Mathematisches Forschungsinstitut Oberwolfach

Report No. 48/2017

DOI: 10.4171/OWR/2017/48

Mini-Workshop: PDE Models of Motility and Invasion in Active Biosystems

Organised by
Leonid Berlyand, State College
Jan Fuhrmann, State College
Anna Marciniak-Czochra, Heidelberg
Christina Surulescu, Kaiserslautern

22 October – 28 October 2017

Abstract. Cell migration is crucial for the development and functioning of multicellular organisms; it plays an essential role in, e.g., morphogenesis, immune system dynamics, wound healing, angiogenesis, bacterial motion and biofilm formation, tumor growth and metastasis. Cell motility is a highly complex phenomenon involving a plethora of biophysical and biochemical events occuring on several time and space scales. The associated dynamics range from the subcellular level over individual cell behavior and up to the macroscopic level of cell populations; all these scales are tightly interrelated.

For decades, partial differential equations have been used to model the motility of single cells as well as the collective motion of cell assemblies like tumors. Mathematical models for both individual motile cells and invading tumors have major features in common. The active nature of cells leads to very similar nonlinear systems of coupled equations, the solutions of which often determine the position and shape of the objects of interest. Recently, several types of models attracted particular attention in the description of these systems: free boundary problems, phase field models, reaction-diffusion-taxis and kinetic transport equations. Both tumor growth/invasion and cell motility can be described by parabolic, hyperbolic, or elliptic equations; in case of free boundary problems, the boundary conditions are very similar. Thereby, the involved free boundaries can describe cell membranes, tumor margins, or interfaces between different tissues.

In this mini-workshop applied mathematicians and biophysicists using these model classes to describe different but related biological systems came together, presented their recent work and identified commonalities and differences in their approaches. Moreover, they discussed possible model extensions and their application to different, but related problems, along with the innovative utilization of certain mathematical tools to the analysis of the resulting systems.

Mathematics Subject Classification (2010): 92C17, 92C37, 35Q92.

Introduction by the Organisers

Understanding the behavior of mobile cellular assemblies such as microbial colonies, embryos, or tumors requires knowledge about both the motility of individual cells and how this motion together with mutual interactions gives rise to collective motion and tissue growth. Thus, on the one hand, the size and shape of a given tissue is determined by the movement of the single cells comprising it, and on the other hand, the resulting stress in the tissue strongly affects the motility of each single cell. Coupling the scales of individual cells and cell assemblies is therefore of utmost importance for the mathematical description of tumors and other biologically relevant systems. Remarkably, the models for cell motility and tissue development are not only coupled by these interactions between scales but moreover share significant mathematical similarities. Looking closely at the respective models which have independently been proposed for the cytoskeleton of a single cell and e.g., for the growth of tumors, it is observed that not only do the bulk equations have very similar structure but also the boundary conditions are closely related. Single cell motility and tissue development are biologically dependent on one another, but they also share these striking similarities in their mathematical description, thus it is obvious that collaboration between the communities working on either problem should be fostered. This was one of the main goals of our mini-workshop.

More than 30 years ago, the actin cytoskeleton has first been described as an active viscoelastic gel (e.g., [6]) which allowed for a whole class of continuum models for individual cell motility. In this context, two main approaches have been considered:

(1) In *phase field models* the equations are to be solved on the whole space (or a domain much larger than the cell). Together with the equations describing the cytoskeleton an additional scalar phase field is introduced which takes the value 1 inside the cell and 0 outside the cell. The cell membrane is located in the narrow region where the phase field changes from 1 to 0. The evolution of the phase field therefore describes the motion of the cell. Since the solution of the equations is typically trivial in the region where the phase field takes the value zero (that is, outside the cell), the introduction of the additional phase field variable can be understood as a computational trick to avoid free boundaries.

(2) *Free boundary problems* explicitly model the region occupied by the cell as a domain which is variable in time according to prescribed boundary velocity conditions. The equations are solved inside this time-varying domain, which affects the boundary values of the solution. On the other hand, the solution of the bulk equations determines the shape of the moving domain.

Although free boundary problems have been used to model cell motility for a long time (e.g., [1]), new models have recently been proposed in two space dimensions

to allow a more accurate modeling of cells on a flat substrate (e.g., [2]), and in addition, analytical investigation of effectively one dimensional models has been advanced (e.g., [22], [26], [10]) to supplement earlier, purely numerical results.

The use of phase field models as a computational tool to describe cell motility is also well established (e.g., [15]) and has seen a recent upsurge (e.g., [37], [16]). However, analytical results have only been obtained for a small number of models (e.g., [21]), and their derivation requires subtle applications of asymptotic analysis.

A particular focus of recent work has been the analytical derivation and numerical observation of *traveling wave solutions* to both types of models. These solutions correspond to persistent motion of cells which is a salient feature of keratocytes on homogeneous substrates. These specific skin cells are of practical interest as key players in wound healing and are well suited for experimental investigation: they comfortably crawl on flat substrates (allowing for 2D modeling, observation by most microscope techniques, and measurement of traction forces), can move at high velocity, and once in motion tend to maintain direction, speed, and shape for a long time. These convenient features enabled the development of a particularly well studied model system (see e.g., [14]).

Since in the typical free boundary problems the motion of the boundary is part of the traveling wave solution, the study of the latter is much more intricate for these problems than for systems defined on the whole space. Moreover, the shape of a moving cell is evolving and has to be taken into account as well. Plane waves as solutions are therefore out of question, and new solution techniques have to be developed. For a phase field equation the difficulty in finding traveling wave solutions is augmented by the nonlinear gradient coupling between the phase field and the physical variables describing the cytoskeleton. Therefore, sharp interface limits are derived where the diffuse interface between the phases shrinks to a curve satisfying a nonlinear evolution equation featuring geometric and physical terms. Traveling wave solutions to this equation (with stationary shape of the curve) then correspond to a cell moving at constant velocity in the original phase field model.

Our mini-workshop brought together expertise for phase field and free boundary problems and encouraged lively discussions about commonalities and differences in the modeling approaches, different analytical tractability as well as (quantitative) numerical results and comparability with experiments. The latter issue benefited from the attendance by leading experimentalists who strongly collaborate with theoreticians to allow for modeling work taking into account the essential biological aspects. To calibrate models and provide predictions of use to biological and medical practitioners, advanced numerical methods are indispensable as well. Therefore, the mini-workshop was also attended by experts in simulation of nonlinear free boundary problems.

Understanding the movement of single cells is necessary to assess their behavior in an environment crowded with other cells and complex extracellular material. A major area of research of obvious practical interest is the growth, development,

and metastasis of tumors. The main approaches to modeling tumor growth and invasion are discrete (single cells evolve on a lattice under the influence of diverse motion and proliferation rules) [11, 35], semidiscrete/hybrid [27, 20] (combine discrete descriptions with continuum formulations via differential equations for densities, concentrations or volume fractions controling the innovations of cell positions and/or velocities), or continuous. The latter describe the space-time evolution of cell populations under the influence of various biochemical and biomechanical factors in their surroundings. The most popular ones involve reaction-diffusion-taxis (RDT) equations in which the type of tactic behavior (e.g., chemo-, hapto-, and/or pH-taxis) is determined by the mentioned factors acting alone or in a conjugate manner. While the vast majority of these continuum models are set on the macroscopic level, the actual processes dictating the population dynamics are taking place on several scales (subcellular, cellular, mesoscopic, macroscopic), which calls for multiscale formulations. So-called micro-macro models connecting subcellular level information (described by deterministic or random ODEs) with macroscale behavior (RDT equations) have been recently introduced and analyzed, also by the organizers [31, 30, 28, 13]. We refer e.g., to [19, 34] for other multiscale models coupling macroscopic with lower level dynamics. Some macroscopic models of RDT type have been obtained from cell level dynamics by mean field approximations, see e.g., [23, 24], however the rigorous deduction of macroscopic equations from descriptions of cell motions e.g., via SDEs for the velocity process coupled with subcellular dynamics is still open. From an analytical point of view, most of the models in the RDT class give rise to quite a few challenges, among others due to the typically occurring nonlinear cross-diffusive terms, possibly with different types of taxis [32, 33]. Especially haptotaxis is connected with lack of regularity and hence with nontrivial problems, often hindering the proof of boundedness and uniqueness of solutions and limiting the results to global existence [30, 29, 36].

Another class of PDE models features kinetic transport equations of Boltzmann or Vlasov type for cell density functions depending on time, space, and cell velocities (directions). Unlike gas theory, the involved integral operators do not model particle collisions, but characterise innovations (both w.r.t. speed and direction) of the cell velocities, which are also triggered by cell-tissue and cell-cell interactions [4, 12, 17]. The issue of multiscality is relevant in this mathematical context, too. Bellomo et al. (2010) [3] proposed a general framework for such kinetic models on the mesoscopic level (also allowing for the inclusion of the "cell state" to reflect dynamics on the microlevel) that they called the kinetic theory of active particles (KTAP). Open questions in this context relate to the choice of turning kernels in the integral operators, a realistic modeling of the turning rates, and the well-posedness in less regular function spaces, under less restrictions on the data [17]. Effective macroscopic equations which are more suitable to numerical handling can be derived from mesoscopic or multiscale models involving the mesoscale by means of averaging leading to evolution equations for the moments of the cell distribution function [7, 12]. Yet other PDE models involve again free boundaries (e.g., [5, 9, 25], [34]) and some of them exhibit remarkable similarities to the free

boundary models for individual cell motility. Thereby the major difference is that cell motility tends to have domains of fixed size which move at a given velocity whereas tumor models should provide predictions not only on the shape and position but first and foremost on the size of the domain. Accordingly, the analogue of the traveling domain solutions from cell motility are growing domain solutions for tumors (e.g., [25]).

Another major aim of the mini-workshop was to provide an exchange of ideas and techniques between experts from cell motility and tissue modeling, as the two fields are tightly connected. In particular, we discussed appropriate ways of connecting dynamics of single cells with that of a cell population, the latter described via cell densities in a continuum framework. Mean field approaches and various types of upscaling can provide a way, but do not need to be the only one and –depending on the specific biological scenario under investigation– it is often very difficult to perform them rigorously. Also, the issues of how much modeling detail should be included (and in which way), and therefore of model selection are still open and challenging.

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-1049268, "US Junior Oberwolfach Fellows".

References

[1] W. Alt, M. Dembo, Cytoplasm dynamics and cell motion: two-phase flow models, *Math Biosci* (1999) **156**, 207–228.

