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Mini-Workshop: Mathematical Models for Cancer Cell Migration

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Abstract. Tumour cell invasion is an essential hallmark in the progression of malignant cancer. Thereby, cancer cells migrate through the surrounding tissue (normal cells, extracellular matrix, interstitial fluid) towards blood or lymph vessels which they penetrate and thus access the blood flow. They are carried by blood circulation to distant locations where they extravasate and develop new tumours, a phenomenon known as *metastasis*. The invasive spread of cancer cells is highly complex – it involves several mechanisms, like *diffusion*, *chemotaxis* and *haptotaxis*; these in turn are conditioned by and influence the subcellular dynamics.

Mathematical models offer a powerful tool to gain insight into the complicated biological processess connected to tumour invasion and have also stimulated advanced mathematical research. Some of the new developments in the field of biomedical oncology were inspired by such models. A significant challenge arises due to the interactions of cancer cells with a complicated and structured microenvironment of healthy tissue. Many of the models of cancer cell migration are based on partial differential equations (PDEs) including spatial heterogeneity, orientational tissue structure, tissue stiffness and deformability. Specific settings relate to reaction-diffusion equations, transport equations, continuum equations, and to their multi-scale analysis, to local and global existence and uniqueness, to pattern formation, blow-ups and invasions. A further approach involves agent-based models providing a characterisation of cell migration by way of simulating the (inter)actions of autonomous agents (individual cells, collective dynamics) and aiming for assessing their effects on the entire system. (Abstract continues on the next page.)

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

In this meeting we covered the full spectrum between macroscopic PDE models and microscopic individual based models with the common goal of modelling cancer cell migration. Of particular interest was the derivation of macroscopic properties from microscopic details. Similar multiscale models have been used in other contexts (such as chemotaxis for example), and we gained some significant insight from the collaborations in this workshop. In this one week meeting we posted nine open ended problems (outlined below), which will form the seed for new collaborations going far beyond this workshop.

Introduction by the Organisers

The traditional understanding of cancer is the view that through mutations a very aggressive cell type is created, which grows unlimited, is able to evade treatment and, at later stages, invades into other parts of the body (metastasis). All cells of the tumour were considered as basically identical clones. In recent years, however, the picture has changed drastically. It is now well accepted that cancer does not describe one disease, or one type of aggressive cells, but rather a complicated interaction of many abnormal features (Merlo et al. 2006, [10, 11]). Hanahan and Weinberg state in their 2011 hallmark paper [11]:

> *... tumours are more than insular masses of proliferating cancer cells. Instead they are complex tissues composed of multiple distinct cell types that participate in heterotypic interactions with one another. ... tumours can no longer be understood simply by enumerating the traits of the cancer cells but instead must encompass the contributions of the "tumour microenvironment" to tumourigenesis.*

Most of the existing time-continuous models for cancer invasion can be assigned to three categories:

Microscopic models are concerned with the events at the subcellular level initiating and controlling (tumour) cell migration. These processes are usually characterised with systems of ordinary differential equations (ODEs) for the concentrations of the involved biochemical substances. ODE models have been used on the microscopic level to focus on the expression of matrix degrading enzymes and proteolysis [3], whereas others emphasise cell polarisation and onset of lamellipod protrusion [17], a crucial step in integrin-mediated haptotactic motility. Yet other models (see e.g., [8, 16, 18, 19, 20]) pay attention to the integrin dynamics, i.e. binding of receptors on the cell surface to soluble (chemoattractant molecules) and insoluble (tissue fibers) components of the peritumoral environment. A still open question is which subcellular processes are essential for the invasive behavior and what should be the level of detail one has to account for in order to provide a realistic, yet simple enough description. This issue can only be successfully addressed by way of interdisciplinary cooperations.

In the **mesoscopic framework**, tumour cell migration is characterised by Boltzmann-like kinetic transport equations for the cell density function. Unlike gas

theory, the integral operators here 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 ([6, 8, 14, 16, 18, 22]). Bellomo et al. (2010) 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 modelling of the turning rates, and the well-posedness in less regular function spaces, under less restrictions on the data.
Another approach on the mesoscopic level are individual based models (IBMs), or agent-based models such as cellular automata, cellular Potts models or lattice gas models. They have attracted particular interest in the last years and have been applied to cancer cell invasion ([7, 12, 26]) to analyse collective effects at the macroscopic cell population level starting from microscopic cell interactions. One focus of the meeting was to compare the IBM models with the above mentioned kinetic equation approach.

Macroscopic descriptions can be derived from mesoscopic models by means of averaging leading to evolution equations for the moments of the cell distribution function (see, e.g., [8, 14]). Apart from the kinetic setting, macroscopic models for cell migration were also derived using mass conservation and mechanical force balance, respectively the theory of mixtures [25]. Further models for cell population migration that rely on mass balance equations were proposed by Gatenby et al. (2006), Anderson et al. (2000) and Chaplain (2008), for example.

From a point of view of mathematical analysis, most of the resulting PDE systems are far from fully understood. Especially the typically occurring taxis-type nonlinear cross-diffusive terms give rise to numerous challenges. These already occur at the level of basic existence theory, but beyond this also concern questions related to the structure-generating potential of the respective systems, the latter often being related to certain dynamical processes of singularity formation. Although quite a number of corresponding results has been derived for various versions of the paradigmatic Keller-Segel chemotaxis system ([13, 15, 27]), in presence of more complex interactions such as in coupled chemotaxis-haptotaxis systems, the knowledge is much less complete, and the analysis yet concentrates on topics of global existence ([23, 24]).

Combining two or all three of these modelling levels leads to a **multiscale setting**, which has received increasing interest over the last decade. Many of the models– in particular those involving couplings between micro and mesoscales – align to the mentioned general KTAP by Bellomo et al. (2010). Another class of multiscale models connecting the microscopic and macroscopic levels of cancer cell migration was considered e.g., by Meral et al. [19, 20], where the focus was on the effect of subcellular events on the tumour cell motility with a more or less detailed description of the microscopic dynamics.

The information content can be much increased with such approaches, however, a model should still be as simple as possible. Keeping this balance is a nontrivial modelling task; the level of detail has to be chosen according to the phenomena one would like to focus. Transforming their interconnections into mathematical models has to be done correspondingly and is again not straightforward, due to complex events taking place at different time and space scales.

These multiscale settings offer interesting mathematical challenges as they usually consist of several types of differential equations (like kinetic transport, ordinary, and parabolic differential equations), or of individual based stochastic processes (IBMs, cellular Potts models etc.). Moreover, due to their high dimensionality and the different scales under consideration, full micro-meso-macro models pose nontrivial problems with respect to simulations. A way to overcome numerical difficulties is to deduce *macroscopic limits* of the corresponding kinetic equation, but due to the highly nonlinear couplings and the large gaps between the scales, it is in general not clear how to specify such a limit in a rigorous manner, unless generous assumptions are made about the kernels involved in the haptotaxis and chemotaxis operators on the mesolevel ([21, 28]).

The participants of the meeting brought expertise in all relevant fields outlined above. At the beginning of the workshop days, leading experts introduced a certain topic and they presented their respective view of the cancer invasion problem. Later, groups formed to discuss interrelations between the different approaches, to identify interesting mathematical problems, and to discuss the biological implications of these models. First ideas were very promising and we expect considerable progress towards the common goal of understanding, modeling and controlling cancer invasion.

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References

[1] Anderson, A.R.A., Chaplain, M.A.J., Newman, E.L., Steele, R.J.C., and Thompson, A.M., Mathematical modeling of tumour invasion and metastasis, *J. of Theoretical Medicine* **2** (2000), pp.129-154.

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

[3] Berry, H., Oscillatory behavior of a simple kinetic model for proteolysis during cell invasion, *Biophys. J.* **77** (1999), pp.655-665.

[4] Bournaveas, N. and Calvez, V., Global existence for the kinetic chemotaxis model without pointwise memory effects, and including internal variables, *Kinetic and Related Models* **1** (2008), pp.29-48.

[5] Chaplain, M.A.J., Modelling aspects of cancer growth: Insight from mathematical and numerical analysis and computational simulation, in: Capasso, V., and Lachowicz, M. (eds.), *Multiscale Problems in the Life Sciences. From Microscopic to Macroscopic.* CIME LNM 1940, pp.147-200. Springer, Berlin, 2008.

