites), cellular epigenetic states may be tied to changing conditions associated with cofactor variability. The aim of this study is to analyse the relationships between cofactor fluctuations, epigenetic landscapes, and cell state transitions. Using Approximate Bayesian Computation, we generate an ensemble of epigenetic regulation (ER) systems whose heterogeneity reflects variability in cofactor pools used by histone modifiers. The heterogeneity of epigenetic metabolites, which operates as regulator of the kinetic parameters promoting/preventing histone modifications, stochastically drives phenotypic variability. The ensemble of ER configurations reveals the occurrence of distinct epi-states within the ensemble. Whereas resilient states maintain large epigenetic barriers refractory to reprogramming cellular identity, plastic states lower these barriers, and increase the sensitivity to reprogramming. Moreover, fine-tuning of cofactor levels redirects plastic epigenetic states to re-enter epigenetic resilience, and vice versa. Our ensemble model agrees with a model of metabolism-responsive loss of epigenetic resilience as a cellular aging mechanism. Our findings support the notion that cellular aging, and its reversal, might result from stochastic translation of metabolic inputs into resilient/plastic cell states via ER systems. This is joint work with Núria Folguera-Blasco (Crick Institute, London, UK), Rubén Pérez-Carrasco (University College London, UK), Elisabet Cuyàs (ICO-IDIBGI, Girona, Spain), and Javier A Menéndez (ICO-IDIBGI, Girona, Spain)

Partial Differential Equations as Models for Social Complex Systems

Nancy Rodríguez

We discuss two stories related to the use of Partial Differential Equations as models for social phenomena. The first part of the talk focused on discussing the analysis of traveling waves solutions for a system which was introduced to model riot dynamics. The existence and stability of such solutions was motivated by the 2005 French riots which displayed a "wave-like" spread of activity. Through our analysis we conclude that this riot was likely displayed tension-inhibitive dynamics where the outburst of activity helped release social tension. The second part of the talk was devoted to the introduction of a model for wealth-dynamics. We found parameter regimes that lead to neighborhoods of wealth concentration and discussed the effect of economic downturns.

The interest of a microscopic approach in the study of cross diffusion systems appearing in population dynamics

Laurent Desvillettes

In the situation when two species (represented by number densities $u := u(t,x)$ and $v := v(t,x)$) are in competition and are spatially structured, the traditional Lotka-Volterra equations (together with homogeneous Neumann boundary conditions) read

$$\begin{cases} \partial_t u - d_u\,\Delta_x u = u\,(r_u - r_a\,u - r_b\,v) & \text{in } [0,\infty[\times\Omega, \\ \partial_t v - d_v\,\Delta_x v = v\,(r_v - r_c\,v - r_d\,u) & \text{in } [0,\infty[\times\Omega, \\ \nabla_x u\cdot n = \nabla_x v\cdot n = 0 & \text{on } [0,\infty[\times\partial\Omega, \end{cases} \tag{1}$$

where $d_u, d_v > 0$ are diffusion rates, $r_u, r_v > 0$, and $r_a, r_b, r_c, r_d > 0$ are related to the intraspecific and interspecific competition.

The above model is known not to give rise to spatial patterns. Indeed, depending on the coefficients $r_u, r_v,\ r_a, r_b,\ r_c, r_d$, the stable steady states are spatially homogeneous, of the form $(\bar u, 0)$, $(0,\bar v)$, or $(\bar u,\bar v)$, with $\bar u, \bar v > 0$.

In order to observe patterns, it is possible to consider systems of reaction diffusion (with reaction terms which are polynomials of degree 2) with strictly more than two equations. An alternative approach consists in considering more complex diffusion processes for one of the species (say, species u). If the individuals of this species increase their diffusion rate when the other species has an higher (local) concentration, one is led to write down the model introduced by Shigesada, Kawasaki and Teramoto in the late 70s (cf. [7]):

$$\begin{cases} \partial_t u - \Delta_x(d_u\,u + d_{12}\,u\,v) = u\,(r_u - r_a\,u - r_b\,v) & \text{in } [0,\infty[\times\Omega, \\ \partial_t v - d_v\,\Delta_x v = v\,(r_v - r_c\,v - r_d\,u) & \text{in } [0,\infty[\times\Omega, \\ \nabla_x u\cdot n = \nabla_x v\cdot n = 0 & \text{on } [0,\infty[\times\partial\Omega. \end{cases} \tag{2}$$

Here, $d_{12} \geq 0$ is an extra parameter added to the model. One can show that when d_{12} is large enough, spatial patterns indeed appear.