[2] E. Barnhart, K. Lee, G. M. Allen, J. A. Theriot, and A. Mogilner. Balance between cell-substrate adhesion and myosin contraction determines the frequency of motility initiation in fish keratocytes, *Proc Natl Acad Sci U.S.A.* (2015) **112**(16), 5045–5050.

[3] N. Bellomo, A. Bellouquid, J. Nieto, and J. Soler, Complexity and mathematical tools toward the modeling of multicellular growing systems, *Math. Computer Modelling* (2010) **51**, 441–451.

[4] A. Chauviere, T. Hillen, and L. Preziosi, Modeling cell movement in anisotropic and heterogeneous network tissues, *Netw. heterog. media* (2007) **2**, 333–357.

[5] X. Chen, F. Reitich, Local existence and uniqueness of solutions of the Stefan Problem with surface tension and kinetic undercooling, *J Math Ana Appl* (1992) **164**, 350–362.

[6] M. Dembo, F. Harlow, Cell motion, contractile networks, and the physics of interpenetrating reactive flow, *Biophys J* (1985) **50**, 109–121.

[7] C. Engwer, T. Hillen, M. Knappitsch, and C. Surulescu, Glioma Follow White Matter Tracts; a Multiscale DTI-based Model, *J. of Math. Biol.* (2015) **71**, 551–582.

[8] H. Freistühler, J. Fuhrmann, A. Stevens, Traveling waves emerging in a diffusive moving filament system, in *Managing complexity, reducing perplexity. Modeling biological systems* (2014), Eds. G. Ajmone-Marsan G, M. Delitala, Springer.

[9] A. Friedman, F. Reitich, Symmetry-breaking bifurcation of analytic solutions to free boundary problems: an application to a model of tumor growth, *Trans AMS* (2001) **353**, 1587–1634.

[10] J. Fuhrmann, A. Stevens, A free boundary problem for cell motion, *Differential and Integral Equations* (2015) **28**, 695–732.

[11] Hatzikirou, H., Basanta, D., Simon, M., Schaller, K., and Deutsch, A., Go or Grow: the key to the emergence of invasion in tumour progression? *Math. Med. Biol.* **29** (2012), 49–65.
[12] T. Hillen, M^5 Mesoscopic and macroscopic models for mesenchymal motion, *J. Math. Biol.* (2006) **53**, 585–616.
[13] S. Hiremath and C. Surulescu, A stochastic model featuring acid-induced gaps during tumor progression, *Nonlinearity* (2016) **29**, 851–914
[14] K. Keren, Z. Pincus, G. M. Allen, E. L. Barnhart, G. Marriott, A. Mogilner, and J. A. Theriot, Mechanism of shape determination in motile cells, *Nature* (2008) **453**, 475–480.
[15] J. Kockelkoren, H. Levine, and W.-J. Rappel, Computational approach for modeling intra- and extracellular dynamics, *Phys Rev E* (2003), **68**, 037702.
[16] H. Levine, D. Shao, and J.W. Rappel. Coupling actin flow, adhesion, and morphology in a computational cell motility model, *Proc Nat Acad Sci* (2015) **109**, 6851–6856.
[17] T. Lorenz and C. Surulescu, On a class of multiscale cancer cell migration models: Well-posedness in less regular function spaces, *Mathem. Models and Methods in the Applied Sciences* (2014) **24**, 2383–2436.
[18] S. Luckhaus, Solutions for the two-phase Stefan problem with the Gibbs-Thomson Law for the melting temperature, *European J Appl Math* (1990).
[19] P. Macklin, S. McDougall, A.R. Anderson, M.A. Chaplain, V. Cristini, and J. Lowengrub. Multiscale modeling and nonlinear simulation of vascular tumour growth, *J. Math. Biol.* (2009) **58**, 765–798.
[20] P. Macklin, M.E. Edgerton, J.S. Lowengrub, and V. Cristini. Discrete cell modeling. In: V. Cristini and J.S. Lowengrub, Multiscale Modeling of Cancer: An Integrated Experimental and Mathematical Modeling Approach, chap. 6, pp. 88-122, Cambridge University Press, Cambridge, UK (2010).
[21] M. S. Mizuhara, L. Berlyand, V. Rybalko, and L. Zhang. On an evolution equation in a cell motility model, *Physica D* (2015) **318-319**, 12–25.
[22] H. Monobe, H. Ninomiya, Multiple existence of traveling waves of a free boundary problem describing cell motility, *Disc Cont Dyn Sys B* (2014) **19**, 789–799.
[23] K. Oelschlaeger, On the derivation of reaction-diffusion equations as limit dynamics of systems of moderately interacting stochastic processes, *Probability Theory and Related Fields* (1989) **82**, 565–586.
[24] H.G. Othmer and A. Stevens, Aggregation, Blowup and Collapse: The ABC's of taxis in reinforced random walks, *SIAM J. Applied Math.* (1997) **57**, 1044–1081.
[25] B. Perthame, M. Tang, and N. Vauchelet, Traveling wave solution of the Hele-Shaw model of tumor growth with nutrient, *Math Mod Meth Appl Sci* (2014) **24**(13), 2601–2626.
[26] T. Putelat, P. Recho, and L. Truskinovsky. Contraction-driven cell motility, *Phys Rev Lett* (2013) **111**, 108102.
[27] M. Scianna and L. Preziosi. A Hybrid Model Describing Different Morphologies of Tumor Invasion Fronts, *Math. Model. Nat. Phenom.* (2012) **7**, 78-104.
[28] C. Stinner, C. Surulescu, and G. Meral. A multiscale model for pH-tactic invasion with time-varying carrying capacities, *IMA J. Appl. Math* (2015) **80**, 1300-1321.
[29] C. Stinner, C. Surulescu, and A. Uatay. Global existence for a go-or-grow multiscale model for tumor invasion with therapy, *Math. Mod. Methods Appl. Sci.* (2016) **26**, 2163-2201.
[30] C. Stinner, C. Surulescu, and M. Winkler: Global weak solutions in a PDE-ODE system modeling multiscale cancer cell invasion. *SIAM J. Math. Anal.* (2014) **46**, 1969–2007.
[31] Z. Szymańska, J. Urbański, and Marciniak-Czochra, A.: Mathematical modeling of the influence of heat shock proteins on cancer invasion of tissue. *J. Math. Biol.* (2009) **58**, 819–844.
[32] Y. Tao and M. Wang, Global solution for a chemotactic-haptotactic model of cancer invasion, *Nonlinearity* **21** (2008), 2221–2238.

[33] Y. Tao and M. Winkler, A chemotaxis-haptotaxis model: the roles of porous medium diffusion and logistic source, *SIAM Journal of Mathematical Analysis* **43** (2011), 685–704.

[34] D. Trucu and M.A.J. Chaplain. Multiscale Analysis and Modelling for Cancer Growth and Development, Managing Complexity, Reducing Perplexity, Springer Proceedings in Mathematics & Statistics (Springer 2014), Vol 67 (eds. M. Delitala and G. Ajmone Marsan), 45–53.

[35] A. Voß-Böhme, Multi-scale modeling in morphogenesis: a critical analysis of the cellular Potts model, *PLoS ONE* (2012) **7** , e42852.

[36] A. Zhigun, C. Surulescu, and A. Uatay. Global existence for a degenerate haptotaxis model of cancer invasion, *Z. Angew. Math. Phys.* (2016) **67**:146.

[37] F. Ziebert, S. Swaminathan, and I. S. Aranson. Model for self-polarization and motility of keratocyte fragments, *J. R. Soc. Interface* (2012) **9**, 1084–1092.

Mini-Workshop: PDE Models of Motility and Invasion in Active Biosystems

Table of Contents

Abstracts

Mixed parabolic systems arising in the modeling of cancer invasion

Anna Zhigun

(joint work with Christina Surulescu, Alexander Hunt, and Aydar Uatay)

Cancer cell migration is an essential stage in the development and expansion of tumours and their metastases. Once a tumour develops in some part of the body, it can grow and make its way through the surrounding tissue in order to reach the blood vessels. After transportation across the blood system and subsequent extravasation, further tumours thus emerge. This process is known as metastasis. Migrating through the extracellular matrix (ECM), the cells need to adhere to it for support and information exchange with their surroundings. Mathematical models of cancer invasion and their subsequent analysis and simulation can contribute to better understanding the involved biological phenomena and enable predictions about the development and the extent of a tumour. Therefore, they can suggest approaches to therapy improvements.

The tissue surrounding a tumor plays a crucial role in its further development and dispersion. Thereby, diffusion and haptotaxis are among the main vehicles of cancer cell motility inside the ECM. Biological experiments suggest that:

(i) enhanced interactions with the surrounding tissue favour cell diffusivity;
(ii) in those areas where cells and tissue are tightly packed, the diffusivity is limited;
(iii) no diffusion occurs in those regions where tissue is absent (no "diffusion through holes");
(iv) cells propagate through the tissue with a finite speed.

Until very recently, only semilinear models for haptotaxis were treated analytically. Such models do not capture properties (i), (iii), and (iv). In [2], we introduced a new model for the tumor cell density (c) and the density of fibers (v) which implements all four conditions (i)-(iv):

$$\begin{cases} \partial_t c = \nabla \cdot \left(\dfrac{\kappa_c v c}{1+vc} \nabla c - \dfrac{\kappa_v c}{(1+v)^2} \nabla v \right) + \mu_c c(1-c-\eta v), & \text{(1a)} \\ \partial_t v = \mu_v v(1-v) - \lambda v c. & \text{(1b)} \end{cases}$$

The most important feature of this highly nonlinear PDE-ODE system is the non-standard diffusion coefficient in the PDE (1a), which is degenerate in both PDE- and ODE-variables. This kind of twofold degeneracy is new in the context of haptotaxis models. In [2], we established for (1) the existence of a global weak solution.

In a subsequent work [1] we extended (1) to a PDE-ODE-ODE coupling which also accounts for the 'go-or-grow' hypothesis asserting that cancer cells can either move or proliferate. The latter implies tumor heterogeneity and is tightly connected to compromised treatment response.

The talk covers both the modelling aspects and a discussion of the analytical challenges for the two systems from [1, 2]. Some numerical simulations are presented which illustrate a possible model behaviour in a two-dimensional setting. The numerical results recover qualitatively the infiltrative patterns observed histologically. They further allow to establish a qualitative relationship between the structure of the tissue and the expansion of the tumor, thus paying heed to its heterogeneity.