[6] Chauviere, A., Hillen, T., and Preziosi, L., Modeling cell movement in anisotropic and heterogeneous network tissues, *Netw. heterog. media* **2** (2007), pp.333-357.
[7] Deutsch, A. and Dormann, S., *Cellular Automaton Modeling of Biological Pattern Formation: Characterization, Applications, and Analysis*, Birkhäuser, Boston, 2005.
[8] Engwer, C., Hillen, T., Knappitsch, M., and Surulescu, C., A DTI-based multiscale model for glioma spread including cell-ECM interactions, preprint, WWU Münster, 2013.
[9] Erban, R. and Hwang, H.J., Global Existence Results for Complex Hyperbolic Models of Bacterial Chemotaxis, *Discrete and Continuous Dyn. Syst. B* **6** (2006), pp.1239-1260.
[10] Gatenby, R.A., Gawlinski, E.T., Gmitro, A.F., Kaylor, B., and Gillies, R.J., Acid-Mediated Tumor Invasion: a Multidisciplinary Study, *Cancer Res.* **66** (2006), pp.5216-5223.
[11] Hanahan, D. and Weinberg, R.A., Hallmarks of cancer: the next generation, *Cell* **144** (2011), pp.646-674.
[12] 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), pp.49-65.
[13] Hillen, T. and Painter, K. A User's Guide to PDE Models for Chemotaxis. *J. Math. Biol.*, **58**(1), 183-217, 2009.
[14] Hillen, T., M^5 Mesoscopic and macroscopic models for mesenchymal motion, *J. Math. Biol.* **53** (2006), pp.585-616.
[15] Jäger, W. and Luckhaus, S., On explosions of solutions to a system of partial differential equations modelling chemotaxis, *Trans. Am. Math. Soc.* **329** (1992), pp.819-824.
[16] Kelkel, J. and Surulescu, C., A multiscale approach to cell migration in tissue networks, *Math. Models and Methods in Appl. Sci.* **23** (2012), 1150017, 25 pages.
[17] Lin, B., Holmes, W.R., Wang, C.J., Ueno, T., Harwell, A., Edelstein-Keshet, L., Inoue, T., and Levchenko, A., Synthetic spatially graded Rac activation drives cell polarization and movement, *PNAS* **109** (2012), pp.21194-21195.
[18] Lorenz, T. and Surulescu, C., On a class of multiscale cancer cell migration models: Well-posedness in less regular function spaces, preprint, TU Kaiserslautern, 2013.
[19] Meral, G. and Surulescu, C., Mathematical modeling, analysis and numerical simulations for the influence of heat shock proteins on tumour invasion, *J. of Math. An. Appl.*, in press.
[20] Meral, G., Stinner, C., and Surulescu, C., On a multiscale model involving cell contractivity and its effects on tumour invasion, preprint TU Kaiserslautern, 2013.
[21] Othmer, H. and Hillen, T., The diffusion limit of transport equations II: Chemotaxis equations, *SIAM J. Applied Math.* **62** (2002), pp.1222-1250.
[22] Painter, K.J. and Hillen, T., Mathematical modelling of glioma growth: the use of Diffusion Tensor Imaging (DTI) data to predict the anisotropic pathways of cancer invasion, *J. Theor. Biol.* **323** (2013), pp.25-39.
[23] Tao, Y. and Wang, M., Global solution for a chemotactic-haptotactic model of cancer invasion, *Nonlinearity* **21** (2008), pp.2221-2238.
[24] Tao, Y. and Winkler, M., A chemotaxis-haptotaxis model: the roles of porous medium diffusion and logistic source, *SIAM Journal of Mathematical Analysis* **43** (2011), pp.685-704.
[25] Tosin, A. and Preziosi, L., Multiphase modeling of tumour growth with matrix remodeling and fibrosis, *Math. Comput. Modelling* **52** (2010), pp.969-976.
[26] A. Voß-Böhme, Multi-scale modeling in morphogenesis: a critical analysis of the cellular potts model, *PLoS ONE* **7** (2012), e42852.
[27] Winkler, M., Finite-time blow-up in the higher-dimensional parabolic-parabolic Keller-Segel system, *Journal de Mathématiques Pures et Appliquées*, to appear. `arXiv:1112.4156v1`
[28] Xue, C. and Othmer, H.G., Multiscale models of taxis-driven patterning in bacterial populations, *SIAM J. Appl. Math.* **70** (2009), pp.133-169.

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Abstracts

Living Systems, Complexity, and Mathematics – A Personal Quest Toward a Mathematical Theory of Living Systems

Nicola Bellomo

This lecture is devoted to the development of mathematical tools for the modeling, qualitative analysis, and simulations of complex systems in life and human sciences. Specifically, systems of many living individuals interacting in a non-linear manner. The presentation is developed through three steps:

I: Detailed analysis of the common complexity features of living systems;

II: Derivation of a unified mathematical approach based on suitable developments of methods of the kinetic theory, where interactions described by theoretical tools of stochastic evolutive game theory;

III: A critical analysis of applications and related analytic and computational problems looking ahead to research perspectives.

The presentation aims at providing an answer to the following questions:

Do complex living systems exhibit common features and which are the mathematical structures able to capture them?

Can these structures act as a paradigm for the derivation of models in life science?

Can an overview of applications suggest hallmarks toward a mathematical theory of living systems?

Part I: The first part of the lecture is devoted to understand the main common features of living, hence complex, systems. As it is known, it is very difficult to understand and model these systems based on the sole description of the dynamics and interactions of a few individual entities localized in space and time. In fact, interactions are nonlinearly additive and their modeling should take into account the ability of living entities to develop specific strategies based on the states and localization of the surrounding entities [1],[2]. Specifically the following features can be considered:

(1) Heterogeneous ability to express a strategy;
(2) Nonlinear interactions and learning ability;
(3) Darwinian selection and time as a key variable;
(4) Tipping points detecting rare non predictable events.

As it is known, the hint to look for appropriate structures can contribute non only to modeling, but also to the development of mathematical sciences [3]. Indeed, as observed by Gromov [3], structures might include a descriptive ability of physical reality which goes beyond the specific field, which they refer to.

Part II: The second part presents a unified mathematical approach to derive a mathematical structure suitable to retain, as far as it is possible, the aforesaid

common features and to provide the conceptual basis for the derivation of specific models. The hallmarks toward this search can be summarized as follows:

i) The overall system is subdivided into *functional subsystems* constituted by entities, called *active particles*, whose individual micro-scale state is called *activity*, where this variable refers to their ability to develops specific strategies also based on interactions.
ii) The micro-scale state of each functional subsystem is defined by a suitable, time dependent, probability distribution over the micro-scale state, which includes position, velocity, and activity variables.
iii) Interactions are modeled by stochastic, evolutive games, where the state of the interacting particles and the output of the interactions are known in probability, and where the rules of interactions evolve in time due to the learning ability of the active particles.
iv) The evolution of the probability distribution is obtained by a balance of particles within elementary volume of the space of the micro-states, where the dynamics of inflow and outflow of particles is determined by interactions. Detailed calculations yield a system of nonlinear integro-differential equations [1].

Part III: The third part focuses on applications in various fields of life sciences. More in detail:

- The dynamics of multicellular systems where interactions can generate both modification of biological functions and mutations with Darwinian selection, and proliferative destructive events [4],[5] also related to interactions with the external environment.
- Derivation of flux limited chemotaxis models from the underlying description at the cellular scale [6] with special focus on the celebrated Keller and Segel model [7],[8].
- Pedestrian crowd dynamics viewed as a large system of interacting entities [9].

The final critical analysis focuses on the detection of rare events, namely the so-called black swan [10], and looks at designing a mathematical theory of living systems based on the mathematical tools presented in Part II. This challenging objective is pursued by linking the aforesaid mathematical structure to theories modeling interactions specific of each class of systems under consideration.

References

[1] Bellomo, N., Knopoff, D., Soler, J.: *On the difficult interplay between life, "complexity", and mathematical sciences.* Mathematical Models Methods Applied Sciences, 23, 1861-1913 (2013)
[2] Bellomo, N., Coscia, V.: *Sources of nonlinearity in the kinetic theory for active particles with focus on the formation of political opinions.* In: Recent Trends in Nonlinear Partial Differential Equation I: Evolution problems, Series Contemporary Mathematics of AMS 594, 99-114 (2013)
[3] Gromov, M.: *In a Search for s Structure, Part 1: On Entropy.* Preprint, http://www.ihes.fr/∼gromov/ (2013)

[4] Bellouquid, A., De Angelis, E., Knopoff, D.: *From the modeling of the immune hallmarks of cancer to a black swan in biology.* Mathematical Models Methods Applied Sciences, 23, 949-978 (2013)
[5] De Angelis, E.: *On the mathematical theory of post-Darwinian mutations, selection, and evolution.* Mathematical Models Methods Applied Sciences, 24, to appear (2014)
[6] Bellomo, N., Bellouquid, A., Nieto, J., Soler, J.: *On the asymptotic theory from microscopic to macroscopic growing tissue models.* Mathematical Models Methods Applied Sciences, 22, paper n.1130001 (2012)
[7] Keller, E.F., Segel, L.A.: *Models for chemotaxis.* J. Theoretical Biology, 30, 225-234 (1971)
[8] Hillen, T., Painter, K.J.: *A user's guide to PDE models for chemotaxis.* J. Mathematical Biology, 58, 183-217 (2009)
[9] Bellomo, N., Bellouquid, A., Knopoff, D.: *From the micro-scale to collective crowd dynamics.* SIAM Multiscale Modelling and Simulations, 11, 943-963 (2013)
[10] Bellomo, N., Herrero, M.A., Tosin, A.: *On the dynamics of social conflicts looking for the black swan.* Kinetic and Related Models, 6, 459-479 (2013)

The role of multiple communication pathways on collective cell movement: insights from modeling self-organised animals and Dictyostelium Discoideum cells

Raluca Eftimie

Cancer is the result of loss of co-ordination among different cell processes, such as cell-cell communication, cell proliferation, cell differentiation and cell migration. In many cases, the same cell-cell communication pathways control multiple processes involved in cancer progression (e.g., the Wnt signaling pathway, which has been associated with breast cancer, controls cell migration, differentiation and proliferation). Here we propose hypotheses on the role of cellcell communication on the movement and segregation of cells that interact via slightly different communication pathways. To this end, we present some results on the interplay between communication, movement and spatial segregation of cells and animals. First, we focus on investigating the role of communication on collective movement of self-organised particles/animals [1], and show that the simultaneous use of multiple communication mechanisms leads to unexpected aggregative and movement behaviours (which cannot be predicted by the behaviours of the subpopulations that use only one communiation mechanisms). In particular, it can also lead to chaotic movement [2]. Next we focus on Dictyostelium Discoideum, a classical toy model for understanding biological processes in development, and discuss the effect of two mutually inhibitory cell-cell signalling pathways (cAMP and DIF-1) on the coordinated movement and segregation of different cell types. We show that cAMP alone can control the movement and spatial segregation of cells, while in combination with DIF-1 it controls the de-differentiation of cells and their proportionality inside the slug.

References

[1] Eftimie, R., de Vries, G., Lewis, M.A.: *Complex spatial group patterns result from different animal communication mechanisms.* PNAS, 104 (17), 6974- 6979 (2007)

[2] Eftimie, R.: *Simultaneous use of different communication mechanisms leads to spatial sorting and unexpected collective behaviours in animal groups.* J. Theoretical Biology, 337, 42-53 (2013)

DTI-based multi-scale modelling and simulation of glioma growth

Christian Engwer

(joint work with Thomas Hillen, Markus Knappitsch, Christina Surulescu)

We present a DTI based model for glioma tumor growth and spread. Based diffusion tensor imaging the model allows to incorporate local structural information. We assume that cancer cells use neuronal fibre tracts as invasive pathways. DTI is able to provide information about fibre orientation, thus opening the way for patient specific modelling of glioma invasion.