Following [6], this system can be seen as the formal singular limit of a (so called microscopic) reaction diffusion system, which writes

(3)
$$\begin{cases} \partial_t u_A^\epsilon - d_u\,\Delta_x u_A^\epsilon = [r_u - r_a\,(u_A^\epsilon + u_B^\epsilon) - r_b\,v^\epsilon]\,u_A^\epsilon \\ \qquad\qquad + \dfrac{1}{\epsilon}[k(v^\epsilon)\,u_B^\epsilon - h(v^\epsilon)\,u_A^\epsilon] & \text{in } [0,\infty[\times\Omega, \\ \partial_t u_B^\epsilon - (d_u + d_B)\,\Delta_x u_B^\epsilon = [r_u - r_a\,(u_A^\epsilon + u_B^\epsilon) - r_b\,v^\epsilon]\,u_B^\epsilon \\ \qquad\qquad - \dfrac{1}{\epsilon}[k(v^\epsilon)\,u_B^\epsilon - h(v^\epsilon)\,u_A^\epsilon] & \text{in } [0,\infty[\times\Omega, \\ \partial_t v^\epsilon - d_v\,\Delta_x v^\epsilon = [r_v - r_c\,v^\epsilon - r_d\,(u_A^\epsilon + u_B^\epsilon)]\,v^\epsilon & \text{in } [0,\infty[\times\Omega, \\ \nabla_x u_A^\epsilon \cdot n = \nabla_x u_B^\epsilon \cdot n = \nabla_x v^\epsilon \cdot n = 0 & \text{on } [0,\infty[\times\partial\Omega, \end{cases}$$

where $d_B > 0$, and h, k are two (continuous) functions from $[0,\infty[$ to $[0,\infty[$ satisfying (for all $v \geq 0$) the identity

$$d_B\,\frac{h(v)}{h(v)+k(v)} = d_{12}\,v.$$

The limit holds (at the formal level) in the following sense: if u_A^ϵ, u_B^ϵ, and v^ϵ are solutions to system (3) (with ϵ-independent initial data), the quantity $(u_A^\epsilon + u_B^\epsilon, v^\epsilon)$ converges towards (u, v), where u and v are solutions to system (2).

The advantages of this microscopic approach appear at the level of modeling as well as at the level of the mathematical analysis. From the point of view of modeling, it shows that it is meaningful to consider a term like $\Delta(u\,v)$ in the model by Shigesada, Kawasaki and Teramoto, rather than terms like $\nabla\cdot(v\nabla u)$ (or more generally $\nabla\cdot(v\nabla u) + \beta\,\nabla\cdot(u\nabla v)$, where $\beta \geq 0$ is different from 1). Of course this is true provided that the microscopic model represents somewhat the reality, that is, when the individuals of the species u can be in the "quiet" state u_A or the "stressed" state u_B (this last state corresponding to a larger diffusion rate), and when they switch from one state to the other according to the local value of the concentration of v. This switch is done on a time scale ϵ which is very small in front of the time scale of the life of a given individual.

From the point of view of analysis, it is interesting to see that the microscopic model (that is for $\epsilon > 0$ small) leads to pattern formation, like the model of Shigesada, Kawasaki and Teramoto. Bifurcation diagrams are shown to converge when $\epsilon \to 0$ at the numerical level (cf. [6]). They can also be shown to rigorously hold thanks to computer-assisted methods (cf. [2] and [1]).

Another interesting feature of this microscopic model is the existence of functionals with an interesting ϵ-invariant behavior (enabling thus to put in evidence the same kind of functionals for the limiting model).

We present here such an estimate, valid for some $p \in]0,1[$:

$$
\begin{aligned}
&\int_\Omega \left[h(v^\epsilon(0,\cdot))^{p-1} \frac{(u_A^\epsilon(0,\cdot))^p}{p} + k(v^\epsilon(0,\cdot))^{p-1} \frac{(u_B^\epsilon(0,\cdot))^p}{p} \right] \\
&\qquad + 2\, d_A \frac{1-p}{p^2} \int_0^T \int_\Omega |\nabla_x[(u_A^\epsilon)^{p/2}]|^2 h(v^\epsilon)^{p-1} \\
&\qquad + 2\,(d_A + d_B) \frac{1-p}{p^2} \int_0^T \int_\Omega |\nabla_x[(u_B^\epsilon)^{p/2}]|^2 k(v^\epsilon)^{p-1} \\
&\quad - \frac{1}{\epsilon} \int_\Omega [k(v^\epsilon) u_B^\epsilon - h(v^\epsilon) u_A^\epsilon][(u_B^\epsilon)^{p-1} k(v^\epsilon)^{p-1} - (u_A^\epsilon)^{p-1} h(v^\epsilon)^{p-1}] \le Cst(T).
\end{aligned} \tag{4}
$$

