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Mini-Workshop: Mechanics of Cell Motion

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Abstract. This mini-workshop brought together established researchers and newer entrants in the field of cell motility, a challenging research area located at the crossroads of biology, mathematics and physics.
Cell locomotion occurs through complex interactions that involve, among others, actin polymerization, matrix degradation, chemical signaling, adhesion and pulling on the substrate and fibers. In recent years the spatial resolution of experiments at a cellular and sub-cellular level have revealed a landscape of unexpected behaviors that demand for the application of physics and classical mathematical methods to reveal the principles that are at the basis of cell motion in terms of adhesion, directionality, internal engines. The focus of the mini-workshop was on the fundamental research in mathematical methods for biophysics of the cell, especially on the mathematical framework for the mechanics of the actin network, the *encadrement* of cellular traction as an inverse problem and the relation between cell-to-cell communication and morphogenesis.

Mathematics Subject Classification (2000): 92C17.

Introduction by the Organisers

The topic of the mini-workshop was intended to bring together modelers and analysts from medicine, biology, physics and mathematics, working on central research aspects of cell motion mechanics - which comprise intracellular signaling and motor dynamics, single cell adhesion and locomotion analysis as well as cell-cell interaction and tissue formation. The noticeable result was that a "crew" of 15 mostly younger scientists from more than 10 countries met for 5 days in the smaller "Sitzungssaal" around its oval table, giving an ideal opportunity for excellent presentations about current research work and for long-lasting and lively

on-talk-discussions.
Despite of tremendous recent developments, the mathematical aspect of the mechanics of cell motility is still in its infancy. The goal of the mini-workshop was to critically discuss and classify state-of-the-art models which capture the essence of mechanical and biological interactions. Supplemented by appropriate computational simulation techniques these mathematical models are expected to provide further insight into complex biomechanical phenomena and capture basic dependencies and trends. The talks pointed out the main assumptions, simplifications and predictions of a wide variety of mathematical models. The following discussions clarified the similarities and contradictions between predictions of different approaches, with the scope of understanding the advantages and the range of validity for each model.
The topics discussed covered several levels of description - from single actin filaments to cell fragments, whole cells and tissues. Part of the talks focussed on the initiation process of cell motility and the pre-merging conditions. A second group of talks concerned the perpetuation mechanisms, once movement is initiated, and the interaction with the extra-cellular matrix. Other talks concentrated on cell-to-cell communication and group dynamics of moving cells.
It became clear from the discussion that the emphasis on the processes involved in cell motility - protrusion, adhesion and retraction, matrix degradation, chemical signaling - differs between models, that are necessarily based on simplifying assumptions on this complex biological system. It was very inspiring for the different participants to see the problem they are working on from a totally different perspective.
Scientist working experimentally in this field were also present, not only giving an insight into remarkable, yet not clarified biological behaviors, but also pointing out the mathematical problems that arise in the analysis and interpretation of their experimental data. It also became clear from these talks how important research on cell motility for future application in prevention and treatment of diseases is: Understanding the basic mechanisms of cell adhesion might be the key tool to inhibit tumor cell migration; the mechanotransduction of intercellular signals plays a relevant role in determining the pathways of cells in embryos and the related cardiac malfunctions, to name just a couple of examples.
Particularly interesting was that everybody could communicate with everybody, since independent of the different educational origins and working areas, for understanding the underlying mechanics of cell motility, very similar or analogous modeling ideas and analysing methods were used. Thus, the effects of this intense and fruitful mini-workshop were manifold: not only that each participant gave and received impulses, but also the whole community gained new insights and proposals for further research in this growing interdisciplinary field.

Mini-Workshop: Mechanics of Cell Motion

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Abstracts

Elementary mechanical models for analysing and understanding cell motility

Wolfgang Alt

After introducing the different spatio-temporal scales, on which cellular motion is occurring, namely from the molecular processes of polymer assembly and interaction towards the apparent phenomena of cell shape deformation and cell translocation, we concentrated on the questions of their mechanical control and regulation: How is, for a typical tissue cell migrating on an 2-dimensional adhesive substratum, force transduction and cell locomotion related to the mechanisms of force generation and cell polarization (with an advancing front and a retracting rear)?