Starting from a multiscale model involving subcellular (micro-scale) and individual (meso-scale) cell dynamics, we do a parabolic scaling and obtain a reaction-diffusion-transport for the tumor cell density equation on the macro-scale. The mathematical modelling follows the multiscale approach proposed by [6]. The subcellular dynamics lead to additional advective phenomena, which corresponds to haptotactic movement [2]. Proliferation is modelled on the meso-scale and relies on the *go-or-grow* hypothesis, which states that cancer cells can either move or proliferate [5]. We use scaling arguments to deduce an advection-diffusion-reaction model on the macro-scale.

On the micro-scale integrin receptors of the cell bind to aligned ECM fibres, where $Q(t,\mathbf{x})$ denotes their fibre volume fraction. The dynamics of the integrin receptors are modelled as an ODE:

$$\dot{\mathbf{y}} = k^+(R_0 - \mathbf{y})Q - k^-\mathbf{y},$$

with R_0 overall number of receptors of the cell and $\mathbf{y}(t)$ those receptors bound to ECM at t. On the meso-scale we observe densities $p(t,\mathbf{x},\mathbf{v},\mathbf{y})$ of moving cells and $r(t,\mathbf{x},\mathbf{y})$ of resting cells, at position $\mathbf{x}$, with velocity $\mathbf{v}$, internal state $\mathbf{y}$, at time t. Formulating a kinetic transport model we get the following PDE system:

$$\partial_t p + \nabla_{\mathbf{x}} \cdot (\mathbf{v}p) + \nabla_{\mathbf{y}} \cdot (\mathbf{G}(\mathbf{y})p) = \mathcal{L}[\lambda]p - \alpha(\mathbf{x})p + \frac{\beta q}{\omega} r - l(N)p,$$

$$\partial_t r = \alpha(\mathbf{x}) \int_V p d\mathbf{v} - \beta r + g(N)r - l(N)r.$$

With receptor dynamics $\mathbf{G}(\mathbf{y},Q) := k^+(R_0 - \mathbf{y})Q - k^-\mathbf{y}$ and a *turning operator*

$$\mathcal{L}p = -\lambda(\mathbf{y})p + \int_V \lambda(\mathbf{y})K(\mathbf{x},\mathbf{v},\mathbf{v}')p(\mathbf{v}')d\mathbf{v}'$$

which describes velocity changes of the cells due to the *turning kernel* $K(\mathbf{x},\mathbf{v},\mathbf{v}')$. The probability for a chosen direction depends on the orientation distribution $q(\mathbf{x},\hat{\mathbf{v}})$ of tissue fibres. We choose $K(\mathbf{x},\mathbf{v},\mathbf{v}') = \frac{q(\hat{\mathbf{v}})}{\omega}$ with $\omega = \int_V q(\hat{\mathbf{v}})d\mathbf{v} = s^{n-1}$ a scaling constant, as proposed in [4], according to our assumption that cells choose new directions of movement due to contact guidance. On the meso-scale

we consider a logistic growth law with the gain factor $g(N) = c_g$ and a loss term $l(N) = c_l N$, $c_g, c_l \geq 0.0$. Using a parabolic scaling we obtain the macroscopic equation

$$\partial_t N_0 - c_D \nabla\nabla \left(\mathbb{D}_T(\mathbf{x}) N_0\right) - \lambda_1 c_D \nabla \left(\mathbf{u}(\mathbf{x}) N_0\right) = \frac{\alpha}{\alpha + \beta} c_g N_0 - c_l N_0^2,$$

with the total tumor cell density N_0, a velocity $\mathbf{u}$, and a diffusion coefficient $\mathbb{D}_T$.

The macroscopic parameters $\mathbb{D}_T$ and $\mathbf{u}$ are computed from patient specific DTI data and are spatially varying. We observe regions where the system is diffusion dominated and regions where it is drift dominated. Numerical simulations of this non-linear degenerated parabolic equation with spatially varying anisotropic tensors are performed using first order discontinuous Galerkin (dG) scheme in space and an implicit Euler scheme in time. For the dG scheme we have chosen locally mass conservative WIPG scheme. The non-linearities are handled using an outer Newton scheme for each time step. The numerical simulations are implemented using the DUNE framework [1].

Using DTI data of a young healthy male we simulate the growth of a highly localised tumor. Compared to pure diffusion based models, the tumor shapes are much more structured, and we clearly observe preferential growth along the white matter tracks. This approach illustrates how a full pipeline from patient specific data to individual simulation results can work.

References

[1] Bastian, P., Blatt, M., Dedner, A., Engwer, C., Klöfkorn, R., Kornhuber, R., Ohlberger, M., Sander, O.: *A generic grid interface for parallel and adaptive scientifc computing. Part II: Implementation and tests in DUNE.* Computing **82**, 121-138 (2008)

[2] Engwer, C., Hillen, T., Knappitsch, M., Surulescu, C.: *Glioma follow white matter tracts; a multiscale dti-based model.* Journal of Mathematical Biology, to appear.

[3] Engwer, C., Knappitsch, M., Surulescu, C.: *A multiscale model for glioma spread including cell-fibre interactions and proliferation.* Technical report, Universität Münster (2014)

[4] Hillen, T.:*On the L^2-moment closure of transport equations: the general case.* Discrete and Continuous Dynamical Systems - Series B **5**, 299-318 (2005)

[5] Hoek, K.S., Eichhiff, O.M., Schlege, N.C., Döbbeling, U., Hemmi, S., Dummer, R.: *In vivo switching of human melanoma cells between proliferative and invasive states.* Cancer Res. **68**, 650-656 (2008)

[6] Kelkel, J., Surulescu, C.: *A multiscale approach to cell migration in tissue networks.* Mathematical Models and Methods in Applied Sciences **23** (2012)

A Stochastic Multiscale Model for Acid Mediated Cancer Invasion

Sandesh Athni Hiremath

(joint work with Christina Surulescu)

Cancer research is not only a fast growing field involving many branches of science, but also an intricate and diversified field rife with anomalies. One such anomaly is the consistent reliance of cancer cells on glucose metabolism for energy production even in a normoxic environment. glycolysis is an inefficient process for energy

production and used normally only during hypoxic conditions. So it is somehow paradoxical for cancer cells to rely on such mechanism, given their high demand for energy (e.g., for proliferation). An emerging conjecture aiming to explain this behavior is that cancer cells preserve this aerobic glycolytic phenotype for its use in invasion and metastasis. As per authors knowledge, Gatenby [3] was the first to use this hypothesis to model cancer invasion. However, no intracellular dynamics were taken into account. Although, the papers [11] and [12] include intracellular mechanisms attributing to the reverse pH gradient of tumor microenvironment, they completely neglect spatial dynamics. We shall build upon the above models and [8] to propose a new model for cancer invasion depending on the dynamics of extra and intracellular protons. Since intracellular processes are not only highly intricate but also random, we include a noise functional in the intracellular proton dynamics, which altogether culminates in a stochastic multi-scale model having the following form:

$$\begin{aligned}
\partial_t H_i &= -T(H_i, H_e) + S_1(v) - Q(H_i) + H_i F(\chi_t) \\
\partial_t H_e &= T(H_i, H_e) - S_2(v) H_e + \Delta H_e \\
\partial_t C &= \Lambda_1(H_i)\omega_1 C(1 - \eta_1 C - \eta_2 N) + \nabla.(D(C, N)\nabla C) \\
\partial_t N &= -\Lambda_2(H_e)\omega_2 CN,
\end{aligned}$$

where

(1) H_i is the intracellular proton concentration of cancer cells.
(2) H_e is the extracellular proton concentration due to cancer cells.
(3) C is the cancer cell density.
(4) N is the normal cell density.
(5) χ_t is a stochastic process representing noise.

In case of a growing and decaying type of proliferation function $\Lambda_1(H_i)$ (which is biologically motivated) numerical simulations indicate that, due to the large perturbations in H_i induced by some sample paths of the noise functional $F(\chi_t)$, cancer cells may exhibit a behavior of dormancy and even extinction. Although, monte-carlo average of the sample paths predicts the invasive behavior of the cancer cells, individual sample paths sheds light on the hidden struggle of cancer cells to survive in extreme pH conditions.

We also analyze the wellposedness of the model and show the boundedness and existence of the weak solution for a finite 2D domain and for finite time interval.

References

[1] Boyer, Tannock: *Regulation of intracellular ph in tumor cell lines: Influence of microenvironmental conditions.* Cancer Research.