In the above estimate, $Cst(T)$ is a constant which depends on T and on the parameters of the equation, but not on ϵ. From such an estimate, it is possible to get the ingredients enabling to pass to the limit rigorously when $\epsilon \to 0$ in the microscopic model. Indeed it yields estimates for the gradients in x of u_A^ϵ and u_B^ϵ, which together with the use of Aubin-Lions theorem entail the strong compactness of u_A^ϵ and u_B^ϵ. Also the last part of the estimate shows that $k(v^\epsilon)u_B^\epsilon - h(v^\epsilon)u_A^\epsilon$ converges to 0 a.e. (up to the extraction of a subsequence).

Finally, the microscopic model provides a well-suited approximation procedure for showing existence to the final system (2).

Putting together the previous considerations, we end up with the following result, published in [5].

Theorem: Let Ω be a smooth bounded domain of $\mathbb{R}^N$. We suppose that h, k are of class C^1 and that the initial data $u_{in} \ge 0$, $v_{in} \ge 0$ are such that $u_{in} \in L^2(\Omega)$, $v_{in} \in L^\infty(\Omega) \cap W^{2,3}(\Omega)$, and satisfy a compatibility (with the homogeneous Neumann boudary condition) assumption.

Then, for any $\epsilon \in]0,1[$, there exists a strong (global, with nonnegative components) solution $(u_A^\epsilon, u_B^\epsilon, v^\epsilon)$ to the microscopic model (3).

Moreover, when $\epsilon \to 0$, $(u_A^\epsilon, u_B^\epsilon, v^\epsilon)$ converges, up to extraction of a subsequence, for almost every $(t,x) \in \mathbb{R}_+ \times \Omega$, to a limit (u_A, u_B, v) lying in $L^2_{\rm loc}([0,\infty[\times\overline{\Omega}) \times L^2_{\rm loc}([0,\infty[\times\overline{\Omega}) \times L^\infty_{\rm loc}([0,\infty[\times\overline{\Omega})$, and such that $u_A \ge 0$, $u_B \ge 0$, $v \ge 0$. Furthermore, $\nabla_x v$ lies in $L^{2+\eta}_{\rm loc}([0,\infty[\times\overline{\Omega})$ for some $\eta > 0$, and the quantity $u := u_A + u_B$ satisfies $\nabla_x u, \nabla_x(u\,\phi(v)) \in L^1_{\rm loc}([0,\infty[\times\overline{\Omega})$, and for some $p > 0$ (and all $T > 0$),

$$
\sup_{t\in[0,T]} \int_\Omega u(t) < +\infty \qquad \text{and} \qquad \int_0^T \int_\Omega |\nabla_x(u^{p/2})|^2 < +\infty. \tag{5}
$$

Finally, $h(v(t,x))\, u_A(t,x) = k(v(t,x))\, u_B(t,x)$ for a.e. $(t,x) \in \mathbb{R}_+ \times \Omega$, and (u,v) is a (global, with nonnegative components) weak solution to (2).

A somewhat different microscopic approach was recently proposed by E. Daus, L. Desvillettes, and H. Dietert (cf. [4]), for models of cross diffusion with an arbitrary number of cross diffusion with the so called detailed balance condition

(cf. [3]). It consists in introducing a Markov process which naturally possesses an entropy, and which converges in some (mean field) limit towards a cross diffusion model, inheriting this entropy structure.

References

[1] M. Breden, R. Castelli; *Existence and instability of steady states for a triangular cross-diffusion system : a computer-assisted proof*, Journal of Differential Equations 264(10): 6418-6458, 2018.

[2] M. Breden, J.-P. Lessard and M. Vanicat, *Global bifurcation diagrams of steady states of systems of PDEs via rigorous numerics: a 3-component reaction-diffusion system*, Acta Applicandae Mathematicae 128(1): 113-152, 2013.

[3] X. Chen, E. S. Daus, A. Jüngel, *Global existence analysis of cross-diffusion population systems for multiple species*, Arch. Ration. Mech. Anal. 227 (2) (2018) 715-747.

[4] Esther Daus, Laurent Desvillettes and Helge Dietert, *About the entropic structure of detailed balanced multi-species cross-diffusion equations*, to appear in J. Diff. Eq.