Image analysis of moving keratinocytes. The first method, which we proposed to answer these questions, consists of model supported image processing and statistical correlation analysis of phase contrast movies from single human skin cells (keratinocytes). Due to the bright "halo" that surrounds the two-dimensional cell projection,the "edges" of a peripheral lamellipod seam can be detected by letting a "stochastic elastic chain" shrink from outside, due to a centripetal drift, eventually being repelled by a strong enough negative gradient of "pixel brightness". Similarly, the border of a cell body can be detected and, thus, scalar and vector correlations be investigated between the changing cell protrusion strength/direction and cell translocation velocity. The underlying hypothesis is that any "new area" under the cell also induces new adhesion sites, serving as anchoring points for the application of force pulling at the substratum.

Dynamics of a basic 2-dimensional fluid-adhesion model. A two-phase "reactive and contractive fluid" continuum model (hyperbolic-elliptic system of Navier-Stokes type) was presented to reproduce the observed chaotic dynamics of actin/myosin cluster formation ([1]) and to be combined with a suitable system of diffusion-transport-reaction equations for free and bound myosin dimers and integrin adhesion sites ([2]). Corresponding numerical simulations of two simplifying one-dimensional situations (longitudinal section through a moving cell fragment, and, circular lamellipod seam model) reveal the emergence of spontaneous and induced front-rear polarization and subsequent directional persistence of cell migration.

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Collective cell motility in monolayers and sprouts

András Czirók

To analyze movement patterns within endothelial cell monolayers, we studied cultures of three different kinds of endothelial cells – bovine capillary (BCE), bovine aortic (BAEC) and human umbilical cord vein (HUVEC) – on Matrigel- or fibronectin-coated tissue culture plastic. Endothelial cells form streams in monolayers: 5-20 cells move together in narrow, chain-like groups. The monolayers contain vortices, and adjacent streams moving in opposite directions.

As cells of a monolayer constrain the possible movements in their vicinity, correlation is expected in the motion of adjacent cells. In particular, immediately in front of a moving cell movement in the opposite direction (i.e., towards the cell) is unsustainable and therefore expected to be rare. We suggest the average flow field around moving cells as a measure sensitive to the local cell movement pattern. For a given configuration of cell positions and velocities this procedure assigns reference systems co-aligned with the movement of each cell, and averages the velocity vectors observed at similar locations (e.g., immediately in front, behind, left and right). Flow fields derived from monolayer cultures reveal the presence of velocity correlations exceeding a spatial range of 200 μm, much larger than the typical cell diameter (mean distance between adjacent cell centers) of 30-40 μm. Streaming behavior is indicated by the similarity of average velocity vectors obtained within an elongated area surrounding the origin. In the lateral direction, the average velocity drops quickly and in some cases reverses direction – an indication that streams are narrow and adjacent streams move in opposite directions. Remarkably, very similar correlation structures are seen in all three types of endothelial cell monolayer cultures investigated, irrespective of the underlying extracellular matrix substratum used. In subconfluent cultures, where fewer constraints are imposed by the behavior of adjacent cells, the correlated (co-moving) area shrinks.

To explain and model the emergence of collective flow patterns in cell monolayers, we adopted the two dimensional cellular Potts model (CPM) approach. The main advantage of the CPM approach is that cell shape is explicitly represented; thus, the simulation has the potential to describe dynamics in which controlled cell shape plays an important role. To obtain a biologically plausible, yet simple, model we consider below a positive feedback loop between cell polarity and cell movement in addition to the surface tension-like intercellular adhesion and cell compressibility. The model assumptions are the following:

A1: Cells form a monolayer and each cell is simply connected.
A2: Each cell has an approximately constant, pre-set size.
A3: Cells adhere to their neighbors.
A4: Each cell is capable of autonomous biased random motion. The direction bias (in a homogeneous environment) is set by an internal polarity vector.
A5: The polarity vector has a finite lifetime, but it is reinforced by co-directional displacements of the cell.

The proposed model includes a positive feedback loop involving cell movements and the vector representing cell polarity. Thus, steric constraints may result in co-migration of adjacent cells as the retraction of one cell allows for the expansion of the other. The resulting expansion of cell bodies (like the actin polymerization process in real cells) therefore can alter and synchronize cell polarity. The molecular mechanism for cell polarity reinforcement by cell motility may involve either the stabilization of PIP_3 accumulation by actin polymerization, or the activation of Rac1 by microtubule dynamics.

Monolayer simulations result in behavior similar to the experimentally observed streaming motion, with shear lines and vortices present. Motion within the monolayer is somewhat hindered when compared with individual cells, as the speed and persistence time decrease by 20%. In addition to qualitative similarity, the calculation of flow fields allows a more rigorous comparison of model simulations to empirical data. In agreement with experimental observations, lateral correlations and back-flow are reduced when non-adherent cells are simulated at lower cell densities. At subconfluent densities the average flow field still reveals the 'steric' repulsion of cells in the path of an actively moving cell.