[2] Casey, Grinstein, Orlowski: *Sensors and regulators of intracellular ph.* Nature Review Molecular Cell Biology (2010)

[3] Gatenby, R.A., Gawlinski, E.T.: *A reaction-diffusion model of cancer invasion.* Cancer Research (1996)

[4] Hanahan, Weinberg: *Hallmarks of cancer:the next generation.* Cell (2011)

[5] Jentzen, Kloeden: *Pathwise taylor schemes for random ordinary differential equations. rm BIT Numerical Mathematics (2009)*

[6] Lagadic, Huc, Lecureur: *Alterations of intracellular ph homeostasis in apoptosis: origins and roles.* Cell Death Differ, Nature Pub (2004)
[7] Lee, Tannock: *Heterogeneity of intracellular ph and of mechanisms that regulate intracellular ph in populations of cultured cells.* Cancer Res (1998)
[8] Märkl, C., Meral, G., Surulescu, C.: *Mathematical analysis and numerical simulations for a system modeling acid mediated tumor cell invasion.* International Journal of Analysis (2013)
[9] Shrode, L.D., Tapper, H., Grinstein, S.: *Role of intracellular ph in proliferation, transformation, and apoptosis.* Journal of Bioenergetics and Biomembranes (1997)
[10] Webb, Chimenti, Jacobson, Barber:*Dysregulated ph: a perfect storm for cancer progression.* Nature Review Cancer (2011)
[11] Webb, Sherratt, Fish: *Mathematical modelling of tumor acidity: Regulation of intracellular ph.* Journal of Theoretical Biology (1999)
[12] Webb, Sherratt, Fish: *Alterations in proteolytic activity at low ph and its association.* Clin. Exp. Metastasis (1999)

Keller-Segel systems with critical diffusion

Philippe Laurençot

The aim of this talk is to review some properties of solutions to the Keller-Segel system

$$\partial_t u = \mathrm{div}\,(\nabla A(u) - u\nabla v)\ , \quad t>0\ ,\ x\in\mathbb{R}^d\ , \tag{1}$$

$$\tau\partial_t v = \Delta v - \alpha v + u\ , \quad t>0\ ,\ x\in\mathbb{R}^d\ , \tag{2}$$

$$(u,\tau v)(0) = (u_0,\tau v_0)\ , \quad x\in\mathbb{R}^d\ , \tag{3}$$

with a particular focus on the critical diffusion case $A(u)=u^{2(d-1)/d}$. In (1), u denotes the density of cells which evolves under the combined effect of diffusion which spreads the cells in space and chemotaxis which induces a biased movement of the cells towards high gradients of the chemoattractant with concentration v. According to (2) the latter is produced by the cells and diffuse in space while being degraded at rate $\alpha\ge 0$. Other data in (1)-(3) are the space dimension $d\ge 2$, $\tau\ge 0$, the (possibly nonlinear) diffusion coefficient A' which is a non-negative function, and the initial conditions which are assumed to be smooth and satisfy

$$u_0\in L^1(\mathbb{R}^d;(1+|x|^2)\,dx)\ ,\ u_0\ge 0\ ,\quad v_0\in L^1(\mathbb{R}^d)\cap H^1(\mathbb{R}^d)\ ,\ v_0\ge 0\ . \tag{4}$$

Assuming for simplicity that

$$A(r)=r^m \quad \text{for some} \quad m\ge 1\ , \tag{5}$$

different qualitative behaviors of solutions to (1)-(3) are expected according to the value of m and can be roughly summarized as follows:

- **(i)** if $m>m_c:=2(d-1)/d$, then solutions exist globally,
- **(ii)** if $m\in[1,m_c)$, then solutions exist globally for suitably small initial data,
- **(iii)** if $m\in[1,m_c)$, then solution blow up in finite time for suitably large initial data,

(iv) if $m = m_c$, a further threshold parameter appears, namely the mass $M_0 := \|u_0\|_1$ of the initial condition for u, and separates two different behaviors: there is a critical value $M_c(d) > 0$ of the mass such that the solutions exist globally if $M_0 \in [0, M_c(d)]$ and, given any $M_0 > M_c(d)$, there are initial data (u_0, v_0) satisfying $\|u_0\|_1 = M_0$ and such that the corresponding solution (u, v) to (1)-(3) blows up in finite time.

It is worth pointing out that, in contrast to the critical case $m = m_c$, there are solutions blowing up in finite time for $m \in [1, m_c)$ for all positive values M_0 of the mass of the initial condition u_0.

When $\tau = 0$, that the above picture is true is by now well-known but that it is true as well for $\tau > 0$ was only established rather recently, in particular the occurrence of finite blowup as depicted in **(iii)**, see [CS12], [CS14], [MWxx], [Wi13]. Concerning the critical case $m = m_c$ with $\tau = 0$, the existence of a critical mass $M_c(2) = 8\pi$ is known for a long time in space dimension 2 and is proved in [BCL09], [ST09a], [ST09b] in higher space dimensions $d \geq 3$. An interesting connection with functional inequalities (the logarithmic Hardy-Littlewood-Sobolev inequality if $d = 2$ and a modified Hardy-Littlewood-Sobolev inequality if $d \geq 3$) is established in [BCL09], [DP04]. Additional results have been obtained when $m = m_c$ and $\tau = 0$:

(1) Existence and stability of integrable self-similar solutions with mass in the range $(0, M_c(d))$.
(2) Existence and stability of steady states with critical mass $M_c(d)$, $d \geq 2$.
(3) Existence and non-existence of integrable self-similar solutions.
(4) Identification of a stable and non-self-similar blowup regime for initial data with mass in $(M_c(2), M_c(2) + \delta)$ for δ sufficiently small.

When $m = m_c$ and $\tau > 0$, the results obtained so far are sparser and include:

(1) Global existence of solutions if $M_0 \in (0, M_c(d))$ [BL13], [CC08], [Mi13].
(2) Finite time blowup for radially symmetric solutions in space dimension two [MWxx].
(3) Existence of global (self-similar) solutions with a mass greater than $M_c(2) = 8\pi$ [BCD11].

References

[BCD11] Biler,P., Corrias, L., Dolbeault, J.: *Large mass self-similar solutions of the parabolic-parabolic Keller-Segel model of chemotaxis.* J. Math. Biol., 63, 1-32 (2011)

[BCL09] Blanchet, A., Carrillo, J.A., Laurençot, Ph.: *Critical mass for a Patlak-Keller-Segel model with degenerate diffusion in higher dimensions.* Calc. Var. Partial Differential Equations, 35, 133–168 (2009)

[BL13] Blanchet, A., Laurençot, Ph.: *The parabolic-parabolic Keller-Segel system with critical diffusion as a gradient flow in* $\mathbb{R}^d$, $d \geq 3$. Comm. Partial Differential Equations, 38, 658–686 (2013)

[CC08] Calvez, V., Corrias, L.: *The parabolic-parabolic Keller-Segel model in* $\mathbb{R}^2$. Commun. Math. Sci., 6, 417–447 (2008)

[CS12] Cieślak, T., Stinner, C.: *Finite-time blowup and global-in-time unbounded solutions to a parabolic-parabolic quasilinear Keller-Segel system in higher dimensions.* J. Differential Equations, 252, 5832–5851 (2012)

[CS14] Cieślak, T., Stinner, C.: *Finite-time blowup in a supercritical quasilinear parabolic-parabolic Keller-Segel system in dimension* 2. Acta Appl. Math., 129, 135-146 (2014)

[DP04] Dolbeault, J., Perthame, B.: *Optimal critical mass in the two-dimensional Keller-Segel model in* $\mathbb{R}^2$. C. R. Math. Acad. Sci. Paris, 339, 611–616 (2004)

[Mi13] Mizoguchi, N.: *Global existence for the Cauchy problem of the parabolic–parabolic Keller–Segel system on the plane.* Calc. Var. Partial Differential Equations, 48, 491–505 (2013)

[MWxx] Mizoguchi, N., Winkler, M.: *Blow-up in the two-dimensional parabolic Keller-Segel system.* Preprint

[Na95] Nagai, T.: *Blow-up of radially symmetric solutions to a chemotaxis system.* Adv. Math. Sci. Appl., 5, 581–601 (1995)

[ST09a] Suzuki, T., Takahashi, R.: *Degenerate parabolic equation with critical exponent derived from the kinetic theory. I. Generation of the weak solution.* Adv. Differential Equations, 14, 433–476 (2009)

[ST09b] Suzuki, T., Takahashi, R.: *Degenerate parabolic equation with critical exponent derived from the kinetic theory. II. Blowup threshold.* Differential Integral Equations, 22, 1153–1172 (2009)

[Wi13] Winkler, M.: *Finite-time blow-up in the higher-dimensional parabolic–parabolic Keller–Segel system.* J. Math. Pures Appl. (9), 100, 748–767 (2013)

A Review of Possible Applications Related to Cell-Extracellular Matrix Interaction

Luigi Preziosi

From the biological point of view, it is nowadays recognized that the different interactions of the cells with the extracellular matrix (ECM) play a fundamental role both in cell motion and in tumour and tissue development. On the other hand very little is done from the modelling point of view in spite of the importance that such interactions can have in medicine and in tissue engineering.

For instance, probably due to its importance in bacterial motion and to the number of interesting examples in that area, many mathematical models focus on chemotaxis, i.e., the motion toward regions with higher concentrations of a soluble chemoattractant, some on haptotaxis, i.e., the motion toward regions with higher concentrations of cellular adhesion sites or substrate-bound chemoattractant, but almost none focused on durotaxis, i.e., the motion toward regions with a higher rigidity of the subtratum. On the other hand, it is known [8] that when the substratum is heterogeneous from the mechanical point of view, cells tend to move away from softer regions toward stiffer regions. Also cells move towards stretching forces and compressive forces.

There are two processes involved in the response of cells to mechanical cues: mechanosensing and mechanotransduction. The former has to do with the way cells sense the mechanical forces around, which is mediated by the opening or closing of suitable ion channels and by the complex interplay among the actin cytoskeleton, the adhesion complexes, the transmembrane adhesion protein (e.g., the integrin family) and the ECM. Understanding, modeling and reproducing mechanosensitive devices in vitro is fundamental to build sensors, e.g., pressure, shear, and tactile sensors.

The latter has to do with the response of the cells to mechanical cues. This can be done either directly, by the expression of genes in the nucleus that is pulled by the actin cytoskeleton, or through the activation of several chemical pathways.

It is known (see, for instance [1], [7]) that cancer is related to the loss of contact inhibition from its beginning and that ECM stifffness and cell tensile stress influence both proliferation and death. In addition at later stages cancer development is characterized on one hand by the activation of matrix degrading enzymes pathways that cause the rapture of basement membranes, and on the other hand by the excessive production of ECM that trigger the invasion of the surrounding tissue by tumour cells.