[5] Laurent Desvillettes, Ariane Trescases, *New results for triangular reaction cross diffusion systems*, Journal of Mathematical Analysis and Applications, 430, n.1, (2015), 32-59.

[6] Iida, Masato; Mimura, Masayasu; Ninomiya, Hirokazu, *Diffusion, cross-diffusion and competitive interaction*, J. Math. Biol. 53 (2006), no. 4, 617–641.

[7] Shigesada, Nanako; Kawasaki, Kohkichi; Teramoto, Ei, *Spatial segregation of interacting species*, J. Theoret. Biol. 79 (1979), no. 1, 83–99.

Reporter: Nastassia Pouradier Duteil

Participants

Prof. Dr. Tomas Alarcon
Centre de Recerca Matemàtica - CRM
Campus de Bellaterra
Edifici C
08193 Bellaterra
SPAIN

Prof. Dr. Mark S. Alber
Department of Mathematics
University of California
Riverside, CA 92521-0135
UNITED STATES

Prof. Dr. Henri Berestycki
CAMS - EHESS
54, Boulevard Raspail
75270 Paris Cedex 06
FRANCE

Prof. Dr. Leonid Berlyand
Department of Mathematics
Pennsylvania State University
University Park, PA 16802
UNITED STATES

Federica Bubba
UPMC
Université Paris VI
CNRS UMR 7598
Laboratoire Jacques-Louis Lions
4, Place Jussieu
75252 Paris Cedex 05
FRANCE

Maria Jose Cáceres
Departamento de Matematica Aplicada
Universidad de Granada
18071 Granada
SPAIN

Dr. Vincent Calvez
ENS - UMPA
46, allee d'Italie
69007 Lyon
FRANCE

Dr. Cécile Carrère
Laboratoire Jacques-Louis Lions
Université Pierre et Marie Curie
4, Place Jussieu
75005 Paris Cedex
FRANCE

Prof. Dr. Jose Antonio Carrillo de la Plata
Department of Mathematics
Imperial College London
Huxley Building
London SW7 2AZ
UNITED KINGDOM

Prof. Dr. Tom Chou
Department of Biomathematics
University of California
School of Medicine
10833 Le Conte Avenue
Los Angeles, CA 90024-1766
UNITED STATES

Dr. Jean Clairambault
INRIA Rocquencourt
Domaine de Voluceau
B. P. 105
78153 Le Chesnay Cedex
FRANCE

Prof. Dr. Chris Cosner
Department of Mathematics and
Computer Science
University of Miami
P.O. Box 248011
Coral Gables, FL 33124
UNITED STATES

Dr. Pierre Degond
Department of Mathematics
Imperial College London
Huxley Building
London SW7 2AZ
UNITED KINGDOM

Prof. Dr. Laurent Desvillettes
Institut de Mathématiques de Jussieu - PRG
UMR 7586 du CNRS and Université Paris-Diderot
Bâtiment Sophie Germain
8, place Aurélie Nemours
75013 Paris Cedex
FRANCE

Prof. Dr. Odo Diekmann
Mathematisch Instituut
Universiteit Utrecht
Budapestlaan 6
P. O. Box 80.010
3508 TA Utrecht
NETHERLANDS

Dr. Arjen Doelman
Mathematisch Instituut
Universiteit Leiden
Postbus 9512
2300 RA Leiden
NETHERLANDS

Dr. Marie Doumic-Jauffret
INRIA Paris
2, rue Simone Iff
75013 Paris Cedex
FRANCE

Dr. Raluca Eftimie
Department of Mathematics
University of Dundee
23 Perth Road
Dundee DD1 4HN
UNITED KINGDOM

Heiko Gimperlein
Department of Mathematics
Heriot-Watt University
Riccarton
Edinburgh EH14 4AS
UNITED KINGDOM

Prof. Dr. Piotr Gwiazda
Institute of Applied Mathematics
Warsaw University
ul. Banacha 2
02-097 Warszawa
POLAND

Prof. Dr. Mats Gyllenberg
Department of Mathematics and Statistics
University of Helsinki
P.O. Box 68
00014 University of Helsinki
FINLAND

Dr. Jan Haskovec
4700 King Abdullah University of Science
and Technology (KAUST)
Mathematics and Computer Sciences
P.O. Box 2360
Thuwal 23955-6900
SAUDI ARABIA

Sophie Hecht
Department of Mathematics
Imperial College London
Huxley Building
180 Queen's Gate
London SW7 2AZ
UNITED KINGDOM