References

[1] A. Zhigun, C. Surulescu, and A. Hunt, *Global existence for a degenerate haptotaxis model of tumor invasion under the go-or-grow dichotomy hypothesis*, arXiv:1605.09226 (2016).
[2] A. Zhigun, C. Surulescu, A. Uatay, *On the global existence for a degenerate haptotaxis model for cancer cell invasion*, Z. Angew. Math. Phys. **67**:146 (2016).

On a structured nonlocal model for tumor invasion

Christian Stinner
(joint work with Christian Engwer, Christina Surulescu)

Invasion of tumor cells is an important step for metastasis and is governed by several processes. In [3] we propose a structured model focusing on the influence of the interaction with tissue fibers and of the peritumoral acidity on tumor cell migration. More precisely, our model accounts for cell-cell and cell-tissue adhesion via a nonlocal adhesion term (see e.g. [1, 4, 5]) as well as pH-taxis via a cross-diffusion term. In addition, the cancer cell density not only depends on time and spatial position, but also on a structure variable y describing the concentration of cell surface receptors bound to tissue fibers or protons (see also [2]).
Denoting by $c(t,x,y)$ and $v(t,x)$ the densities of cancer cells and tissue fibers of the extracellular matrix (ECM), respectively, by $h(t,x)$ the concentration of extracellular protons, and by $\widehat{c}(t,x) := \int_Y c(t,x,\widetilde{y})d\widetilde{y}$ the total cancer cell density, we arrive at the following PDE-ODE system (see [3]):

$$
(1)\quad \begin{cases} \partial_t c = \nabla\cdot(D(v,h)\nabla c) - \nabla\cdot(\chi(c,h)\nabla h) - \nabla\cdot(c\mathcal{A}) - \partial_y(g(t,x,y,h,v)c) \\ \qquad + \int_Y (1-\widehat{c})\,\beta(y,\widetilde{y})c(t,x,\widetilde{y})d\widetilde{y} \;+\; v\,\sigma(x,v)\int_Y \kappa(y,\widetilde{y})c(t,x,\widetilde{y})d\widetilde{y} \\ \qquad -\delta_c(x,y,h)c, \qquad\qquad (t,x,y)\in(0,\infty)\times\Omega\times Y, \\ \partial_t v = -\delta_v v h + \mu_v v\,(1-v-\widehat{c}\,), \qquad (t,x)\in(0,\infty)\times\Omega, \\ \partial_t h = D_h\Delta h + \frac{\alpha\,\widehat{c}}{1+\widehat{c}} - \lambda h, \qquad (t,x)\in(0,\infty)\times\Omega, \end{cases}
$$

endowed with homogeneous Neumann boundary conditions, where $\Omega\subset\mathbb{R}^n$ is a bounded smooth domain and $Y := (0,1)\subset\mathbb{R}$. In the nonlocal adhesion term $-\nabla\cdot(c\mathcal{A})$, the adhesion velocity $\mathcal{A}$ is given by

$$
\mathcal{A}(t,x,y,c,v) = \frac{1}{R}\int_{B_R(0)} F(|\xi|,\rho,h)G\big(t,y,c(t,x+\xi,\cdot),v(t,x+\xi)\big)\frac{\xi}{|\xi|}d\xi
$$

with effective cell-cell and cell-tissue interactions

$$G(t,y,c(t,x+\xi,\cdot),v(t,x+\xi)) = \Big(\int_Y S_{cc}(t,y,\widetilde{y})c(t,x+\xi,\widetilde{y})d\widetilde{y} + S_{cv}(t,y)v(t,x+\xi)\Big)\Big(1-\widehat{c}(t,x+\xi)-v(t,x+\xi)\Big)_+.$$

We prove the existence of a global weak solution to (1) (see [3]). In the proof we approximate (1) by a system, where the first equation contains the additional term $+\varepsilon\partial_y^2 c$ so that this equation is parabolic with respect to $(x,y)\in\mathbb{R}^{n+1}$ and we may adapt the method from [6] to prove the global existence. We further present numerical simulations to illustrate the solution behavior. In particular, tumor invasion into the tissue is observed in conjunction with an oscillatory spatial pattern behind the tumor front. The simulations suggest that these patterns are only present in model (1) and not in the model without y-structure, while in addition cell-tissue adhesion seems to have a higher impact on the tumor cell invasion than cell-cell adhesion or pH-taxis (see [3]).

References

[1] N.J. Armstrong, K.J. Painter, J.A. Sherratt, *A continuum approach to modelling cell-cell adhesion*, J. Theor. Biol. **243** (2006), 98–113.

[2] P. Domschke, D. Trucu, A. Gerisch, M.A.J. Chaplain, *Structured models of cell migration incorporating molecular binding processes*, arxiv:1607.05353 (2016).

[3] C. Engwer, C. Stinner, C. Surulescu, *On a structured multiscale model for acid-mediated tumor invasion: the effects of adhesion and proliferation*, Math. Models Methods Appl. Sci. **27** (2017), 1355–1390.

[4] A. Gerisch, M.A.J. Chaplain, *Mathematical modelling of cancer cell invasion of tissue: Local and non-local models and the effect of adhesion*, J. Theor. Biol. **250** (2008), 684–704.

[5] K.J. Painter, N.J. Armstrong, J.A. Sherratt, *The impact of adhesion on cellular invasion processes in cancer and development*, J. Theor. Biol. **264** (2010), 1057–1067.

[6] C. Stinner, C. Surulescu, G. Meral, *A multiscale model for pH-tactic invasion with time-varying carrying capacities*, IMA J. Appl. Math. **80** (2015), 1300–1321.

Acknowledgements

This work was partially supported by the Carl-Zeiss Foundation (C. Stinner) and the German Research Foundation DFG in the project SU 807/1-1 (C. Surulescu).

A short summary of biased random walk models by W. Alt / Wavenumber selection in coupled transport equations

Angela Stevens

(joint work with Wolfgang Alt and Arndt Scheel)

First, we summarize stochastic models of biased random walks based on [1], which describe the population dynamics of chemosensitive cells. The turning frequency and the turn angle distributions are derived from experimental findings. Chemotaxis equations are obtained, whose coefficients can be expressed in terms of microscopic parameters.

Further, a minimal model for run-and-tumble dynamics is studied, see [4]. Its nonlinear tumbling rates can induce a plethora of wave patterns. A subtle selection mechanism for the wavenumbers of spatio-temporally periodic waves, as they can be observed in colonies of myxobacteria, is explained.

Consider cells or bacteria, whose motion is piecewise linear, with a mean speed $c(t,x)$ of each such run. Let $\sigma(t,x,\theta,\tau)$ describe the density of individuals moving at time t at position x in direction θ and having started their run a time τ ago. Then their run-and-tumble process can be modeled by

$$\partial_t\sigma(\cdot,\theta,\tau)+\partial_\tau\sigma(\cdot,\theta,\tau)+\theta\cdot\nabla_x(c\sigma(\cdot,\theta,\tau))=-(\beta\sigma)(\cdot,\theta,\tau)\ ,$$

where $\sigma(\cdot,\eta,0)=\int_0^\infty\int_S(\beta\sigma)(\cdot,\theta,\tau)k(\cdot,\theta;\eta)d\theta d\tau$ for each $\eta\in S$, with S denoting the unit sphere in n-dimensions, and $d\theta$ being the surface measure on S. Individuals stop their run per unit time with 'stopping' or 'turning' frequency $\beta(t,x,\theta,\tau)$ and immediately turn into a new direction η along the turn angle distribution $k(t,x,\theta;\eta)$. Here $\sigma(t,x,\eta,0)$ is the density of individuals which start a new run in direction η at (t,x).
If β is independent of the run time τ the dynamics for the time-space-velocity density $\bar\sigma(t,x,\theta):=\int_0^\infty\sigma(t,x,\theta,\tau)d\tau$ reads

$$\partial_t\bar\sigma(\cdot,\theta)+\theta\cdot\nabla_x(c\bar\sigma(\cdot,\theta))=-(\beta\bar\sigma)(\cdot,\theta)+\int_S(\beta\bar\sigma)(\cdot,\eta)k(\cdot,\eta;\theta)d\eta\ .$$

The probability distribution $q_{t,x,\theta}(\tau)$ of individuals, starting a run at (t,x) in direction θ and running at least for time τ can be calculated from the related backward equation as

$$q_{t,x,\theta}(\tau)=\exp\left(-\int_0^\tau\beta(t+s,x+\zeta_{t,x,\theta}(s),\theta,s)\ ds\right)\ , \tag{1}$$

where $\zeta_{t,x,\theta}(s)$ denotes the vector which the individual runs from the point x in the time interval $[t,t+s]$. For constant speed c we have $\zeta_{t,x,\theta}(s)=cs\theta$.
In an isotropic medium the stopping frequency β is nearly constant and independent of θ. In a medium with a given concentration gradient $\nabla_x\rho$ of a chemotactic signal ρ the value of β is smaller if the sensed gradient $\theta\cdot\nabla_x\rho$ is positive, and larger, if it is negative. Typical dependencies are

$$\begin{aligned}\beta(t,x,\theta)&=\beta_0\left(\rho(t,x),\partial_t\rho(t,x)+c\theta\cdot\nabla_x\rho(t,x)\right)\ ,\\ \beta(t,x,\theta)&=\beta_0\left(\rho(t,x),\rho(t-T,x-Tc\theta)\right)\ .\end{aligned}$$

We want to see how changes in the amount of bound ρ-receptors at the cell surface regulate the respective turning frequency β of its locomotive apparatus. Assume that the locomotion mechanism of a cell is controlled by an internal chemical activator a, and that the cell continues its run as long as the concentration of a is above (below) a critical level a^*. During locomotion this activator is decreased (increased) with rate λ. In case some receptor-sensor-mechanism at the cell membrane regulates the additional generation of the activator this can lead to changes of the run length.