Our model for actively moving cells in a monolayer culture is thus capable of explaining most experimental observations. Furthermore, the simple model structure allows a thorough mapping of the parameter space. We find it remarkable that a given pair of parameters yield individual cell speeds, persistence times in the correct range as well as a collective behavior comparable with the observed streaming. In particular, $T = 5$ minutes is a plausible value for the time needed to alter cell polarity. With this value, it is possible to obtain cell speeds in the range of 20-40 μm/h within monolayers and 50 μm/h for individual cells. Our empirical data show cell speeds between 10 and 30 μm/h for monolayers. A similarly close, and independent agreement is obtained for the persistence times, at approximately one hour both in the model and in the experiments. The spatial structure of streams is strongly anisotropic, being approximately 200-300 μm long and 100 μm wide in both the experiments and in the simulations.

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The stress exerted by a cell on a flat flexible substrate: recent advances

Davide Ambrosi
(joint work with Guido Vitale)

Several cells exhibit a motile activity, that can be observed in different physiological frameworks as embryogenesis, tumor extravasation and wound healing. This migration ability is due to the complex internal engine, a sophisticated combination of polimerization treadmill and myosin generated stress, that produces the

typical elongation-adhesion-retraction sequence characterizing the cellular motility. When adhering on a flat flexible surface, living cells become a particularly attractive *in vitro* system for a few reasons: the external environment is geometrically simple, easy to observe, the cell does not need to degrade it in order to move and the strain of the substrate can be easily detected.

This "simple and complex" system attracts the interest of biophysicists since twenty years; the aim to determine the stress field exerted by a cell in its migration on the basis of the observed displacement of some beads, typically dispersed in the substrate medium. An as alternative to the standard approach based on Green functions [3], one may consider the introduction of a suitable adjoint problem, typically coupled with the two–dimensional linear elasticity equations, derived on the basis of the minimization of a suitable cost functional [1].

In this miniworkshop we have reported recent developments of the theory and in its applications. From a biological point of view, a numerical code that implements the mathematical model has been applied to the migration of fish keratocytes in conjunction with tracking the motion of the actin network [2]. This combined source of information has given the opportunity to devise the basic difference in the nature of the forces that are transmitted by the cells to the substrate: the force field in the front and the rear are aligned with the actin velocity, at least in the central party of the cell body. However, the force at the front is typically oriented in the same direction as actin, while the converse happens at the tail. This kind of arguments suggests that the cells grips at the fronts and slips in the rear, a physical characterization not yet addressed until now.

From a theoretical point of view, a few steps have been made in the rigorous analysis of the problem, both in two and in three dimension. In two dimensions the problem can be reformulated as follows: Find $\mathbf{u} \in H_0^1(\Omega)$ s.t. $\forall \mathbf{v} \in H_0^1(\Omega)$

$$\int_\Omega \mathbf{u} \cdot (\nabla \cdot \mathbb{C}[\nabla \mathbf{v}]) = \int_\Omega \mathbf{f} \cdot \mathbf{v}. \tag{1}$$

where $\mathbf{f}$ (the optimal control) is related to the solution of the adjoint problem (arising form the minimization of a penalty functional): Find $\mathbf{p} \in L^2(\Omega)$ s.t. $\forall \mathbf{q} \in H^2(\Omega)$

$$\int_\Omega \mathbf{p} \cdot (\nabla \mathbb{C}[\nabla \mathbf{q}]) = (\mathcal{P}\mathbf{u} - u_0) * \mathcal{P}\mathbf{q} \tag{2}$$

where $\mathcal{P} := (\delta_{x_1}, ..., \delta_{x_N}) \in Lin(H^2(\Omega), \mathbb{R}^{2N})$ is the Dirac δs list representing pointwise observation of the solution $\mathbf{u}$. The optimal control $\mathbf{f}$ must belong to the closed subspace of $L^2(\Omega)$ with null average and null average momentum, this causing the introduction of Lagrange multiplier. In fact it can be shown $\mathbf{f} = -\frac{1}{\varepsilon}\mathbf{p} + \mathbf{f}^\perp$, with $\mathbf{f}^\perp$ belongs to the orthogonal (in $L^2(\Omega)$) of the null average and null average momentum linear space.

A proof of the well posedness of the problem above can be given (even in three dimension) with variational techniques, using the regularity properties of the solutions of elliptic equations, Sobolev embeddings and inf–sup condition.