In addition, many diseases are related to incorrect mechanotransduction and therefore the understanding and the mathematical modelling of mechanotransduction pathways would be of great importance. For instance, [6]

- Atrial fibrillation might be due an abnormal conversion of mechanical stress into intracellular gradient of electrical activity;
- Intimal hyperplasia can be related to the stretch activated signalling cascades due to the presence of stents and grafts;
- Scleroderma and diabetic nephropathy is due to an abnormal accumulation of ECM;
- Glomerulosclerosis is due to the stretching of mesangial cells via ECM and integrins due to glomerular hypertension;
- Enphysema is due to enhanced ECM breakdown;
- Pulmonary fibrosis and all other fibrosis characterizing many aging diseases are due to the excessive production of ECM.

Among the previous examples only some papers devoted to cancer modelling have paid attention to the effect of the microenvironment and on the possibility of healing tumours by normilizing the surrounding environment (see, for instance, [2], [5]).

Understanding the mechanical interplay between cells and the surrounding envirronment is also of crucial importance in tissue engineering. In fact, the fate of stem cells depend not only on genetic and molecular mediators, e.g., growth factors and transcription factors, but also on the interactions they have with the surroundings, which include ECM elasticity and morphology and ECM mediated stress.

One amazing evidence of the importance of the mechanical characteristics of the environment is the observation that stem cells differentiate in different cell types according to the stiffness of the substratum [1]. For instance, they are likely to become

- neurons if the ECM stiffness well below 1 kPa;
- adipocytes in the range 0.1-2 kPa;
- skeletal muscle cells in the range 3-20 kPa;
- osteoblasts above 20 kPa.

It seems that this is one of the reason of the unsuccess in using stem cells to cure neudegenerative diseases. In fact, scars in the neural tissue are too stiff for the stem cells to be neurogenic.

Stem cell fate is also sensitive to the morphology of the adhesion sites, e.g., smaller areas are more adipogenic while larger areas are more neurogenic or osteogenic depending on the substrate stiffness [4].

The common aim of all these observations is the construction of proper stem cell niche to culture them and to govern their differentiation in order to build tissues in vitro. In this respect, a valuable support could be given by the development of proper mathematical and mechanical models.

Another area of interest is the optimization of scaffolds in which cells can grow to build artificial tissues. One of the project we were involved had the aim of identify the morphological characteristics of an artificial scaffold able to enhance the motility of fibroblasts and keratocytes. This was needed in order to speed up wound healing, in particular for burns.

This requires the undestanding of the migration strategies and the aspects favouring or hampering cell motion. It was found that the elasticity of the nucleus plays a crucial role as well as the ability of the cell to actively exert traction forces via the adhesion sites. We then presented an energetic approach that allowed to identify a criterium for a cell to pass through a regular network of fibres [3]. The criterium compares the ratio of some parameters related to the traction force the cell can exert on the ECM and the density of active adhesion sites versus the nucleus rigidity with a function of the ratio of the nucleus versus microchannel size. A cellular Potts model allowed then to prove that the optimal size of the microchannel is a bit larger than the diameter of the nucleus [9], [10] and smaller than the size of the nucleus.

References

[1] Butcher, D.T., Alliston, T., Weaver, V.: *A tense situation: forcing tumour progression.* Nat. Rev. Cancer **9**, 108-122 (2009)

[2] Chaplain, M., Graziano, L., Preziosi, L.: *Mathematical modelling of the loss of tissue compression responsiveness and its role in solid tumour development.* Math. Med. Biol. **23**, 197-229, (2006)

[3] Giverso, C., Grillo, A., Preziosi, L.: *Influence of nuclear deformability on cell entry into cylindrical structures.* Biomech. Model. Mechanobiol. **13**, 481-502 (2014)

[4] Guilak, F., Cohen, D.M., Estes, B.T., Gimble, J.M., Liedtke, W., Chen, C.S.: *Control of stem cell fate by phisical interactions the the extracellular matrix.* Cell Stem Cell **5**, 1726 (2009)

[5] Hohme, S., Drasdo, D.: *Biomechanical and nutrient controls in the growth of mammalian cell populations.* Math. Popul. Studies **17** 166-187 (2010)

[6] Ingber, D.: *Mechanobiology and diseases of mechanotransduction.* Annals Medicine **35**, 1-14 (2009)

[7] Kass, J., Erler, M., Dembo, M., Weaver, V.: *Mammary epithelial cell: Influence of ECM composition and organization during development and tumorigenesis.* Int. J. Biochem Cell Biol **39**, 1987-94 (2007)

[8] Lo, C.M., Wang, H.B., Dembo, M., Wang, Y.L.: *Cell movement is guided by the rigidity of the substrate.* Biophys. J. **79**, 144152 (2000)

[9] Scianna, M., Prezisi, L., Wolf, K.: *A Cellular Potts Model simulating cell migration on and in matrix environments.* Math. Biosci. Engng. **10**, 235–261 (2013)
[10] Scianna, M., Preziosi, L.: *Modeling the influence of nucleus elasticity on cell invasion in fiber networks and microchannels.* J. Theor. Biol. **317**, 394-406 (2013)

On a multiscale model involving cell contractivity and its effects on tumor invasion

Christian Stinner
(joint work with Gülnihal Meral, Christina Surulescu, Michael Winkler)

Invasion of tumor cells is an important step for metastasis and is governed by several subcellular processes. A number of them affect the contractivity, by which we describe the ability of the cancer cells to adapt their shape and orientation according to the surrounding tissue. In [1], we propose a multiscale model focusing on the influence of the cell contractivity on tumor cell migration. It takes into account both the subcellular (microscopic) level, where changes of contractivity are initiated, and the macroscopic level of the cell population and aims to assess their interdependence. More precisely, our model accounts on the microscale for integrin binding to soluble and insoluble components present in the peritumoral environment, which is seen as the onset of biochemical processes leading to changes in the cell's ability to contract and modify its shape. On the macroscale of the cancer cell population this leads to modifications in the diffusion and haptotaxis performed by the tumor cells and implicitly to changes in the tumor environment.

Denoting by c and v the densities of cancer cells and tissue fibers of the extracellular matrix (ECM), respectively, by l the concentration of proteolytic residuals (resulting from the degradation of ECM by cancer cells), by y_1 and y_2 the concentrations of integrins bound to ECM fibers and proteolytic residuals, respectively, and by κ the contractivity function, we arrive at the following PDE-ODE system which involves in particular haptotactic and chemotactic cross-diffusion as well as a temporal delay (see [1]):

$$
(1)\qquad \begin{cases} \partial_t c = \nabla \cdot \left(\frac{D_c \kappa}{1+\frac{cv}{K_c K_v}} \nabla c \right) - \nabla \cdot \left(\frac{D_H \kappa v}{K_v + v} c \nabla v \right) - \nabla \cdot \left(\frac{D_k}{1+\frac{cl}{K_c \lambda}} c \nabla l \right) \\ \qquad\quad + \mu_c c \left(1 - \frac{c}{K_c} - \eta_1 \frac{v}{K_v} \right), \\ \partial_t v = -\delta_v c v + \mu_v v \left(1 - \eta_2 \frac{c}{K_c} - \frac{v}{K_v} \right), \\ \partial_t l = \alpha \Delta l + \delta_l c v - \beta l, \\ \partial_t y_1 = k_1 (R_0 - y_1 - y_2) v - k_{-1} y_1, \\ \partial_t y_2 = k_2 (R_0 - y_1 - y_2) l - k_{-2} y_2, \\ \partial_t \kappa = -q\kappa + \frac{M y_1(t-\tau)}{R_0 + y_2(t-\tau)} \end{cases}
$$

in $(0,T) \times \Omega$ endowed with homogeneous Neumann boundary conditions, where $\Omega \subset \mathbb{R}^n$ is a bounded smooth domain and $n \leq 3$.

We provide the local well-posedness of (1) by using a fixed point argument and the method of steps (see [1]). Furthermore, we prove the existence of a global solution within a suitable concept of weak solutions (see [2]). The proof of the global existence is based on the construction of a functional which inter alia involves the cell and tissue densities in the diffusion and haptotaxis terms, respectively, and which has a quasi-dissipative property. The latter is used as a starting point for the derivation of a series of integral estimates finally allowing for the construction of a generalized solution to (1) as the limit of solutions to suitably regularized problems. We further present numerical simulations to illustrate the effect of contractivity on the migration of cancer cells in our model (see [1], [2]).

References

[1] Meral, G., Stinner, C., Surulescu, C.: *On a multiscale model involving cell contractivity and its effects on tumor invasion.* Preprint TU Kaiserslautern (2013), submitted.

[2] Stinner, C., Surulescu, C., Winkler, M.: *Global weak solutions in a PDE-ODE system modeling multiscale cancer cell invasion.* SIAM Journal on Mathematical Analysis, to appear

Modelling Brain Tumor Spread Using an Anisotropic PDE Model

Amanda Swan

(joint work with Thomas Hillen)

Brain tumours of glial cell origin, or gliomas, are currently one of the most difficult cancers to treat. Mean survival with treatment is only about a year. Brain tissue architecture offers many challenges for treatment, thus leaving lots of room for potential improvement. Currently, standard treatment involves surgery when possible, with radiation being administered uniformly beyond the visible tumour boundary. We suggest that if a mathematical model could predict the cancer cell distribution beyond what is visible, a more appropriate treatment boundary could be prescribed.

The first model of this type was proposed by Swanson [1] in 2000. This model used diffusion to model cell movement, allowing for spatial heterogeneity of the diffusion coefficient. It was proposed that the rate of diffusion was higher in the white matter tracts. It was later discovered that cells not only travelled faster in the white matter tracts, but that they actually travelled along them. Our model thus incorporates anisotropy, where we allow the diffusion coefficient to vary both spatially and directionally. We begin with a transport equation describing individual cell movement at a mesoscopic scale, then perform a parabolic scaling to obtain the macroscopic diffusion equation [2], [3]. After adding a logistic growth term with growth rate r, we obtain

$$u_t(x,t) = \nabla\nabla(D_c(x)u(x,t)) + ru(x,t)(1-u(x,t)),$$

where $u(x,t)$ gives the cancer cell density at location x and time t, and $D_c(x)$ is the anisotropic diffusion tensor at location x. This is obtained using Diffusion Tensor Imaging (DTI), which measures rates of diffusion in the brain.