Assume that the fast binding of an extracellular diffusing chemotactic signal with concentration ρ induces a momentary portion of bound receptor sites $b = b(\rho)$. An enzyme system e, related to the receptor, is then instantaneously switched into an active state e^*, with association constant $A = A(b(\rho))$, which depends on the receptor state. The active enzyme e^* converts the substrate s into the activator a, or induces an active transport of extracellular s to become intracellular a.
A simple reaction scheme for this is

$$s + e^* \to_{\kappa_1} \kappa \to_{\kappa_{-2}} a + e$$
$$s + e^* \leftarrow_{\kappa_{-1}} \kappa \leftarrow_{\kappa_2} a + e$$

where $\kappa_1, \kappa_2, \kappa_{-1}, \kappa_{-2} >> 1/\bar{\tau}$ with average run time of a cell $\bar{\tau}$. Then the steady state kinetics can be written as

$$a = \pi s/K \ , \text{ where } \pi = e^*/e = A(b(\rho)) \text{ and } (a+s)' = -\lambda \ .$$

When reaching the critical a-level a^*, the cell stops for a short time, and during this tumble or reorientation phase the a-level is raised from a^* to a new value a_0 according to a Poisson distribution $\exp(-(a_0 - a^*)/\mu_0)/\mu_0$, where μ_0 expresses the mean locomotive activation of a cell at the beginning of a new run phase.
If the activator level of a cell at the beginning of a run in direction θ at (t_0, x_0) has the value $a_0 > a_0^*$, it will reach the critical value a_τ^* after a time τ iff

$$a_\tau^*(1 + K/\pi_\tau) = a_0(1 + K/\pi_0) - \int_0^\tau \lambda_\tau d\tau \ ,$$

where $a_\tau^* := a^*(\rho(t_0 + \tau, x_0 + \zeta_{t_0,x_0,\theta}(\tau)))$ and π_τ, λ_τ analogously. This implies

$$a_0 - a_0^* = \frac{\pi_0}{K + \pi_0} \int_0^\tau \left(\lambda_\tau + \left(a_\tau^* \frac{K + \pi_\tau}{\pi_\tau} \right)' \right) d\tau \ .$$

Since the distribution of run lenghts exceeding this value is
$q_{t_0,x_0,\theta}(\tau) = \exp(-(a_0 - a_0^*)/\mu_0)$
we can calculate a formula for the turning frequency $\beta(\cdot, \theta, \tau)$ during a run phase with the help of (1).
Some cells have active protrusions, i.e. pilot pseudopods, on the cell surface, occuring symmetrically w.r.t. the direction θ of the preceding cell displacement according to the η-dependent probability distribution $h(\cdot, |\eta - \theta|)$. The testing protrusions enlarge with mean speed $c_0 = c_0(\rho)$ in direction η and bear fast binding ρ-specific receptors.
The portion of bound receptors $b = b_\eta(\rho)$ fulfills $b'_\eta(p) \approx p(\rho, |\eta - \theta|)$. The change of bound receptor sites during a relatively short protrusion period of mean length $\delta_0 < \bar{\tau}$ is proportional to $\delta_0 b'_\eta(\rho)(\partial_t \rho + c_0 \eta \cdot \nabla_x \rho)$, i.e. the chemotactic gradient along a testing protrusion in direction η.
The probability $k(\cdot, \theta; \eta)$ for a reorientation from direction θ to η is proportional to $h(\cdot, |\eta - \theta|) \cdot [1 + \delta_0 p(\rho, |\eta - \theta|)(\partial_t \rho + c_0 \eta \cdot \nabla_x \rho)]$. After normalization and linearization the turn angle distribution reads

$$k(\cdot, \theta; \eta) = h(\cdot, |\eta - \theta|)[1 + \delta_0(p(\cdot, |\eta - \theta|) - \bar{p})\partial_t \rho + \delta_0 c_0 (p(\cdot, |\eta - \theta|)\eta - \bar{p}\psi^p \theta) \cdot \nabla_x \rho]$$

where h, c_0, p are evaluated at the momentary concentration level ρ, and with $\mathbf{1} := (1, 0, ..., 0) \in S$ the mean protrusion sensitivity over the whole cell surface is $\bar{p} := \int_S (h \cdot p)(\cdot, |\eta - \mathbf{1}|) d\eta$. The forward index of this protrusion sensitivity is $\psi^p := \frac{1}{\bar{p}} \int_S (h \cdot p)(\cdot, |\eta - \mathbf{1}|) \eta_1 \, d\eta$.
Finally, a scaled chemotaxis equation is derived, under the following conditions:
the speed of cell displacements and of testing protrusions is relatively large,
i.e. $c_0 > c >> X/T$, for typical scales of space and time,
the mean turning frequency is relatively small, i.e. $\bar{\tau} \approx \tau_0/\beta_0 << T$,
such that the product of mean step length $\bar{\tau} c$ and speed c remains bounded,
i.e. $(\bar{\tau} c)c \leq (1 - \psi) X^2/T$,
and the quotient of both of them (up to a constant) is the motility
$\mu = \frac{1}{n} \frac{(\bar{\tau} c)c}{(1-\psi)X^2/T}$,
the ration of mean protrusion length $\delta_0 c_0$ and mean step length $\bar{\tau} c$ remain bounded,
i.e. $(1 - \psi) \frac{\delta_0 c_0}{\bar{\tau} c} \leq 1$,
and the chemotaxis coefficient is $\chi = \mu(1 - \psi) \left(\tilde{\chi} + \bar{p} \frac{\delta_0 c_0}{\bar{\tau} c} \tilde{\psi} \right)$.
Here $\psi := \int_S h(\cdot, |\eta - \mathbf{1}|) \eta_1 \, d\eta$, $\tilde{\chi} = (\beta_0'/\beta_0) - (a^*/\mu_0)'$ provided that λ is independent of ρ, $\beta_0 = \frac{\lambda}{\mu_0} \frac{\pi}{K+\pi}$, and $\tilde{\psi} = 1 + \psi \frac{1-\psi^p}{1-\psi}$.
Then the density $\bar{u}(t, x) = \int_S \bar{\sigma}(t, x, \theta) d\theta$ fulfills

$$\partial_t u = \nabla_x \left(\frac{\mu}{c} \nabla_x (cu) - \chi u \nabla_x \rho \right)$$

up to a small error and for the accordingly rescaled parameters.

Now we are looking at a simple one-dimensional system of run-and-tumble dynamics. Individuals/cells move with the same speed to either right or left, may change orientation, and start moving in the opposite direction. The probability of this tumbling events is assumed to be a pointwise function of the densities of left- and right-moving individuals. Thus the tumbling rates can be thought of as encoding probabilities of encounters between left- and right-moving individuals, which in turn induce changes of orientation. This caricature picture is motivated by observations of rippling patterns in colonies of myxobacteria. The ripple crests are oriented approximately perpendicular to the movement direction of the bacteria. The so-called C-signal, bound to their cell surface, is transmitted upon end-to-end contact of bacteria, and increases the reversal probability of individual bacteria, see also [2, 3].
We look at the model

$$\begin{aligned} u_t &= u_x - r(u, v) + r(v, u) \ , \\ v_t &= -v_x + r(u, v) - r(v, u) \ , \end{aligned}$$

where u, v encode the densities of the left- and right-moving bacteria and with tumbling rates $r(u, v) = ug(v)$, where $g(v) = 1 + v^2/(1 + \gamma v^2)$.
The results in [4] can be summarized as follows:

- linear growth favors wavenumbers $k_{lin} = 0$ or $k_{lin} = 1$, that is, linear instabilities do not select finite wavenumbers from white-noise perturbations;
- localized perturbations of asymmetric states may generate traveling waves with a selected non zero wavenumber k_{loc}, that is, instabilities do select finite wavenumbers from short-noise perturbations;
- localized perturbations of symmetric states result in the creation of asymmetric states and subsequent evolution of traveling and standing waves, with nonzero wavenumber k_{loc}, that is, localized instabilities eventually do select finite wavenumbers from shot noise perturbations.

The key insight is that localized perturbations result in a spatio-temporal spreading of perturbations. The resulting invasion process is oscillatory in nature with a well-defined spreading speed and finite temporal frequency.
In other words, oscillatory invasion selects spatial wavenumbers.

References

[1] W. Alt, *Biased Random Walk Models for Chemotaxis and Related Diffusion Approximations*, J. Math. Biology **9** (1980), 147–177.
[2] F. Lutscher and A. Stevens, *Emerging patterns in a hyperbolic model for locally interacting cell systems*, J. Nonlinear Sci., **12**, No. 6, 619–640.
[3] I. Primi, A. Stevens and J.J.L. Velázquez, *Pattern forming instabilities driven by non-diffusive interaction*, Netw. Heterog. Media **8**, No. 1, (2013), 397–432.
[4] A. Scheel and A. Stevens, *Wavenumber selection in coupled transport equations*, J. Math. Biology **75** (2017), 1047–1073.

Live cell motility under the FBLM-FEM prism: from numerical convergence to cell-cell adhesion

Nikolaos Sfakianakis

(joint work with Christian Schmeiser, Diane Peurichard, and Aaron Brunk)

The lamellipodium is a thin, sheet-like structure that is found in the propagating front of fast moving cells, such as fibroblasts, keratocytes, cancer cells, and more. It is a dense network of linear biopolymers of the protein actin, termed actin-filaments. These actin-filaments are highly dynamic structures that constantly polymerize by addition of new monomers on their one end, and participate in a plethora of other processes such as nucleation, capping, fragmentation, and many more.
These processes are important for the structure and functionality of the lamellipodium, and the motility of the cell. They are to a large extent affected by the extracellular environment; for example, the chemical landscape in which the cell of resides and the local composition and architecture of the Extracellular Matrix (ECM), lead to biased motility responses of the cell that are typically termed as chemotaxis, haptotaxis, and durotaxis.

We model this phenomenon upon using the Filament Based Lamellipodium Model (FBLM); an anisotropic, two-phase, two-dimensional, continuum model that describes the dynamics the lamellipodium at the level of actin-filaments and their interactions. The model distinguishes between two families (phases) of filaments and includes the interactions between them, as well as between the network of the filaments and the extracellular environment. The FBLM was first proposed in [1] and later extended in [2, 3, 5]. When the FBLM is endowed with a problem specific Finite Element Method (FEM) that we have previously developed in [4], the combined FBLM-FEM is able to reproduce realistic, crawling-like moving cells, [4, 6].
In this talk we present the basic components of the FBLM and the FEM and focus on a series of numerical simulations that illustrate the motility properties of the FBLM-FEM combination. In particular, we embed the FBLM in a complex extracellular environment with multiple chemical sources, and a non-uniform and adaptive ECM, and subsequently study the response of our cells to variations of the chemical and haptic environment. We moreover present some of our newest results in cell-cell collision and cell-cell adhesion. We consider a large number of cells an make the first steps in the direction of simulation the formation of a tissue.