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Modeling the Genesis of Lymphoid Tissue using Delaunay Triangulations

Tilo Beyer

Primary lymphoid follicles (PLFs) are tissue structures which are important for adaptive immune responses in mammals. Understanding PLF development is relevant for their role during autoimmune diseases. The typical developmental sequence is the following [1]. A network of immobile stromal cells is populated by lymphocytes, i.e. B and T cells, entering through blood vessels. The dynamics of the stromal network corresponds to a two-fold excitable medium. The first excitation state - differentiation into fibroblastic reticular cells (FRCs) - is induced upon contact with B and T cells. FRCs themselves chemotactically attract lymphocytes thus creating a positive feedback. The second excitation state - follicular dendritic cells (FDCs) generated from FRCs - requires extensive B cell contact and only attracts B cells. These rules induce the final dynamically stable morphology of the lymphoid tissue in which B cells and FDCs form the spheroid PLF structure adjacent to a T zone harboring all vessels relevant for lymphocyte influx and efflux, T cells, and FRCs.

The tissue formation is simulated using an agent-based three level model [1]. Level one is the representation of the dynamics of the phenotype of cells. The signaling molecules mediating chemotaxis are described using a reaction-diffusion system representing the second level of the model. The third level is focused on the biomechanics of the tissue and in particular cell migration. At this level cells are represented as self-propelled soft adhesive particles.

The self-propelling forces are derived from a migration model termed 'squeezing' model [3] describing lymphocyte migration in a three-dimensional environment. The cells periodically organize their cytoskeleton into a constriction ring and attach it firmly to the extra-cellular matrix. By contracting their rear, cells generate an outward directed pressure at their front and thereby squeeze themselves through the constriction ring. At the same time, cells collide which gives rise to deformation forces which are described by the Johnson-Kendall-Roberts model for soft adhesive spheres [4]. The deformation and self-propelling forces of each cell are balanced by drag forces that depend on relative cell velocities of cells in contact with each other. The movement of cells due to these forces is described by a set of Newtonian

equations of motion in overdamped approximation:

$$0 = \mathbf{F}_i^{\mathrm{drag}} + \sum_{j\in\mathcal{N}_i} \mathbf{F}_{ij}^{\mathrm{act}} + \sum_{j\in\mathcal{N}_i^{\mathrm{c}}} \left[-\mathbf{F}_{ji}^{\mathrm{act}} + \mathbf{F}_{ij}^{\mathrm{JKR}}\right] \tag{1}$$

A Delaunay triangulation is used to determine the dynamically changing cellular neighborhood ($\mathcal{N}^i$ and $\mathcal{N}_i^{\mathrm{c}}$ for cells in contact) and the geometry of cells which is important to calculate the different force contributions [2].

The major consequence of the inclusion of a detailed biomechanical model for cell migration is the formation of an intermediate state during PLF formation termed B-cell ring. This structure is frequently observed when the PLF formation process is interrupted prematurely. The PLF has not yet been formed and B cells surround an already formed T zone. The sorting process separating B and T cells was termed "speed sorting". Reducing the lymphoid tissue simulation in the ring stage to its essence, which is a pool of lymphocytes responding to a chemoattractive point source, reveals that a difference in the self-propelling forces underlies the sorting process. The stronger/faster population aggregates around the source and the weaker/slower cells remain outside the aggregate (Fig. 1). The sorting is almost complete after one hour allowing cells in a flow equilibrium to stay sorted despite a constant source of disorder due to newly influxing cells like in the intermediate stage of PLF development.

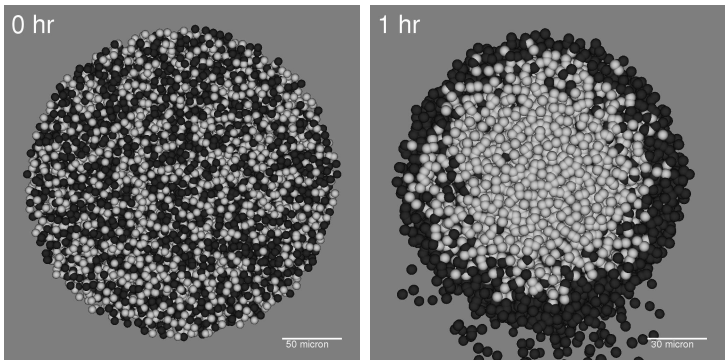

FIGURE 1. Speed sorting of cells. Shown is a cut through a three-dimensional simulation. Two cells types efficiently sort into a ring pattern when the self-propelling forces are different, white cells are faster and "stronger" than dark cells.