Finally, the results of our model simulations are compared to real patient data. Preliminary results are promising, indicating that our model could help doctors to prescribe radiation treatment regions based on the cancer cell density beyond the visible tumour boundary.

References

[1] Swanson, R.E., Alvord Jr., E.C., Murray, J.D.: *A Quantitative Model for Differential Motility of Gliomas in Grey and White Matter.* Cell Proliferation, 33, 317–329 (2000)

[2] Painter, K.J., Hillen, T.: *Mathematical modelling of glioma growth: the use of Diffusion Tensor Imaging (DTI) data to predict the anisotropic pathways of cancer invasion.* Journal of Theoretical Biology, 323, 25–39 (2013)

[3] Engwer, C., Hillen, T., Knappitsch, M.P., Surulescu, C.:*A DTI-Based multi scale model for glioma growth including cell-ECM interactions.* Submitted

[4] Cobzas, D., Mosayebi, P., Murtha, A., Jagersand, M.: *Tumor invasion margin on the Riemannian space of brain fibers.* MICCAI (2009)

Global dynamics of a coupled chemotaxis-haptotaxis system for cancer invasion

Youshan Tao

(joint work with Michael Winkler)

This talk addresses a coupled chemotaxis-haptotaxis system modeling cancer cell invasion of surrounding tissue (cf. [1]), which describes the interplays between the cancer cell density, the concentration of a matrix-degrading enzyme and the density of extracellular matrix (ECM). In addition to random movement, cancer cells are supposed to bias their movement both towards increasing concentrations of urokinase plasminogen activator by chemotaxis, and towards increasing densities of the non-diffusible ECM through detecting the macromolecules adhered therein by haptotaxis. It is assumed that the cancer cells undergo birth and death in a logistic manner, competing for space with the ECM. The MDE is assumed to be produced by cancer cells, and to diffuse and decay, whereas the ECM is assumed to be degraded upon contact with MDE. We first discuss the global existence and boundedness of the solutions to the system for appropriate parameter conditions (cf. [9] and [10]). Then we consider the dominance of chemotaxis whenever the initial ECM density is "small" in certain sense (cf. [9]). We next study the asymptotic behavior of solutions when the initial cell density has a positive lower bound in addition to some smallness assumption on initial ECM density (cf. [8]). Finally, we briefly review some related results for haptotaxis-only system (cf. [11] [4], [3], [6]) and for coupled chemotaxis-haptotaxis system (cf. [7], [2], [5]).

References

[1] Chaplain, M.A.J., Lolas, G.: *Mathematical modelling of cancer invasion of tissue: dynamic heterogeneity.* Net. Hetero. Med. **1**, 399-439 (2006)

[2] Hillen, T., Painter, K.J., Winkler, M.: *Convergence of a cancer invasion model to a logistic chemotaxis model.* Math. Mod. Meth. Appl. Sci. **23**, 165-198 (2013)

[3] Liţcanu, G., Morales-Rodrigo, C.: *Asymptotic behaviour of global solutions to a model of cell invasion.* Math. Mod. Meth. Appl. Sci. **20**, 1721-1758 (2010)

[4] Marciniak-Czochra, A., Ptashnyk, M.: *Boundness of solutions of a haptotaxis model.* Math. Mod. Meth. Appl. Sci. **20**, 449-476 (2010)

[5] Stinner, C., Surulescu, C., Winkler, M.: *Global weak solutions in a PDE-ODE system modeling multiscale cance cell invasion.* SIAM J. Math. Anal., to appear

[6] Tao, Y.: *Global existence for a haptotaxis model of cancer invasion with tissue remodeling.* Nonlinear Analysis: RWA **12**, 418-435 (2011)

[7] Tao, Y., Winkler, M.: *Energy-type estimates and global solvability in a two-dimensional chemotaxis-haptotaxis model with remodeling of non-diffusible attractant.* Journal of Differential Equations, doi: 10.1016/j.jde.2014.04.014, to appear

[8] Tao, Y., Winkler, M.: *Boundedness and stabilization in a multi-dimensional chemotaxis-haptotaxis model.* Proceeding of the Royal Society of Edinburg, Section: A Mathematics, to appear

[9] Tao, Y., Winkler, M.: *Dominance of chemotaxis in a chemotaxis-haptotaxis model.* Nonlinearity, to appear

[10] Tello, J.I., Winkler, M.: *A chemotaxis system with logistic source.* Commun. Partial Differential Equations **32**, 849-877 (2007)

[11] Walker, C., Webb, G.F.: *Global existence of classical solutions for a haptotaxis model.* SIAM J. Math. Anal. **38**, 1694-1713 (2007)

On a mathematical model of tumor growth based on cancer stem cells with chemotactic sensitivity

José Ignacio Tello del Castillo

We consider a simple mathematical model of tumor growth based on cancer stem cells. The model consists of four differential to describe the evolution of different subpopulations of cells: cancer stem cells (CSC), progenitor cells, differentiated cells and dead cells. The problem is considered in a moving boundary domain. The model is considered for the early stage of the cancer when the tumor size is small and necrosis is not present. Experiments show that the growth of the tumor at this stage follows an exponential growth. CSC?s mitosis may originate two CSC or two progenitor cells through symmetric division or one of each class through asymmetric division. Regulation of symmetric or asymmetric division is a complex process which depends on a range of conditions, as concentration of cytokines, growth factors etc, existing in the microenvironment of the cell. The regulation process still posseses several steps not well understood. The system includes nonlocal terms of integral type in the coefficients to modelize the process. Under some restrictions in the parameters we study the stability of the homogeneous steady state. The analysis uses a sub and super solutions approach based on a comparison principle.

References

[1] Molina-Pena, R., Alvarez, M.M.: *A simple mathematical model based on the cancer stem cell hypothesis suggests kinetic commonalities in solid tumor growth.* PLoS ONE, 7 (2012)

[2] Negreanu, M., Tello, J.I.: *On a comparison method to Reaction-diffussion systems and its applications to chemotaxis.* Discrete and Continuous Dynamical Systems-Series B, 18 (10), 2669 - 2688 (2013)

[3] Tello, J.I.:*On a mathematical model of Tumor Growth based on cancer stem cells.* Mathematical Biosciences and Engineering, 10 (1), 263-278 (2013)

Challenges in modeling interacting and migrating cell populations

Anja Voss-Böhme

Cancers have been proposed to result from defects of tissue organization. To deduce the consequences of existing hypotheses on carcinogenesis and to provide a basis for experimental testing and theoretical understanding, mathematical models are essential. However, there is considerable freedom in the choice of the mathematical model and the criteria for appropriate model selection are not well-defined. Cell-based models, such as interacting particle systems (IPS) and probabilistic cellular automata (PCA), provide a spatio-temporal framework to describe and analyze interacting cell populations in developing tumors. Such models have been successfully applied to study characteristic collective cell behaviors that result from specific cellular interaction rules. There are considerable differences in the construction of these models, in particular concerning the implementation of cell motility. In the talk, we compare exemplary IPS and PCA models where one cell occupies one lattice node to spatially more resolved models, such as the cellular Potts model. We will expose the mechanistic structures of these models and discuss their implications for modeling and mathematical analysis.

References

[1] Voss-Böhme, A.: *Multi-Scale Modeling in Morphogenesis: A Critical Analysis of the Cellular Potts Model.* PLoS 7(9): e42852 (2012)

[2] Peruani, F., Deutsch, A., Klauss, T., Voss-Böhme, A.: *Traffic jams, gliders and band in the quest for collective motion of self-propelled particles.* Physical Review Letters, 106, 128101 (2011)

[3] Voss-Böhme, A., Deutsch, A.: *The cellular basis of cell sorting kinetics.* Journal of Theoretical Biology, 263 (4), 419-436 (2010)

[4] Klauß, T., Voss-Böhme, A.: *Modelling and Simulation by Stochastic Interacting Particle Systems.* Mathematical Modelling of Biological Systems, vol. II, 353-367 (2008)

Principles of cell migration in physiology and cancer

Katarina Wolf

Cell migration is a complex process that takes place during a wide range of functions in the organism, reaching from cell positioning during embryogenesis to immune response and tissue regeneration, and can be re-activated during disease, such as in cancer. Cell locomotion during both normal and malignant processes is underlaid by several levels of complexity which are: (A) locomotion-preceding basic requirements1, (B) additional cell type- and environmental context-specific determinants defining the mode of migration (amoeboid, mesenchymal, collective) and (C) molecular and functional change of these determinants resulting in transition between migration modes (=plasticity)2-4. In general, normal and malignant cell migration share the same basic principles; however, whereas homeostatic cell migration is tightly regulated in a mostly transient manner, neoplastic migration represents an exaggerated form of normal migration, with deregulated upregulation and activation of pro-migratory molecules and extracellular environment components. (A) The very basic requirements for cells to change location are (i) coordinated F-actin polymerization and depolymerization underlying repeated protrusion at the leading edge and retraction of the trailing edge, (ii) gradients of water flux, ion concentration and pH, and (iii) physical interaction with the extracellular surrounding of different dimensionality, structure, and spacing5. F-actin-mediated protrusion takes place after extracellular stimulation such as by growth factor- or chemokine- binding, small GTPase (Rac or Cdc42) and PIP2 activation and subsequent actin nucleation and branching mediated by WAVE/WASP and Arp 2/3 complex, together with ADP-mediated filament disassembly6. This can result in the formation of protrusion structures such as lamellipodia, pseudopodia, filopodia, invadopodia, or blebs7,8. Cell retraction takes place when the rear end slides forward by Rho/ROCK- or calcium/calmodulin- mediated actomyosin contraction where F-actin filaments slide against eachother by myosin light chain activation3. In newer concepts, protrusion and retraction are additionally driven by local hydrostatic pressures regulated by aquaporins and active ion channels (such as leading edge-localized Na+H+ exchangers) causing water permeation and extrusion and thus polarized volume change9-11. Often in parallel to ion exchange, protons are pumped out which causes a local pH increase in the leading edge region and thus a negative pH gradient along the length axis of the cell12. In line with this, alkalization of the leading edge causes actin branching and growth13, whereas acidification of the trailing edge supports calmodulin-dependent actomyosin contraction12. Finally, interaction to surrounding substrate is mediated by either adhesion, i.e. strong attachment via integrins or low adhesion via glycosaminoglycans to extracellular matrix14, or friction induced by confinement5,9,15. Interestingly, whereas for migration over a smooth surface protrusion-contraction cycles, ion channel activity and adhesion is required3,9,16, in porous three-dimensional (3D) networks, i.e. fibrillar collagen lattices, non-adherent cells, i.e. leukocytes, can move by means of protrusion and contraction only (amoeboid migration) 17,18, and in smooth confining channels cells move even independent of protrusion/ contraction