References

[1] D. Oelz, C. Schmeiser. *How do cells move?* in Cell mechanics: from single scale-based models to multiscale modeling, Chapman and Hall, **1** (2010), 1–10.
[2] H. Freistuehler, Chr. Schmeiser, and N. Sfakianakis. *Stable length distributions in co-localized polymerizing and depolymerizing protein filaments*, **72**, (2012), SIAM J. Appl. Math., 1428–1448.
[3] A. Manhart, D. Oelz, C. Schmeiser, N. Sfakianakis, *An extended Filament Based Lamellipodium: Model produces various moving cell shapes in the presence of chemotactic signals.* J. Theor. Biol., **382** (2015) 244–258.
[4] A. Manhart, D. Oelz, C. Schmeiser, N. Sfakianakis. *Numerical treatment of the filament based lamellipodium model (FBLM)* (2016) in Modelling Cellular Systems.
[5] A. Manhart, C. Schmeiser, *Existence of and decay to equilibrium of the filament end density along the leading edge of the lamellipodium*, J. Math. Biol. **74**, 2016.
[6] A. Brunk, N. Sfakianakis. *Stability, convergence, and sensitivity analysis of the FBLM and the corresponding FEM*, (submitted), 2017.

Blow-up phenomena in chemotaxis systems

Michael Winkler
(joint work with Nicola Bellomo, Noriko Mizoguchi and Youshan Tao)

In theoretical descriptions of collective behavior in populations of chemotactically migrating individuals, Keller-Segel-type PDE systems play an outstanding role. Here in view of numerous corresponding experimental findings, phenomena of outstanding interest are related to pattern formation and, more drastically, to the spontaneous emergence of aggregate-like structures in the sense of locally large population densities.

An apparently natural approach toward mathematically capturing the latter type of features aims at detecting solutions which reflect phenomena of singularity formation in that their respective component representing the population density becomes unbounded either in finite or infinite time. In contrast to frequently considered situations of PDE systems in which global regular behavior is expected, and in which thus a large variety of techniques for proving global existence and boundedness is available, rigorously confirming the occurrence of such explosion evidently amounts to developing novel analytical methods; accordingly, the corresponding literature is found to be comparatively sparse.

In this presentation, firstly a brief overview over classical results for the classical Keller-Segel system

$$\left\{ \begin{array}{l} u_t = \Delta u - \nabla \cdot (u \nabla v), \\ v_t = \Delta v - v + u, \end{array} \right. \qquad (\star)$$

is given. Inter alia, it is brought to mind that when posed under homogeneous Neumann boundary conditions in smoothly bounded domains $\Omega \subset \mathbb{R}^n$, $n \geq 1$, for all reasonably regular initial data (u_0, v_0) a corresponding initial value problem always possesses globally defined bounded solutions if either $n = 1$, or $n = 2$ and the total mass of cells satisfies $\int_\Omega u_0 < 4\pi$, or $n \geq 3$ and (u_0, v_0) is suitably small in $L^{\frac{n}{2}}(\Omega) \times W^{1,n}(\Omega)$ ([7], [3]). In contrast to this, well-known unboundedness results are recalled which assert the existence of at least one solution, necessarily corresponding to a suitably large mass level, that blows up in finite time ([5]). Constituting a further development of the latter, a more recent result is presented according to which finite-time blow-up can actually be viewed as an essentially generic phenomenon in the radial version of $(\star)$ in both cases $n = 2$ and $n \geq 3$, in particular occurring within sets of initial data that are dense in the respective sets of all smooth positive radial data within appropriate topologies ([6], [10]).

It is thereafter discussed how far blow-up phenomena can be detected in chemotaxis systems more complex than $(\star)$, and some particular findings obtained through various approaches during the past few years are reported. Firstly, for the variant of $(\star)$ given by

$$\left\{ \begin{array}{l} u_t = \nabla \cdot (D(u) \nabla u) - \nabla \cdot (S(u) \nabla v), \\ v_t = \Delta v - v + u, \end{array} \right.$$

it has been found that essentially the asymptotic behavior of the ratio $\frac{S(u)}{D(u)}$ at large values of the density u decides about whether or not unbounded solutions can be found, with quite a comprehensive knowledge available concerning the question if such explosions must occur in finite time, or only arise in the large time limit in the sense of infinite-time blow-up ([4], [8]).

As a next example, the flux-limited Keller-Segel system

$$\begin{cases} u_t = \nabla \cdot \Big(\dfrac{u \nabla u}{\sqrt{u^2 + |\nabla u|^2}} \Big) - \chi \nabla \cdot \Big(\dfrac{u \nabla v}{\sqrt{1 + |\nabla v|^2}} \Big), \\ 0 = \Delta v - \mu + u \qquad (\mu := \fint_\Omega u_0), \end{cases}$$

is considered, which has been introduced inter alia pursuing the ambition to develop an explosion-suppressing variant of the original system ($\star$). In somewhat surprising contrast to this intention, however, it has recently been found that under the – up to equality sharp – assumption that $\chi > 1$ and either $n \geq 2$ and $m > 0$ is arbitrary, or $n = 1$ and $m > \frac{1}{\sqrt{\chi^2 - 1}}$, finite-time blow-up indeed occurs for a large set of radial initial data ([1], [2]).

Finally, as a prototypical model for chemotaxis involving indirect signal production mechanisms, the radial version of the two-dimensional system

$$\begin{cases} u_t = \Delta u - \nabla \cdot (u \nabla v), \\ 0 = \Delta v - \mu(t) + w \qquad (\mu(t) := \fint_\Omega w(\cdot, t)), \\ \tau w_t = -\delta w + u, \end{cases}$$

is addressed. According to a very recent finding, with regard to the occurrence of unboundedness this system again exhibits a critical mass phenomenon: Although global smooth solutions always can be seen to exist, it can be shown that these solutions remain bounded if the corresponding initial data satisfy $\int_\Omega u_0 < 8\pi\delta$, while for any choice of $m > 8\pi\delta$ one can find initial data u_0 such that $\int_\Omega u_0 = m$, but that the associated solution blows un in infinite time ([9]).

References

[1] N. Bellomo, M. Winkler, *A degenerate chemotaxis system with flux limitation: Maximally extended solutions and absence of gradient blow-up*, Comm. Part. Differential Eq. **42** (2017), 436–473.

[2] N. Bellomo, M. Winkler, *Finite-time blow-up in a degenerate chemotaxis system with flux limitation*, Trans. Amer. Math. Soc. B **4** (2017), 31–67.

[3] X. Cao, *Global bounded solutions of the higher-dimensional Keller-Segel system under smallness conditions in optimal spaces*, Discr. Cont. Dyn. Syst. **35** (2015), 1891–1904.

[4] T. Cieślak, C. Stinner, *Finite-time blowup and global-in-time unbounded solutions to a parabolic-parabolic quasilinear Keller-Segel system in higher dimensions*, J. Differential Eq. **252** (2012), 5832–5851.

[5] M.A. Herrero, J.J.L. Velázquez, *A blow-up mechanism for a chemotaxis model*, Ann. Scuola Normale Superiore Pisa Cl. Sci. **24** (1997), 633–683.

[6] N. Mizoguchi, M. Winkler, *Finite-time blow-up in the two-dimensional parabolic Keller-Segel system*, Preprint.

[7] T. Nagai, T. Senba, K. Yoshida, *Application of the Trudinger-Moser inequality to a parabolic system of chemotaxis*, Funkc. Ekvacioj, Ser. Int. **40** (1997), 411–433.

[8] Y. Tao, M. Winkler, *Boundedness in a quasilinear parabolic-parabolic Keller-Segel system with subcritical sensitivity*, J. Differential Eq. **252** (2012), 692–715.
[9] Y. Tao, M. Winkler, *Critical mass for infinite-time aggregation in a chemotaxis model with indirect signal production*, J. European Math. Soc., to appear.
[10] M. Winkler, *Finite-time blow-up in the higher-dimensional parabolic-parabolic Keller-Segel system*, J. Math. Pures Appl. **100** (2013), 748–767. `arXiv:1112.4156v1`

Living Liquid Crystal with Active Squirmer

Hai Chi
(joint work with Leonid Berlyand and Igor S. Aronson)

Living Liquid Crystal (LLCs) is a general class of active fluids. The suspending medium is a nontoxic liquid crystal (LC) that supports the activity of self-propelled particles, like bacteria [1, 2].

- The bacterial activity modifies the orientational order of the system, by producing well-defined and reproducible patterns with or without topological defects.
- The orientational order of the suspending medium reveals facets of bacterial behavior, allowing one to control trajectories of individual bacteria and to visualize rotation of flagella through birefringence of the host.

We consider another kind of self-propelled particle which is called squirmer(spherical non-deformable particle) suspended in liquid crystal. We proposed a model considering the traditional squirmer model in Stokes flow and surface anchoring behavior in liquid crystal. The interesting part for us is to understand what is the stable steady motion for different squirmer(puller, pusher and neutral). We numerically simulate this model and analytically do some stability analysis for this model.
This is work in progress.

References

[1] S. Zhou, A. Sokolov, O.D. Lavrentovich, and I.S. Aranson, *Living liquid crystals*, Proc. Natl. Acad. Sci. USA **111** (1990), 1265–1270.
[2] M. Genkin, A. Sokolov, O.D. Lavrentovich, and I.S. Aranson, *Topological defects in a living nematic ensnare swimming bacteria*. Physical Review X, **7** (2017), p.011029.

Hierarchy of PDE Models of Cell Motility

Leonid Berlyand
(joint work with Jan Fuhrmann, M. Potomkin, and V. Rybalko)

We consider mathematical PDE models of motility of eukaryotic cells on a substrate [1, 2]. Our goal is to capture mathematically the key biological phenomena such as steady motion with no external stimuli and spontaneous breaking of symmetry.

We first describe the hierarchy of PDE models of cell motility and then focus on two specific models: the phase-field model and the free boundary problem model. The phase-field model consists of the Allen-Cahn equation for the scalar phase field function coupled with a vectorial parabolic equation for the orientation of the actin filament network. The key mathematical properties of this system are (i) the presence of gradients in the coupling terms and (ii) the mass (volume) preservation constraints. These properties lead to mathematical challenges that are specific to active (out of equilibrium) systems, e.g., the fact that variational principles do not apply. Therefore, standard techniques based on maximum principle and Gamma-convergence cannot be used, and one has to develop alternative asymptotic techniques.
The free boundary problem model consists of an elliptic equation describing the flow of the cytoskeleton gel coupled with a convection-diffusion PDE for the density of myosin motors. This PDE system is of Keller-Segel type but in a free boundary setting with nonlocal condition that involves boundary curvature. Analysis of this system allows for a reduction to a Liouville type equation which arises in various applications ranging from geometry to chemotaxis. This equation contains an additional term that presents an additional challenge in analysis.
In the analysis of the above models our focus is on establishing 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 for the free boundary problem model.