The speed sorting can be compared to a similar situation in which cell size underlies the sorting mechanism [5] which can also compared to pebbles of different size in a shaking box that sort such that the smallest are found at the bottom. In conclusion, the mobility determines cell sorting whether differences arise due to self-propelling forces, size, or eventually friction. In case of the latter one may speculate that differential adhesion, when adhesion does not dominante and only influences cell motility, can cause less adhesive cells to form clusters surrounded by stronger adhering cells contrary to the common view [6].

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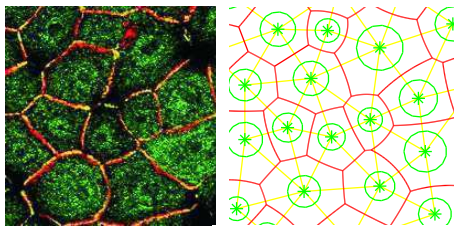
On shape and force – Collective cell dynamics with generalized Voronoi methods

Martin Bock
(joint work with Wolfgang Alt)

In epithelial wound healing and development experiments, groups of cells move in a coordinated fashion and eventually self-organize into stable monolayers. The involved changes in cell shape and neighbor relations are conveniently represented by time-dependent Voronoi tessellations. Thereby, closed cell regions $\mathcal{V}_i$ are identified by attributing bisectors $\Gamma_{ij} := \mathcal{V}_i \cap \mathcal{V}_j$ to pairs (i,j) of point-like generators $\mathbf{x}_i \in \mathbb{R}^d$ [1]. One specific class of bisectors can be constructed from equating distance functions $\mathcal{P}_i = \mathcal{P}_{w_i}\big(|\mathbf{x}-\mathbf{x}_i|\big)$, with parametric dependence on generators $\mathbf{x}_i$ and weights w_i. The emerging bisector is bounded by the global maximal lamella width $\mathcal{P}_{\max}$,

$$\Gamma_{ij} := \Big\{ \mathbf{x} \in \mathbb{R}^d : \mathcal{P}_i = \mathcal{P}_j \ \wedge \ \mathcal{P}_i < \mathcal{P}_{\max} \Big\}.$$



Remarkably, different distance functions of such type give rise to cell-cell contacts of different shapes [2, 3]. Together with multiplicative real weights, the Euclidean distance leads to piecewise spherical cells (see figure). This specific geometry has – in contrast to more conventional planar cell-cell contacts – direct ramifications for possible force generation mechanisms. In particular, the usual assumption of a uniform pressure and surface tension per cell does not hold. We therefore have to define stresses on the cell borders Γ, which are both geometrically and biologically compatible. Currently, however, we lack a good understanding as of how to define such stresses.

Assuming generic multi-particle interactions balanced by the drag acting on the cell body, we perform simulations and study under which conditions the cell aggregates remain stable and do not dissociate. The obtained stability criteria are summarized by means of a semi-analytic expression. As it turns out, in aggregating tissues the cells either (i) need sufficiently wide lamellae $\mathcal{P}_{\max}$ (white in right figure), or (ii) their body sizes w_i (green spheres) need to be rather homogeneous.

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On a minimal model for the initiation of cell movement

Jan Fuhrmann

(joint work with Heinrich Freistühler, Angela Stevens)

Reorganization and filament turnover of the actin cytoskeleton plays a major role in the movement of eucaryotic cells. In [1] we presented a basic one dimensional model for the polarization of an initially symmetric cytoskeleton upon some external stimulus intended to drive the resting cell into motion. One drawback of this model was a fixed spatial domain within which the dynamics took place. We are now going to present a free boundary version of this model where the movement of the boundaries corresponds to displacements of the cell membrane and thus allows for modeling actual cell motion instead of pure polarization.

The model equations remain unchanged and we have a system of four hyperbolic conservation laws of the form

$$\partial_t u^\alpha(t,x) + \partial_x \left(\lambda^\alpha(t,x,a(t,x))u^\alpha(t,x)\right) \;=\; 0, \qquad \alpha = 1,\dots,\ 4 \tag{1}$$

where the u^α are densities of barbed or pointed ends of actin filaments having right or left orientation. These filament tips move with velocities λ^α depending on the concentration of actin monomers which is governed by a reaction diffusion equation

$$\partial_t a(t,x) \;=\; D\partial_{xx} a(t,x) + R(t,x,a(t,x),\mathbf{u}(t,x)) \tag{2}$$