but by hydrostatic pressure change9,16. These growing amount of knowledge will feed into the classical model for cell migration consisting of polarization, actin-mediated protrusion, adhesion and acto-myosin contraction for forward locomotion over a surface1. (B,C) In contrast to laboratory conditions, cell migration in the multicellular organism takes mainly place within complex extracellular matrix (ECM) environments. Hence basic concepts on cell migration have been extended into the 3D context distilling out a number of cell- or ECM-derived parameters that, together, determine amoeboid (roundish, highly deformable, low adhesive), mesenchymal (elongated, adhesive, proteolytic) or collective (multicell clusters) cell migration, mostly in the context on cancer cell migration2,3. As an example, while for 2D migration adhesion is cruicial, in a 3D environment integrin-mediated adhesion becomes dispensable and might be replaced by ECM-directed friction forces of protruding and contracting cells (i.e. leukocytes)17. Further, structural substrate spacing becomes important in terms of the cells ability to either deform and adapt (amoboid), or to proteolytically degrade ECM components to shape a migration path of least resistance (mesenchymal) 19,20. Among a growing list of additional determinants (cell deformability, extracellular matrix stiffness, hypoxia, nutrient deprivation, acidity, micro-RNA), Rho/Rac activity controls cell rounding or elongation21,22. Further, the presence of cell-cell junctions decides over single- or collective cell migration. - Obviously the up- or downregulation of such migration mode-determining molecules or -counterplayers causes reversible transitions between migration modes, such as the mesenchymal-amoeboid transion (MAT, AMT), epithelial-mesenchymal transition (EMT, MET) or collective-amoeboid transition (CAM) (2,23-29 and references therein). The relevance of different migration modes and transitions for the outcome on cancer disease and patient survival rate is a matter of current research. In one of the first examples, Danen and collegues29 show that a switch from collective to single (amoeboid) movement, although reducing tumor growth, does increase systemic tumor dissemination into the lungs which would, in example, hamper surgical tumor resection and could lead to a more severe organ failure. Anticancer therapy approaches focus on tumor resection, and the inhibition of tumor proliferation by radio- or chemotherapy. However, as many cancers are resistant to such approaches, current research identifies ways to circumvent tumor resistance (or enhanced survival) by better targeted therapies, often in combination with surgery or radiotherapy. Interestingly, many of the same signaling pathways control tumor cell growth, survival and invasion together, and by for instance targeting tumor survival also invasion might be inhibited30. One example of increased tumor resistance arises from the fact that migrating tumor cells invading extracellular tissue are better protected from radiation-induced tumor apoptosis because ECM binding integrins send survival signals into the cells. In consequence, anti-beta1-integrin treatment greatly enhances radiation therapy efficacy in breast cancers31. In summary, inhibiting relevant pathways by adequate combination therapies will inhibit tumor invasion, escape, growth, and resistance together.

References

[1] Ridley, A. J. et al.: *Cell migration: integrating signals from front to back.* Science 302, 1704-1709 (2003)

[2] Friedl, P., Wolf, K.: *Plasticity of cell migration: a multiscale tuning model.* J Cell Biol 188, 11-19 (2010)

[3] Friedl, P., Wolf, K.: *Tumour-cell invasion and migration: diversity and escape mechanisms.* Nat Rev Cancer 3, 362-374 (2003)

[4] Brabek, J., Mierke, C. T., Rosel, D., Vesely, P., Fabry, B.: *The role of the tissue microenvironment in the regulation of cancer cell motility and invasion.* Cell Commun Signal 8, 22 (2010)

[5] Heuze, M. L. et al.: *Migration of dendritic cells: physical principles, molecular mechanisms, and functional implications.* Immunol Rev 256, 240-254 (2013)

[6] Pollard, T. D., Borisy, G. G.: *Cellular motility driven by assembly and disassembly of actin filaments.* Cell 112, 453-465 (2003)

[7] Nurnberg, A., Kitzing, T., Grosse, R.: *Nucleating actin for invasion. Nature reviews.* Cancer 11, 177-187 (2011)

[8] Wolf, K., Friedl, P.: *Mapping proteolytic cancer cell-extracellular matrix interfaces.* Clin. Exp. Metastasis 26, 289-298 (2009)

[9] Stroka, K. M. et al.: *Water permeation drives tumor cell migration in confined microenvironments.* Cell 157, 611-623, (2014)

[10] Karlsson, T., Bolshakova, A., Magalhaes, M. A., Loitto, V. M., Magnusson, K. E.: *Fluxes of water through aquaporin 9 weaken membrane-cytoskeleton anchorage and promote formation of membrane protrusions.* PLoS One 8, e59901, doi:10.1371/journal.pone.0059901 (2013).

[11] Martin, C., Pedersen, S. F., Schwab, A., Stock, C.: *Intracellular pH gradients in migrating cells.* Am. J. Physiol. Cell Physiol. 300, 490-495 (2011)

[12] Stock, C., Schwab, A.: *Protons make tumor cells move like clockwork.* Pflugers Arch 458, 981-992 (2009)

[13] Magalhaes, M. A. et al.: *Cortactin phosphorylation regulates cell invasion through a pH-dependent pathway.* The Journal of cell biology 195, 903-920 (2011)

[14] Schmidt, S., Friedl, P.: *Interstitial cell migration: integrin-dependent and alternative adhesion mechanisms.* Cell Tissue Res 339, 83-92 (2010)

[15] Heuze, M. L., Collin, O., Terriac, E., Lennon-Dumenil, A. M., Piel, M.: *Cell migration in confinement: a micro-channel-based assay.* Methods Mol. Biol. 769, 415-434 (2011)

[16] Balzer, E. M. et al.: *Physical confinement alters tumor cell adhesion and migration phenotypes.* FASEB journal : official publication of the Federation of American Societies for Experimental Biology, doi:10.1096/fj.12-211441 (2012)

[17] Lammermann, T. et al.: *Rapid leukocyte migration by integrin-independent flowing and squeezing.* Nature 453, 51-55 (2008)

[18] Friedl, P., Entschladen, F., Conrad, C., Niggemann, B., Zanker, K. S.: *CD4+ T lymphocytes migrating in three-dimensional collagen lattices lack focal adhesions and utilize beta1 integrin-independent strategies for polarization, interaction with collagen fibers and locomotion.* Eur. J. Immunol. 28, 2331-2343 (1998)

[19] Wolf, K. et al.: *Multi-step pericellular proteolysis controls the transition from individual to collective cancer cell invasion.* Nat. Cell Biol. 9, 893-904 (2007)

[20] Wolf, K. et al.: *Physical limits of cell migration: Control by ECM space and nuclear deformation and tuning by proteolysis and traction force.* The Journal of Cell Biology 201, 1069-1084 (2013)

[21] Pankova, K., Rosel, D., Novotny, M., Brabek, J.: *The molecular mechanisms of transition between mesenchymal and amoeboid invasiveness in tumor cells.* Cellular and molecular life sciences : CMLS 67, 63-71 (2010)

[22] Sanz-Moreno, V. et al.: *Rac activation and inactivation control plasticity of tumor cell movement.* Cell 135, 510-523 (2008)
[23] Giannoni, E. et al.: *EphA2-mediated mesenchymal-amoeboid transition induced by endothelial progenitor cells enhances metastatic spread due to cancer-associated fibroblasts.* J. Mol. Med. (Berl) 91, 103-115 (2013)
[24] Taddei, M. L., Giannoni, E., Comito, G., Chiarugi, P.: *Microenvironment and tumor cell plasticity: an easy way out.* Cancer Letters 341, 80-96 (2013)
[25] Ulrich, T. A., de Juan Pardo, E. M., Kumar, S.: *The mechanical rigidity of the extracellular matrix regulates the structure, motility, and proliferation of glioma cells.* Cancer research 69, 4167-4174 (2009)
[26] Pathak, A., Kumar, S.:*Biophysical regulation of tumor cell invasion: moving beyond matrix stiffness.* Integrative biology : quantitative biosciences from nano to macro 3, 267-278 (2011)
[27] Elson-Schwab, I., Lorentzen, A., Marshall, C. J.: *MicroRNA-200 family members differentially regulate morphological plasticity and mode of melanoma cell invasion.* PLoS One 5, doi:10.1371/journal.pone.0013176 (2010)
[28] Yilmaz, M., Christofori, G.: *Mechanisms of motility in metastasizing cells.* Mol. Cancer Res. 8, 629-642 (2010)
[29] Truong, H. H. et al.: *beta1 integrin inhibition elicits a prometastatic switch through the TGFbeta-miR-200-ZEB network in E-cadherin-positive triple-negative breast cancer.* Science signaling 7, ra15, doi:10.1126/scisignal.2004751 (2014)
[30] Alexander, S., Friedl, P.: *Cancer invasion and resistance: interconnected processes of disease progression and therapy failure.* Trends Mol. Med. 18, 13-26 (2012)
[31] Park, C. C., Zhang, H. J., Yao, E. S., Park, C. J., Bissell, M. J.: *Beta1 integrin inhibition dramatically enhances radiotherapy efficacy in human breast cancer xenografts.* Cancer Research 68, 4398-4405 (2008)

Open Discussion Problems

The participants proposed the following nine problems as discussion subjects during the workshop:

(1) Physical movability of cells through obstacles such as small pores.
(2) Mechanics of collective motion.
(3) DTI (diffusion tensor imaging) optimization, and more detailed methods such as the Q-ball.
(4) Model benchmarks to compare cell movement models.
(5) Is there a cell-free gap region between tumour and normal cells/tissue in the process of acid-mediated invasion? Mathematical modelling of the moving boundary problem.
(6) Comparison of movement strategies, individual amoeboid, individual mesenchymal, collective. Which strategy is advantageous in what situations? What are typical invasion speeds for these strategies?
(7) Are there global bounds for the chemotaxis haptotaxis model with tissue remodelling?
(8) Inverse problems in chemotaxis: How to estimate the chemotaxis sensitivity function from experimental observations?