References

[1] L. Berlyand, J. Fuhrmann, and V. Rybalko, *Bifurcation of traveling waves in a Keller-Segel type free boundary model of cell motility*, available on arXiv, 1705.10352, submitted for publication, 2017.
[2] K. Keren, Z. Pincus, G. M. Allen, E. L. Barnhart, G. Marriott, A. Mogilner, and J. A. Theriot, *Mechanism of shape determination in motile cells*, Nature, **453** (2008), 475-480.

Traveling waves in a free boundary problem for cell motion

Jan Fuhrmann
(joint work with Leonid Berlyand and V. Rybalko)

Keratocytes are fish skin cells moving on flat substrates by forming a quasi-two-dimensional fan-shaped structure called the lamellipodium. Once in motion they maintain their shape and velocity and move persistently. The flatness of both their environment and shape makes them perfect objects of experiments and mathematical modeling.
Here, we study a free boundary problem for two partial differential equations in two space dimensions modeling the cytoskeleton of a keratocyte and search for radially symmetric steady states (corresponding to a resting cell) and traveling

wave solutions (persistently moving cell). The cell is described by the unknown time dependent domain Ω_t, its boundary Γ_t moving with the normal velocity

$$V_\perp = \nu^T \nabla\sigma - 2\beta\kappa + V_p \ \text{ on } \Gamma_t,\ V_p = \frac{1}{|\Gamma_t|}\int_{\Gamma_t} 2\beta\kappa - \nu^T\nabla\sigma \mathrm{d}s \tag{1}$$

where κ is the curvature of the boundary and the average velocity V_p results from actin polymerization and mathematically describes area preservation. The stress σ (scalar, the true stress is $\sigma\mathbb{I}$) of the actin cytoskeleton is described by the elliptic equation

$$0 = -\Delta\sigma + \sigma - \alpha m \ \text{ in } \Omega_t,\ \sigma = 0 \ \text{ on } \Gamma_t. \tag{2}$$

It describes the force balance between forces generated by the stress of the network and the friction $\nabla\sigma$ with the substrate (drag coefficient scaled away into the dimensionless parameter α) and is coupled to an advection diffusion equation for myosin motors m which create a contractile stress αm in the actin network:

$$\partial_t m = \Delta m - \nabla^T(m\nabla\sigma) \ \text{ in } \Omega_t,\ \nu^T\nabla m = (\nu^T\nabla\sigma - V_\perp)m \ \text{ on } \Gamma_t. \tag{3}$$

We should note that this model arises from reducing and non-dimensionalizing a much more complex computational model devised in [1]. We also remark that (2), (3) resemble the classical parabolic-elliptic version of the Keller-Segel model. The distinguishing feature of the present system is the free boundary with nonlocal evolution equation (1). The combination of a nonlinear system with cross diffusion and a nonlocal free boundary condition makes the problem particularly interesting. Being interested in traveling wave solutions we introduce the traveling wave variable $\xi = x - Vt$ where we assume without loss of generality $V = (v, 0)^T$, that is, motion to the right. This yields an elliptic free boundary problem with time independent but still unknown domain and nonlocal boundary condition. The equation for myosin can then be explicitly integrated up to a constant of integration yielding a nonlocal free boundary problem for a single integro-differential equation.

Radially symmetric steady states are found by fixing the domain to a disk and solving the resulting singular two-point boundary value problem for an integro-differential equation in one dimension. We find a continuum (curve) of steady states which is up to some point uniquely parametrized by the total myosin mass $M = \int_\Omega m$. However, for large M, there are two steady state solutions (one of them strongly concentrated around the center), and for still larger M, none at all. Mathematically, the concentration of m near the center and the non-existence of solutions for large M is to be expected since Keller-Segel models in two space dimensions are knwon to exhibit blow-up of solutions for large M. Biologically, this blow-up may be interpreted as large amounts of myosin disrupting the cytoskeleton and eventually the whole cell.

Traveling waves are shown to emerge via bifurcation from the curve of steady state solutions via Leray-Schauder degree theory. To this end we use a Lyapunov-Schmidt type reduction to find a necessary bifurcation condition in the form of some quantity ℓ (depending on the steady state solution and related to the leading

eigenvalue of the linearization around the steady state) vanishing. For this quantity, though not being able to precisely calculate it, we show that it does indeed vanish at some point along the steady state curve and does change sign there. The degree jump principle then ensures a curve of traveling waves bifurcating from the steady states.
Simulations supplementing the analytical results allow us to locate the bifurcation point in terms of the physical parameters and show that the bifurcation indeed occurs in the physiologically meaningful range. We also specify a curve of bifurcation points in the parameter space spanned by drag coefficient and total myosin mass (all other parameters being considered as fixed).

References

[1] E. Barnhart, K. Lee, G. M. Allen, J. A. Theriot, A. Mogilner, *Balance between cell-substrate adhesion and myosin contraction determines the frequency of motility initiation in fish keratocytes*, Proc Natl Acad Sci USA **12**.16 (2015), 5045–5050.
[2] L. Berlyand, J. Fuhrmann, V. Rybalko, *Bifurcation of traveling waves in a Keller-Segel type free boundary model of cell motility*, arXiv: 1705.10352

Free boundary model explains cell turning

Alex Mogilner

Cell migration is a fundamental cell biological phenomenon that underlies many physiological processes. To migrate, cells must polarize, sense a direction, and deploy a motile mechanical machinery. Computational modeling of simple motile fish keratocyte cells was an integral part of understanding general mechanochemical mechanisms of these three aspects of cell migration. I demonstrate how a combination of data analysis and detailed mechanistic modeling elucidated mechanics of self-polarization, steady migration and turning of single keratocytes.
To understand shapes and movements of cells undergoing lamellipodial motility, we systematically explore minimal free-boundary models of actin-myosin contractility consisting of the force-balance and myosin transport equations. The models account for isotropic contraction proportional to myosin density, viscous stresses in the actin network, and constant-strength viscous-like adhesion. The contraction generates a spatially graded centripetal actin flow, which in turn reinforces the contraction via myosin redistribution and causes retraction of the lamellipodial boundary. Actin protrusion at the boundary counters the retraction, and the balance of the protrusion and retraction shapes the lamellipodium. The model analysis shows that initiation of motility critically depends on three dimensionless parameter combinations, which represent myosin-dependent contractility, a characteristic viscosity-adhesion length, and a rate of actin protrusion. When the contractility is sufficiently strong, cells break symmetry and move steadily along either straight or circular trajectories, and the motile behavior is sensitive to conditions at the cell boundary. Scanning of a model parameter space shows that the contractile mechanism of motility supports robust cell turning in conditions where short viscosity-adhesion lengths and fast protrusion cause an accumulation

of myosin in a small region at the cell rear, destabilizing the axial symmetry of a moving cell.

References

[1] M. Muster, *Computing certain invariants of topological spaces of dimension three*, Topology **32** (1990), 100–120.

[2] E. L. Barnhart, KC. Lee, G. M. Allen, J. A. Theriot, A. Mogilner, *The balance between cell-substrate adhesion and myosin contraction determines the frequency of motility initiation in fish keratocytes*, PNAS **112** (2015), 5045–5050.

Dynamics of topological defects in a living nematic

Igor Aronson

(joint work with Mikhail Genkin and Andrey Sokolov)

Living nematic is a realization of an active matter combining a nematic liquid crystal with swimming bacteria. The material exhibits remarkable tendency towards spatio-temporal self-organization manifested in formation of dynamics textures of self-propelled half-integer topological defects (disclinations) [1, 2]. Here, by coupling the well-established and validated model of nematic liquid crystals with the bacterial dynamics, we develop a computational model describing intricate properties of such a living nematic. The model yielded a testable prediction on the accumulation of bacteria in the cores of $1/2$ topological defects and depletion of bacteria in the cores of $-1/2$ defects. We also studied of such living nematic near normal inclusions, or tactoids, naturally realized in liquid crystals close to the isotropic-nematic (I-N) phase transition. On the basis of computational analysis, we have established that tactoid's I-N interface spontaneously acquire negative topological charge which is proportional to the tactoid's size and depends on the concentration of bacteria. The observed negative charging is attributed to the drastic difference in the mobilities of $1/2$ and $-1/2$ topological defects in active systems. The effect is described in the framework of a kinetic theory for point-like weakly-interacting defects with different mobilities. Our dedicated experiments fully confirmed both theoretical predictions. The results hint into new strategies for control of active matter.

References

[1] S. Zhou, A. Sokolov, O.D. Lavrentovich, and I.S. Aranson, *Living Liquid Crystals*, Proc. Nat. Acad. Sci. **111** (2014), 1265-1270.

[2] M.M. Genkin, A. Sokolov, O.D. Lavrentovich, and I.S. Aranson, *Topological defects in a living nematic ensnare swimming bacteria*, Physical Review X, **7** (2017), 011029.

Non equilibrium steady state dynamics of contractile actin networks

Kinneret Keren

The actin cytoskeleton plays a major role during the initial stages of embryonic development. In particular, the actin cytoskeleton can switch, in a cell-cycle dependent manner, into a contractile state and exhibit large scale flows which are essential for the organization and the establishment of polarity in early embryos. For example, myosin-driven contractile flows are required for the initial cortical polarization in many species, while bulk actin network contraction can drive directional transport in large oocytes. We developed a reconstituted model system to study the onset of contraction in cortical or bulk actomyosin networks, and emulate these processes in artificial cells [1, 2]. We encapsulate Xenopus cell extracts in cell-sized water-in-oil emulsions, and introduce various auxiliary proteins including actin nucleators, disassembly factors and crosslinkers to modify cytoskeletal dynamics. Importantly, the presence of dynamic turnover in our system allows these networks to attain a dynamic steady state characterized by contractile actin flows which persist for hours. Using this system we are measuring network structure, contractile flows and turnover, at steady state under different conditions, mapping the dynamic interplay between myosin-driven network contractility and actin turnover.

References

[1] E. A. Shah and K. Keren, *Symmetry breaking in reconstituted actin cortices*, eLife 3:e01433 (2014).

[2] E. A. Shah, M. Malik-Garbi, and K. Keren, *Reconstitution of cortical actin networks within water-in-oil emulsions*, in J. Ross and W. Marshall (eds.), *Methods in Cell Biology: Building a cell from its component parts*, Elsevier (2015).

Phase field models for cell motility

Falko Ziebert

(joint work with Jakob Löber, Benjamin Winkler, and Igor S. Aranson)

I described recent progress made in modeling cellular motion on the continuum, cell-resolved level using the phase field approach. The latter is used to circumvent the computational bottleneck of moving and deformable boundaries in nonlinear PDEs by accounting for a continuous auxiliary field (the phase field) that allows to treat the boundaries implicitly and on a diffuse level.