with reaction term R describing the polymerization and depolymerization of monomers at filament tips. The simplest possible form of a moving boundary occurs if we assume the cell membrane to be very soft so that any number of filaments growing against it is capable of pushing the membrane forward. In that case the evolution of the boundary points is just given by the outermost of the characteristic curves of the u^α, so the boundary velocity is always equal to some of the λ^α and in particular depends on the monomer concentration. Due to these so called characteristic boundaries for the hyperbolic part of the system we do not need to impose any explicite boundary values for these equations. For the parabolic equation we note that monomers are assumed to be reflected at the membrane whenever they hit it, resulting in no flux conditions for a. That means that the

diffusive flux $\pm D\partial_x a$ at the boundary has to be exactly balanced by the material flux due to the motion of the boundary.

For the resulting model we can show existence and uniqueness of solutions for short time. The idea is to decompose the model into a characteristic boundary value problem for the hyperbolic system (1) with prescribed monomer density a and a parabolic free boundary problem for the parabolic equation (2). For both of these problems we show well posedness and derive regularity properties and a priori estimates. These in turn allow us to conclude well posedness also for the coupled system.

Another approach to analysing the proposed model is a further reduction to a system of two parabolic equations with advection and nonlinear interaction term of the form

$$\begin{aligned} \partial_t u + \partial_x w &= d_1 \partial_{xx} u && \text{in } (0,\infty)\times(0,L) \\ \partial_t w + \partial_x u &= d_2 \partial_{xx} w + f(u,w) && \text{in } (0,\infty)\times(0,L) \\ w(t,0) = w(t,L) &= 0 && \text{for } t>0 \end{aligned} \tag{3}$$

where $u = u_r + u_l$ describes the total density of right and left moving particles in a one dimensional domain and $w = u_r - u_l$ denotes the polarization of the particle distribution. Note that by u_r and u_l we denoted the densities of right and left moving particles, respectively. The term $f(u,w)$ describes mutual alignment of the particles moving in opposite directions. For this system we perform linear and nonlinear stability analysis and show that for appropriate alignment terms f the stability of the homogenous fully symmetric state $w \equiv 0$ cannot be determined from the linearization around that state but rather depends on the full shape of the nonlinearity. This effect is also illustrated by simulations of the system in different parameter regimes and a wide variety of initial conditions.

The analysis of this reduced model is concluded by a detailed description of traveling wave solutions and discussion of their stability properties.

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Modelling Cell Polarity: Theory and Experiments

Alexandra Jilkine

(joint work with Yoichiro Mori, Leah Edelstein-Keshet)

In response to chemical stimulation, many eukaryotic cells are able to sense direction of stimulus and initiate movement. In order to do so, the cell must break symmetry and develop a front and back in a process known as polarization. Several symmetry breaking mechanisms have been proposed for this self-organizing process. I present one reaction-diffusion model for cell polarization based on switch-like polarity proteins called Rho GTPases, and describe the necessary conditions to obtain a robust stationary polar pattern.

Rho GTPases exist in both active forms (on the surface membrane of the cell), and inactive forms (in the cytosol). The model for protein concentration in the active, membrane-bound form (u) and the inactive cytosolic form (v) is given by

$$\partial_t u = D_u \Delta u + f(u, v), \tag{1a}$$

$$\partial_t v = D_v \Delta v - f(u, v), \tag{1b}$$

with no-flux boundary conditions. It is clear that system (1) obeys mass conservation, that is

$$\int_\Omega (u + v) dx = K_{\text{total}}. \tag{2}$$

I assume that positive feedback in the activation kinetics of the active form u result in bistable reaction kinetics $f(u, v)$. That is, there is some range $v_{\min} < v < v_{\max}$, for which $f(u, v) = 0$ admits three solutions $u_-(v) < u_m(v) < u_+(v)$, with the outer two being stable (and u_m unstable) as solutions to the spatially-homogeneous version of (1), for a fixed v. Given an initial inhomogeneity in protein distribution, a travelling wave of GTPase activation is initiated at one end of the domain, moves across the cell, and eventually stops inside the domain, resulting in a stable polar distribution (see Figure 1).