(9) Find simple microscopic and mesoscopic models for collective motion. Identify the role of a "leader". Can collective movement develop without a leader? What macroscopic limits do result from this?

Five of these problems were chosen to be studied during the workshop. Here we report some results and ideas that were generated.

Problem 1) Physical movability through obstacles.
(Engwer, Hatzikirou, Preziosi)

Question: How is cell movement restricted by obstacles, ECM, fibres etc.?

Moving cancer cells are in general easily deformable, with the exception of the nucleus. In fact, in many cases the nucleus is the limiting component, which would prevent cells to slip through openings which are too small. The cell nucleus is deformable to some extent and cells can squeeze through openings. A static condition for cell squeezing through an obstacle was given in the literature as

$$\frac{\text{traction forces}}{\text{stiffness}} \leq f\left(\frac{R_p}{R_n}\right),$$

where R_p is the radius of an (idealized) cylindrical pore, and R_n is the radius of the cell nucleus. The function f describes the force that needs to be overcome for movement.

We would like to derive a dynamic, time dependent condition such as

$$F - hv = 0,$$

where F is the total force acting on the cell. It can be computed by integration over the cell boundary. In an ideal, cylindrical situation the force is $F = F(R_p, L)$ and L is the longest length of the cell as it squeezes through a cylinder. The function h(normal stress) is computed for an ellipsoid. Then

$$v = \frac{F(R_p, L)}{h(N)} = \begin{cases} 0 & \text{for } R_p \leq R_c. \\ 0 & R_p = \bar{R}_p \\ \text{positive} & \end{cases}$$

This means that there is no force generated if the cell radius R_c is smaller than the pore size. $\bar{R}_p$ is a smallest radius that can be passed.

Alternative way: Use a homogenization procedure, much like in porous media. For example for a well defined periodic case with clearly known pore sizes. Look at paths of minimal efforts. Random environments lead to additional challenges.

Future: Metalloproteinases could be included.

Problem 3) DTI optimization and related models.
(Engwer, Hatzikirou, Preziosi)

Diffusion tensor imaging (DTI) allows us to get an idea of the fiber geometry of brain tissue. It can, however, not distinguish fiber crossing from homogeneous tissue. An alternative method is called Q-ball measurements, which do allow to identify such crossings. However, Q-ball measurements need more effort, and they are not used in clinical practice. A question arises as to what advantage Q-ball modelling would bring, and if it is worth the additional effort. Possible, the DTI information is equally useful in daily treatment planning. To efficiently use the Q-ball we need to:

- Map Q-ball to appropriate basis functions, for example spherical harmonics. There exists one representation in the Q-ball community, which should be explored.
- Estimate the number of significant directions, or the number of significant basis functions and remove insignificant ones. This will give an efficient approximation.
- Get some information about the fiber structure from the measured Q-ball.
- Derive an effective tumor diffusion tensor, e.g., from a transport equation framework as done by Hillen et al.
- Alternatively, one could try to directly use the Q-ball information in simulations of glioma spread.

Problem 6) Comparison of movement strategies.
(Bellomo, Voss-Boehme, Surulescu, Deutsch)

Cancer cells use different strategies to advance into healthy tissue. They can move as individual amoeboid cells, where they keep a roundish morphology and squeeze through the ECM wherever there is space. If they elongate, and possibly degrade the ECM through metalloproteinases, then this movement is called mesenchymal. Finally, clusters of invading tumor cells have been observed as well, leading to the concept of collective motion. Several questions arise from these strategies:

(1) Which of these strategies is advantageous for a tumor to invade?
(2) What triggers the transitions between these modes (amoeboid ¡-¿ mesenchymal ¡-¿ collective) of movement?
(3) What dynamics arises when all three movement strategies are present?
(4) What are transport properties such as invasion speeds for these strategies?

The movement strategies can be characterized as described by Katarina Wolf in her classification table. A suitable ODE model could be used to understand the

dynamics of the transition between the strategies.

$$\begin{aligned}\frac{dA}{dt} &= (r_{aa} - r_{am} - r_{ac})A + r_{ma}M + r_{ca}C\\ \frac{dM}{dt} &= r_{am}A + (-r_{ma} + r_{mm} - r_{mc})M + r_{cm}C\\ \frac{dC}{dt} &= r_{ac}A + r_{mc}M + (-r_{ca} - r_{cm} + r_{cc})C\end{aligned}$$

where A, M, C denote cell densities for amoeboid, mesenchymal and collectively moving cell populations, respectively. The transition rates are summarized in the following table:

	A	M	C
A	r_{aa}	r_{am}	r_{ac}
M	r_{ma}	r_{mm}	r_{mc}
C	r_{ca}	r_{cm}	r_{cc}

Migration speeds and mean path lengths can be derived from appropriate spatial models (PDEs). We propose to use a spatial macroscopic equation to compare invasion speeds of a Fisher KPP model with and without haptotaxis. Thereby, the situation without haptotatixs corrresponds to amoeboid and the one with haptotaxis to mesenchymal motion. A model for collective movement can be taken from problem No 9). A PDE approach (modeling on the macrolevel) could be based on the following system:

$$\begin{aligned}\partial_t a &= \nabla \cdot (\phi_1(\rho, \mu)\nabla a) + g_1(a, m, \mu)\\ \partial_t m &= \nabla \cdot (\phi_2(\rho, \mu)\nabla m) - \nabla \cdot (\chi(\mu)\rho\nabla\mu) + g_2(a, m, \mu)\\ \partial_t \mu &= -\delta m\mu + \beta\mu(1 - \mu - \rho)\end{aligned}$$

$$\begin{aligned}\rho &= a + m\\ \phi(\rho, \mu) &= \rho^e(1 - \rho^e)\\ \rho^e &= \rho + \mu(1 - \rho)\end{aligned}$$

μ:=density of tissue fibres;
a:= density of cells performing amoeboid motion;
m:=density of cells performing mesenchymal motion.
c:=density of cells performing collective motion.
The next steps include an analysis of these models. Understanding the phase diagrams, identification of travelling waves, and finally, extensions to include integrins and other adhesion mechanisms.

Problem 7) Bounds for a haptotaxis-chemotaxis model.
(Stinner, Tao, Hiremath, Winkler, Tello)

The haptotaxis-chemotaxis model with tissue remodelling is given as

$$\begin{aligned} u_t &= \delta u - \nabla(\chi u \nabla v) - \nabla(\zeta u \nabla w) + \mu u(1-u-v) \\ 0 &= \Delta v + u - v \\ w_t &= -vw + \eta w(1 - w - \beta u) \end{aligned}$$

where u describes the cancer cells, v the chemoattractant and w the ECM. It is known that solutions in bounded 2-dimensional domains exists. The question is: In a 2-D bounded domain is $u \in L^\infty(\Omega \times (0,\infty))$?

Answer: u is bounded.
Method: Some fancy pancy L^p-estimates. This cannot be generalized to dimension 3 and higher. Moser Iteration can give us a uniform L^∞ bound.

Next question is about asymptotics. Some ideas are for $0 < \alpha < 1 < \beta$. We expect $(u, v, w) \to (1, 1, 0)$ for $t \to \infty$ for μ large enough.

Problem 9) Models for collective movement.
(Swan, Eftimie, Laurençot, Hillen)

The modelling of collective movement is in full swing. We identified several modelling approaches for collective movement, in particular in the context of swarming and social behavior. The following models can be used, and they should be compared for their ability to describe collective movement.

(1) Non-linear diffusion: We were able to use a microscopic random walk to derive the non-linear diffusion model of Laurençot: $u_t = (u^m)_{xx}$. Then the jump probabilities are

$$T^\pm = \alpha(u) = u^{m-1}.$$

This choice of jump rates means that a particles jump is more likely for larger local populations. Individuals will never move if they are alone. This gives a new interpretation of the porous medium equation in the context of collective movement. The resulting invasion patterns are invasion waves with a sharp edge. These swarms have no leader cell.

(2) The Eftimie model:

$$\begin{aligned} u^+_t + \gamma u^+_x &= -\lambda^+[u^+,u^-]u^+ + \lambda^-[u^+,u^-]u^- \\ u^-_t - \gamma u^-_x &= \lambda^+[u^+,u^-]u^+ - \lambda^-[u^+,u^-]u^- \end{aligned}$$

The turning rates are non-local functions of the distributions u^+, u^-. Under certain conditions on the turning rates, where individuals do not look behind them, you can observe feather patterns, which correspond to groups of individuals which leave a swarm. These swarms have no leader cells either.

(3) Bellomo's model. Nino Bellomo showed simulations of collective movement of groups of people who evacuate a room. There is no leader but there is a specific purpose (like an attractive signal) that makes the people move. They orient among each other.
(4) Preziosi's model is a measure based setting that can combine discrete leader cells with a continuous density field of other cells. The latter are able to follow a leader and show leader-driven collective movement.

Future studies should focus on a comparison of these approaches.

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