Most developed models for cell motility are effectively two-dimensional (2D). This simplification is partly justified by the fact that lamellipodium-based cellular motion along a substrate is governed by very thin protrusions (i.e. with layer thickness much smaller than the length of the actin filaments responsible for the protrusive motion). I hence also started with an effectively 2D minimal model [1], that takes into account the biologically motivated interplay of the phase field with a vectorial order parameter localized inside the domain defined by the cell and describing the local degree of ordering of the actin filaments. The latter is assumed to be able

to push the cell's interface locally forward via ratcheting of the filaments' polymerization kinetics. This simple model correctly displays a subcritical onset of translational motion of the domain (implying also bistability of non-moving and moving states), corresponding to steady moving cells like keratocytes, as seen in experiments [2].

I then reviewed several model generalizations, including the adhesion bond-mediated interplay of the previously discussed system with a deformable and/or inhomogeneous elastic substrate [3], as well as a generalization towards multiple cells moving collectively, based on a multiple phase field approach [4]. These and related works have been recently reviewed also in Ref. [5].

Finally, I presented ongoing work on three-dimensional (3D) phase field modeling of cellular motility [6]. The motivation lies in the increasing experimental research on confining cells and trying to guide them by topographical surface features. The model translation from 2D to 3D is rather direct, and assumes only two additional features, namely that actin polymerization is predominantly in the tangential plane defined locally by the substrate the cell is in contact with, and that it decays rapidly with the distance from the substrate. Using these simple assumptions and a parallel implementation on graphic cards allowed us to reveal several nontrivial effects like a confinement-induced shape hysteresis, confinement-stimulated motility, intricate effects of substrate curvature on cell motion, cell guidance by both the degree or confinement and by topography, as well as complex dynamical modes emerging if cells are confined into narrow channels.

Discussions included the relation of this coarse-grained framework to more detailed and microscopic models [7]. Naturally, as 3D modeling of cellular motility is just beginning, open problems are diverse and relate to biological questions (what defines the thickness of the lamellipodial thin sheet? [8]), to modeling aspects (how can other motility modes, like blebbing and wall-pushing [9], be incorporated in a more general framework?), to fundamental questions of nonlinear PDEs (can proofs of existence of solutions, as recently given in the 1D case [10], be transfered to higher dimensions?) and to computational efficiency [11].

References

[1] F. Ziebert, S. Swaminathan, I. S. Aranson, *Model for self-polarization and motility of keratocyte fragments*, J. R. Soc. Interface **9** (2012), 1084.

[2] A. B. Verkhovsky, T. M. Svitkina, G. G. Borisy, *Self-polarization and directional motility of cytoplasm*, Curr. Biol. **9** (1998), 11-20.

[3] F. Ziebert, I. S. Aranson, *Effects of Adhesion Dynamics and Substrate Compliance on the Shape and Motility of Crawling Cells*, PLoS ONE, **8** (2013), e64511.

[4] J. Löber, F. Ziebert, I. S. Aranson, *Collisions of deformable cells lead to collective migration*, Sci. Rep. **5** (2015), 9172.

[5] F. Ziebert, I. S. Aranson, *Computational approaches to substrate-based cell motility*, npj Computational Materials **2** (2016), 16019.

[6] B. Winkler, I. S. Aranson, F. Ziebert, *Confinement and substrate topography control 3D cell migration*, in preparation (2017).

[7] A. Manhart, D. Oelz, C. Schmeiser, N. Sfakianakis, *An extended Filament Based Lamellipodium Model produces various moving cell shapes in the presence of chemotactic signals*, J. Theoret. Biol. **382** (2015), 244-258.

[8] C. Schmeiser, C. Winkler, *The flatness of Lamellipodia explained by the interaction between actin dynamics and membrane deformation*, J. Theoret. Biol. **380** (2015), 144-155.
[9] R. J. Hawkins, et al., *Pushing off the Walls: A Mechanism of Cell Motility in Confinement*, Phys. Rev. Lett. **102** (2009), 058103.
[10] L. Berlyand, M. Potomkin, V. Rybalko, *Phase-field model of cell motility: Traveling waves and sharp interface limit*, C. R. Acad. Sci. Paris, Ser. I **354** (2016), 986-992.
[11] C. M. Elliott, B. Stinner, C. Venkataraman, *Modelling cell motility and chemotaxis with evolving surface finite elements*, J. R. Soc. Interface **9** (2012), 3027-3044.

Traction forces and cell-edge dynamics during cell polarization

Alexander B. Verkhovsky
(joint work with Alicia Bornert, Zeno Messi, Niccolò Piacentini, and Franck Raynaud)

How cells break symmetry and organize their activity to move directionally is a fundamental question in cell biology. Models of cell polarization commonly rely on front-to-back gradients of functional components or regulatory factors to control cell-edge activity, but it is not clear how the front-back axis is defined in the first place. We have recently proposed a novel and simple principle of self-organizing cell activity, in which local cell-edge dynamics depends on the distance from the cell center, but not on the orientation with respect to the front–back axis [1]. Stochastic modeling demonstrated that distance-sensitivity is sufficient for the symmetry breaking and the emergence of persistent cell motion and stable shape. However, physical mechanisms of distance-sensitivity remain unclear.
Here we show that traction forces exerted on the substrate by polarizing and migrating cells increase with the distance from the cell center, and that traction force dynamics and cell-edge dynamics are correlated both in space and time. However, traction forces are not correlated with the local edge curvature. Inhibition of cell contractility results in diminished traction forces, reduced edge activity, and abnormal cell polarization. On the other hand, in the absence of endogenous cell traction, protrusion-retraction switches could be induced by the application of external force. These results suggest that traction forces could mediate distance-sensitivity and organize cell activity during symmetry breaking. Other possible triggers for protrusion-retraction switches such as membrane tension and 3D shape of the cell edge are also discussed.

Acknowledgements

Supported by Swiss National Science Foundation Grant 31003A-135661.

References

[1] F. Raynaud, M. E. Ambühl, C. Gabella, A. Bornert, I. F. Sbalzarini, J. J. Meister, A. B. Verkhovsky, *Minimal model for spontaneous cell polarization and edge activity in oscillating, rotating and migrating cells*, Nat. Physics, 12 (2016), 367-373.

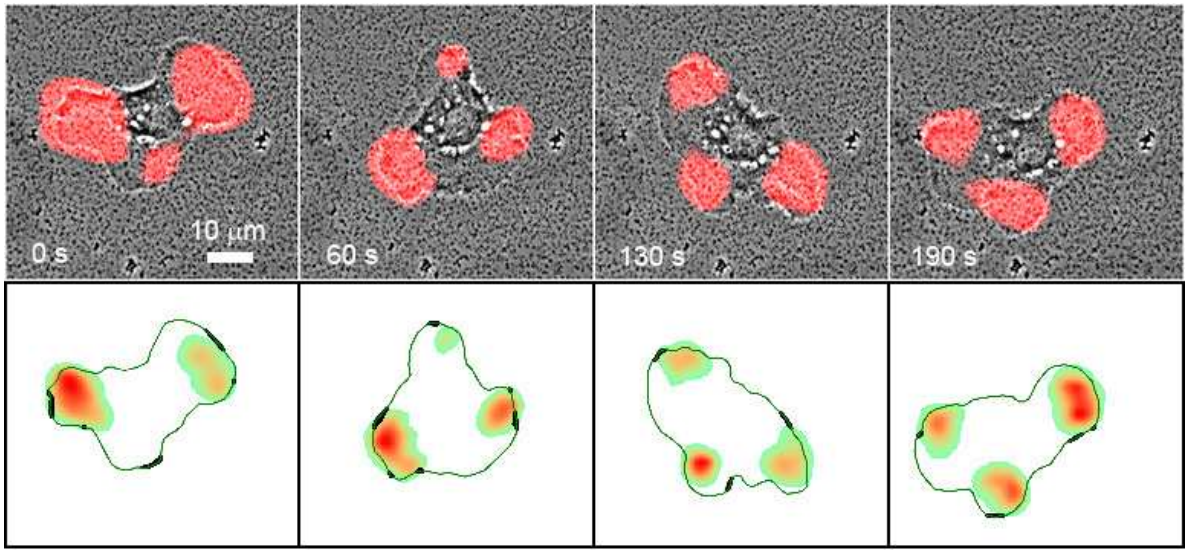

FIGURE 1. Traction force maps (red) superimposed on bright-field images of the cell prior to polarization (top) and on cell contours with protrusion-retraction switches indicated in black (bottom). Switching sites localize at the edges of maximal force areas at the cell extremities.

Partial differential equations in evolving domains: analysis and computation with applications in cell biology

CHARLES M. ELLIOTT

Many physical models give rise to the need to solve partial differential equations in time dependent regions. Our focus in the talk was on the mathematical and computational issues associated with the formulation of PDEs in time dependent domains in both flat and curved space with applications within cell biology to modelling the complex morphology of biological membranes and cells and their motility. These moving boundary problems present significant modelling, analytical and computational challenges. Here in this abstract we mainly point to our own contributions to this field and refer to other abstracts of talks from this workshop in this volume for many more models, methods and mathematical results.

- In $\mathbb{R}^3$ we may think of a cell or vesicle as comprising a bounded domain $\Omega(t)$ with a boundary $\Gamma(t)$. Of course on $\Gamma(t)$ there may be interfaces comprising closed curves $\gamma(t)$ corresponding to line energies and also point effects due to filaments or protein complexes attached to the cell surface. There may be complex processes in the body of the cell and on the cell surfaces which are coupled and determine the morphology and motion of the cell. Many models involve parabolic equations of advection, diffusion and reaction type on evolving domains. The evolution of these domains may be governed by geometric quantities. From the point of view of analysis there are advantages in considering separately equations on domains whose evolution is known and equations for the evolution of the domains.