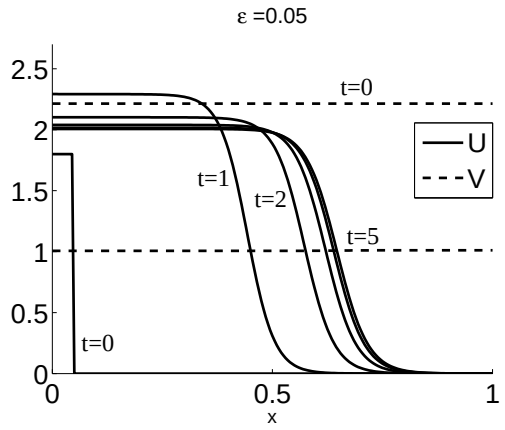

FIGURE 1. Travelling wave behaviour for system (1) with cubic reaction kinetics. The active form u is initialized to be $u = 1.8$ on $0 < x < 0.04$ and $u = 0$ on 0.04. This initiates a moving front that propagates inwards, slows down and stalls by $t = 5$. Solutions to u (solid lines) and v (dotted lines) are shown at the indicated times.

Using singular perturbation theory, I explain the mathematical basis of this wave-pinning behaviour based on three properties of system (1): (i) Mass conservation in a finite domain, (ii) nonlinear reaction kinetics allowing for multiple stable steady states, and (iii) a sufficiently large difference in diffusion of the species. For a range of parameters, a homogeneous distribution (representative of a resting cell) coexists with an asymmetric stationary wave profile (typical of a polarized cell). I show that this mechanism for generating a polar chemical pattern is distinct from Turing-related pattern formation. I analyze the transition from a spatially heterogeneous solution to a spatially homogeneous solution as the diffusion coefficient of the active form is increased, and show the existence of other unstable stationary wavefronts.

I propose that this wave-pinning mechanism can account for a number of features of cell polarization, such as spatial amplification, maintenance of polarity, as well as sensitivity to new stimuli typical in polarization of eukaryotic cells. I also present some preliminary results on ways of experimentally distinguishing which of

the many proposed classes of cell polarity models act in a given cell type. In particular, neutrophil-like cells can be made to undergo drastically shape changes and still establish a unique front. I show that when effects of cell geometry are considered in several proposed classes of models for polarity, the models either give rise to multiple fronts or are not able to re-animate upon cell severing, contradicting experimental data.

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Actin-based propulsion of spatially extended obstacles

Mihaela Enculescu

(joint work with Martin Falcke)

Cell migration is required for important biological processes, such as immune response or metastasis. A variety of eukaryotic cells crawl by extending a thin plane cytoskeleton structure, the lamellipodium, in the direction of motion. The growth of a cross-linked actin network through polymerization behind the membrane generates the protrusion force that pushes the membrane of the lamellipodium forward. The architecture of this network is generated and maintained by complex signaling pathways in response to external stimuli.

Aside from the global movement of the cell, the actin cytoskeleton also determines the dynamics of the membrane shape. Quantitative analysis has revealed that in a variety of crawling cells protrusion and retraction events at the leading edge are organized in lateral waves along the cell membrane and that the wave pattern can be changed by activating signaling molecules [1]. Therefore, actin dynamics generates spatial and temporal structures and cell morphology could be used to evidence the state of the cytoskeleton without direct intervention, if the emergence of different morphodynamic patters were well understood. However, current models show either steady motion only, or require myosin activity for these spatio-temporal dynamics which is in difference to experimental observations. We present here a model reproducing observed wave patterns and complying with the experimental conditions.

Protein coated beads can, like bacteria, hijack the actin-based machinery of the cell for propulsion leaving behind a tail of actin polymer [2]. They are used to reconstitute actin based motility. The regime of motion (steady or oscillatory) depends on the bead diameter as well as on the surface density of the protein activating actin polymerization. This type of motion has been described before by the gel continuum theory. Velocity oscillations were explained by a periodic relaxation of the stress in the gel-like actin tail resulting from polymerization [2]. Hence, despite the similarity of the molecular constituents of lamellipodium and

bead motion, they are described by different modeling concepts (continuum versus microscopic models). The model presented here captures both the shape dynamics of lamellipodia in crawling cells and bead propulsion in an cell-like medium. It thus suggests a unifying mechanism for both systems, expands lamellipodium theory by shape dynamics and bead theory by a microscopic description.
Our approach starts from properties of individual actin filaments and is based on the description of the polymerization, cross-linking and attachment dynamics in the lamellipodium network. It is used to determine the total force exerted on the obstacle at each position in space and each time step.
The model reproduces the marked state switches in the protrusion morphodynamics found experimentally between epithelial cells in control conditions and cells expressing consitutively active Rac, a signaling molecule involved in the regulation of lamellipodium network assembly. We also propose a mechanistic explanation of experimental distortions in protrusion morphodynamics induced by deregulation of Arp2/3 and cofilin activity [3].
For propulsed beads, the model gives rise to both smooth and saltatory movement and can explain the experimentally observed switches of the dynamic regime with changing bead radius and protein surface density.
We suggest oscillations in bead and lamellipodium motion may arise from the same mechanism, based on binding and dissociation of filaments to the membrane or bead, forces exerted by attached and detached filaments, changes of filament free length and gelation processes.