Prof. Dr. Danielle Hilhorst
Laboratoire de Mathématiques
Université Paris Sud (Paris XI)
Batiment 425
91405 Orsay Cedex
FRANCE

Prof. Dr. Florence Hubert
Institut de Mathématiques de Marseille
Aix-Marseille Université
39, Rue Joliot-Curie
13453 Marseille Cedex 13
FRANCE

Prof. Dr. Dr. h.c. mult. Willi Jäger
Interdisziplinäres Zentrum für Wissenschaftliches Rechnen (IWR)
c/o Gabriela Schocke
Im Neuenheimer Feld 368
69120 Heidelberg
GERMANY

Prof. Dr. Shigeru Kondo
Graduate School of Frontier Biosciences
Osaka University
1-3 Yamadaoka, Suita
Osaka 565-0871
JAPAN

Prof. Dr. Doron Levy
Department of Mathematics
University of Maryland
College Park, MD 20742-4015
UNITED STATES

Dr. Tommaso Lorenzi
School of Mathematics and Stochastics
University of St. Andrews
North Haugh
St. Andrews KY16 9SS
UNITED KINGDOM

Prof. Dr. Anna Marciniak-Czochra
Institut für Angewandte Mathematik
Universität Heidelberg
Im Neuenheimer Feld 294
69120 Heidelberg
GERMANY

Prof. Dr. Dominik L. Michels
4700 King Abdullah University of Science
and Technology (KAUST)
Mathematics and Computer Sciences
P.O. Box 2360
Thuwal 23955-6900
SAUDI ARABIA

Dr. Sepideh Mirrahimi
Institut de Mathématiques de Toulouse
Université Paul Sabatier
118, route de Narbonne
31062 Toulouse Cedex 9
FRANCE

Prof. Dr. Kevin Painter
School of Mathematics
Heriot-Watt University
Riccarton
Edinburgh EH14 4AS
UNITED KINGDOM

Prof. Dr. Benoit Perthame
Laboratoire J.-L. Lions
Sorbonne Université
BC 187
4, Place Jussieu
75252 Paris Cedex 05
FRANCE

Dr. Nastassia Pouradier-Duteil
CEREMADE
Université Paris Dauphine
Place du Marechal de Lattre de Tassigny
75775 Paris Cedex 16
FRANCE

Prof. Dr. Nancy Rodriguez-Bunn
Department of Mathematics
University of Colorado, Boulder
Engineering Center, EGT 225
Campus Box 526
Boulder, CO 80309
UNITED STATES

Prof. Dr. Matthias Röger
Fachbereich Mathematik
Technische Universität Dortmund
Vogelpothsweg 87
44227 Dortmund
GERMANY

Delphine Salort
Laboratoire Jacques-Louis Lions
Université Pierre et Marie Curie
175, rue du Chevaleret
75013 Paris Cedex
FRANCE

Markus Schmidtchen
Department of Mathematics
Imperial College London
Huxley Building
180 Queen's Gate
London SW7 2AZ
UNITED KINGDOM

Prof. Dr. Angela Stevens
Institut für Analysis und Numerik
Universität Münster
Einsteinstrasse 62
48149 Münster
GERMANY

Dr. Thomas Stiehl
Institut für Angewandte Mathematik
Universität Heidelberg
Im Neuenheimer Feld 294
69120 Heidelberg
GERMANY

Prof. Dr. Weiran Sun
Department of Mathematics
Simon Fraser University
8888 University Drive
Burnaby BC V5A 1S6
CANADA

Prof. Dr. Agnieszka Swierczewska-Gwiazda
Institute of Applied Mathematics
Warsaw University
ul. Banacha 2
02-097 Warszawa
POLAND

Prof. Dr. Min Tang
Institute of Natural Sciences and
School of Mathematics
Shanghai Jiaotong University
No. 800 Dongchuan Road, Minhang District
Shanghai Shi 200 240
CHINA

Dr. Nicolas Vauchelet
Département de Mathématiques
LAGA - CNRS, UMR 7539
Université Paris Nord (Paris XIII)
99, Avenue J.-B. Clement
93430 Villetaneuse Cedex
FRANCE

Dr. Chandrasekhar Venkataraman
Department of Mathematics
University of Sussex
Falmer
Brighton BN1 9QH
UNITED KINGDOM

Dr. Alexandria Volkening
Mathematical Biosciences Institute
Ohio State University
1735 Neil Avenue
Columbus, OH 43210
UNITED STATES

Prof. Dr. Michael Winkler
Institut für Mathematik
Universität Paderborn
Warburger Strasse 100
33098 Paderborn
GERMANY