- In general we may think of PDE problems posed in domains associated with time dependent d-dimensional hypersurfaces $\Gamma(t)$ in $\mathbb{R}^{d+1}$ whose evolution is given. The surface $\Gamma(t)$ may be the boundary of a bounded open bulk region $\Omega(t)$. In this setting we may also view $\Omega(t)$ as $(d+1)$-dimensional sub-manifold in $\mathbb{R}^{d+2}$. Using this observation we may develop a theory applicable to both surface and bulk equations. An abstract framework for treating the theory of well- posedness of solutions to parabolic equations on evolving Hilbert spaces using generalised Bochner spaces was presented in [1] where the setting is abstract and not restricted to evolving domains or surfaces.
- The aforementioned abstract theory is applicable to variational formulations of PDEs on evolving spatial domains including moving hypersurfaces, [2]. We can show well-posedness to a certain class of parabolic PDEs under some assumptions on the parabolic operator and the data. For example we may study a surface heat equation, an equation posed on a bulk domain, a coupled bulk-surface system and an equation with a dynamic boundary condition, [2]. Recently semilinear coupled bulk surface systems for receptor - ligand dynamics have been studied in [21, 3].
- The development and numerical analysis of evolving surface finite element spaces (ESFEM) and bulk equations may be found in [9, 12, 14, 30, 19, 28, 20]. See [13] for a survey of various approaches to the formulation and computation of parabolic equations on hypersurfaces. including unfitted finite element and implicit surface approaches, [7, 8, 10, 11, 24].
- In applications often the domain has to be computed. See [6] for an account of numerical methods for computing the solution to geometric evolution equations such as motion by mean curvature. Evolving surface triangulations by velocity fields which have arbitrary tangential components give rise to ALE ESFEM, [26, 27]. Recently methods for computing parametrisations with non physical tangential components which evolve triangulations whilst maintaining good mesh properties have been proposed in [16, 15].
- A speculative model for cell motility was considered in [25] . The content of the model is to couple surface reaction diffusion equations to the motion of a geometric evolution law with energetic terms arising from surface tension and bending energy. Further developments of this model were considered in [5] where the issue of parameter identification was addressed. A computational model was developed and then applied to parameter identification for monopolar growth of fission yeast cells using experimental imaging data.
- We refer to [31, 4, 29] for results concerning the numerical analysis of evolving surface finite element approximations of diffusion coupled to surface evolution.
- Mathematical models for the interaction between biomembranes and (a) surface gradient energies modelling line energies and (b) smaller objects

such as finite size and point particles and filaments are studied in (a) [22, 23] and (b) [18, 17] and the references cited therein.

Acknowledgements

The work was partially supported by the Royal Society via a Wolfson Research Merit Award.

References

[1] A. Alphonse, C.M. Elliott and B. Stinner *An abstract framework for parabolic PDEs on evolving spaces* Portugaliae Mathematica **72** (2015) 1–46

[2] A. Alphonse, C.M. Elliott and B. Stinner *On some linear parabolic PDEs on moving hypersurfaces* Interfaces and Free Boundaries **17** (2015) 157–187

[3] A. Alphonse, C. M. Elliott and J. Terra *A coupled ligand receptor model bulk-surface system on a moving domain: well posedness, regularity and convergence to equilibrium* arXiv:1612.03007

[4] J. W. Barrett, K. Deckelnick and V. Styles *Numerical analysis for a system coupling curve evolution to reaction diffusion on the curve* SIAM J. Numer. Anal. **55** (2017)1080–1100

[5] W. Croft, C. M. Elliott, G. Ladds, B. Stinner, C. Venkataraman and C. Weston *Parameter identification problems in the modelling of cell motility* J. Mathematical Biology **71** (2015) 399–436

[6] K. P. Deckelnick, G. Dziuk and C. M. Elliott *Computation of geometric partial differential equations and mean curvature flow* Acta Numerica **14** (2005) 139–232

[7] K. P. Deckelnick, G. Dziuk, C. M. Elliott and C.-J. Heine *An h−narrow band finite element method for elliptic equations on implicit surfaces* IMAJ Num. Anal. **30** (2010) 351–376

[8] K. P. Deckelnick, C. M. Elliott and T. Ranner *Unfitted finite element methods using bulk meshes for surface partial differential equations* SIAM J. Numerical Analysis **52** (2014) 2137–2162

[9] G. Dziuk and C.M. Elliott *Finite elements on evolving surfaces* IMAJ Num. Anal. **27** (2007) 262–292

[10] G. Dziuk and C.M. Elliott *Eulerian finite element method for parabolic equations on implicit surfaces* Interfaces Free Boundaries **10** (2008) 119–138

[11] G. Dziuk and C.M. Elliott *An Eulerian approach to transport and diffusion on evolving surfaces* Computing and Visualization in Science **13** (2010) 17–28

[12] G. Dziuk and C. M. Elliott *Fully discrete evolving surface finite element method* SIAM J. Numer. Anal. **50** 5 (2012) 2677–2694

[13] G. Dziuk and C. M. Elliott *Finite element methods for surface partial differential equations* Acta Numerica **22** (2013) 289–396

[14] G. Dziuk and C. M. Elliott *L2 estimates for the evolving surface finite element method* Math. Comp. **82** (2013) 1–24

[15] C. M. Elliott and H. Fritz, *On algorithms with good mesh properties for problems with moving boundaries based on the Harmonic Map Heat Flow and the DeTurck trick* SMAI Journal of Computational Mathematics **2** (2016) 141–176

[16] C. M. Elliott and H. Fritz, *On approximations of the curve shortening flow and of the mean curvature flow based on the DeTurck trick* IMA Journal Numerical Analysis **37** (2017) 543–603

[17] C. M. Elliott, H. Fritz and G. Hobbs *Small deformations of Helfrich energy minimising surfaces with applications to biomembranes* Math. Mod. Meth. App. Sci. **27** (2017) 1547–1586

[18] C. M. Elliott, C. Graeser, G. Hobbs, R. Kornhuber and M. W. Wolf *A variational approach to particles in lipid membranes* Arch. Rat. Mech. Anal. **222** 1011–1075
[19] C. M. Elliott and T. Ranner *Evolving surface finite element method for the Cahn-Hilliard equation* Numerische Mathematik **129** (2014) 483–534
[20] C. M. Elliott and T. Ranner *A unified theory for continuous in time evolving finite element space approximations to partial differential equations in evolving domains* arXiv preprint arXiv:1703.04679
[21] C. M. Elliott, T. Ranner and C. Venkataraman *Coupled bulk-surface free boundary problems arising from a mathematical model of receptor-ligand dynamics* SIAM J. Math. Anal. **49** (2017) 360–397
[22] C. M. Elliott and B. Stinner *Modelling and computation of two phase geometric biomembranes using surface finite elements* J. Comp. Phys. **229** (2010) 6585–6612
[23] C. M. Elliott and B. Stinner *Computation of two-phase biomembranes with phase dependent material parameters using surface finite elements* Communications in Computational Physics **13** (2) (2012) 325–360
[24] C. M. Elliott, B. Stinner, V. M. Styles and R. Welford *Numerical computation of advection and diffusion on evolving diffuse interfaces* IMAJ Num. Anal. **31** (2011) 786–812
[25] C. M. Elliott, B. Stinner and C. Venkataraman *Modelling cell motility and chemotaxis with evolving surface finite elements* Journal Royal Society Interface **9**(76) (2012) 3027–3044
[26] C.M. Elliott and V.M. Styles *An ALE ESFEM for solving PDEs on evolving surfaces* Milan Journal Mathematics **80** (2012) 469–501
[27] C. M. Elliott and C. Venkataraman *Error analysis for an ALE evolving surface finite element method* Num. Methods for PDEs **31** (2015) 459–499
[28] B. Kovacs and C. Power Guerra *Error analysis for full discretizations of quasilinear parabolic problems on evolving surfaces* Njum. Meth. P.D.E. **32** (2016) 1200–1231
[29] B. Kovacs, B. Li, C. Lubich and C. A. Power Guerra *Convergence of finite elements on an evolving surface driven by diffusion on the surface* Num. Math. **137** (2017) 643–689
[30] C. Lubich, D. E. Mansour and C. Venkataraman *Backward difference time discretization of parabolic differential equations on evolving surfaces* IMA Jour. Num. Anal. **33** (2013) 1365–1385
[31] P. Pozzi and B. Stinner *Curve shortening flow coupled to lateral diffusion* **135** (2017) 1171–1205

Discussions

Angela Stevens, Alex Mogilner, Kinneret Keren, Jan Fuhrmann, Michael Winkler, Christina Surulescu

During the mini-workshop the participants initiated lively discussions about the issues presented in the talks, but also (in small groups) about related issues leading to mathematically very interesting problems.

The talks by Angela Stevens addressed models for alignment, patterns, and waves in populations of myxobacteria, with a focus on pattern formation due to local, i.e. direct cell interactions. An issue of particular interest in this context is the identification of minimal models which are still able to provide valuable information about the relevant dynamics of cell populations. The question arises whether some models can be ruled out and if so, what should be the adequate (mathematical and/or biological) criteria?

In his talk Alex Mogilner addressed the (still open) problem of coupling keratocyte motile behavior in order to study collective motion: What are the proper rules for intercellular adhesion and how do they change when cells are in contact or even overlap? Also, the idea of 'inverse problems' was formulated: Given the biological data, what is the most adequate model to be chosen and how is this to be achieved? Thereby, the search of the data needs itself modeling. One idea would be to use machine learning classification.

A further talk by Kinneret Keren about hydra regeneration led to a discussion about interesting aspects for modeling in this framework, e.g. defect generation, modification of cell organization in response to mechanical and chemical cues, formation of protrusions, evolution of total area during the regeneration process.

Jan Fuhrmann and Michael Winkler payed attention to a problem related to blow-up in a Keller-Segel type free boundary problem:
For a parabolic-elliptic Keller-Segel system with free boundary in two space dimensions arising from a model for cell motion we observed non-uniqueness and non-existence of radially symmetric steady states for certain parameters (corresponding to a large L^1-norm of the cell density in the classical Keller-Segel model). The problem is equipped with no-flux boundary conditions for one variable and homogeneous Dirichlet conditions for the other one, and the motion of the free boundary is described by a non-local (area preservation) kinematic condition involving the curvature of the boundary. From these observations and the known threshold behavior for the Keller-Segel-system with Neumann-boundary in a fixed two-dimensional domain, we arrive at the natural question whether the system at hand exhibits finite time blow-up for certain initial conditions. In more detail, we ask for a blow-up threshold in the radially symmetric case with fixed boundary and further on for blow-up criteria in the problem with free boundary.

In the context of macroscopic equations for the evolution of interacting populations Christina Surulescu and Michael Winkler discussed the possible extension of the chemotaxis system with indirect signal production presented by M. Winkler to a setting for describing the acid-mediated interaction between moving and proliferating tumor cells; a highly nonlinear system coupling an ODE with two PDEs was obtained, which will be further investigated w.r.t. well-posedness and asymptotic behavior.

Reporter: Christina Surulescu