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Modelling of friction effects caused by protein linkages.

Dietmar Oelz

During the last years a mathematical model for the actin filament cytoskeleton was developed ([1, 2, 3, 4]). The model describes an overdamped system of two filament phases, namely two different groups of filaments, which potentially cross each another. The model formulation is based on the balance of the following forces: drag forces due to the cytoskeleton-substrate interaction, interfilamenteous drag forces and torque due to cross-linker proteins between crossing filaments, elastic forces of single filaments and exteriour forces which act on the tips of filaments. The tips are either the so called barbed ends aligned with the membrane of the cell or the pointed ends on the opposite inner side of the filament.

For several special cases of this model analytic results have been obtained. Namely for the rotationally symmetric special case short time existence of solutions

has been shown ([2]). The constructive proof is based on a steepest descent scheme, which can also be used as a numerical method ([1]). For the case of a single filament which is only subject to friction as it moves on the substrate and to elastic relaxation, exponential convergence to a steady state, namely a straight filament, has been shown ([5]).

The modelling procedure actually has been quite involved and more complex as it has been formulated above. The modelling started with a microscopic model which included the description of filament-substrate connections (integrins) and cross-linkers as elastic springs and of their lifecycle based on age-structured models including on- and off-rates. ([3]). A macroscopic limit yields macroscopic coefficients for the filament-substrate friction, the interfilamenteous friction and the torque due to cross-linker proteins and implies the formulation of the model as described in the first paragraph ([4]).

The age-structured model for linkage proteins is actually a powerful modelling tool. In the present talk current analytic results concerning this model are commented and also its use, when it comes to the modelling of linkages the off-rates of which depend on the mechanical load. In this case a modified scaling limit yields a non-linear macroscpic friction model based on a velocity dependent friction coefficient.

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Collective cell motility: leadership, invasion and segregation as emerging processes.

Alexandre J. Kabla

A number of biological processes, such as embryo development, cancer metastasis or wound healing, rely on cells moving in concert [1, 2, 3, 4]. The mechanisms leading to the emergence of group motion remain largely unexplored. Although biomolecular signalling is known to be involved in most occurrences of collective migration, the role of physical and mechanical interactions has been so far poorly addressed.

A simple framework for cell motility is implemented in-silico in order to study the minimal requirements for the coordination of a group of epithelial cells lying on a flat substrate. The model, inspired from theoretical studies on self-propelled

particles [5, 6], is essentially an extension of the Cellular Potts Model [7] in which cells can generate a motile force. The strength μ of this force is constant, but its direction is along the net displacement of the cell during its previous τ time-steps, leading de facto to a persistence time in the cell trajectory. This model appears to be equivalent to the model introduced by Andras Czirok during this workshop (see second abstract).

A key parameter, essentially characterising the ratio between the cohesion of the tissue and the motile force of individual cells, has the ability to control a wide spectrum of behaviours. Considering first a large assembly of identical cells, three different regimes can be observed. At low motile strength, the population behaves as a cohesive epithelium, in which cells slightly fluctuate in position but do not migrate. As the motile force is increased, there is a rapid transition ($\mu = \mu_c$) to a regime where cells form streams and exhibit large correlations in the velocity field; this will be later referred to as the collective regime. This qualitative transition is in some respect similar to the epithelial-mesenchymal transition in live tissues. As the motile force is further increased, the correlations between cell velocities progressively vanish and cell trajectories tend to simple random walks.

When the population is in the collective regime, the dynamics is very sensitive to any orientational bias. It is easy for instance to steer the whole group in a particular direction by introducing a small proportion of "leader cells" which exert a motile force along a constant direction. The alignment of cell velocities is here an emerging feature, which does not require any other form of cell-cell communication than mechanical interactions.

In vivo, groups of motile cells usually travel in a complex environment, having to force their way through other tissues, typically made of cells and extracellular matrix. The behaviour of cells through such a system is intrinsically complex. A minimalist approach to study heterogeneous assemblies is to consider an island of motile cells surrounded by a population of cohesive non-motile cells. A single motile cell in a non-motile tissue will only migrate through the tissue if it can generate a force larger than a critical value μ_s, typically larger than μ_c. A group of motile cells will however manage to migrate through the surrounding tissue at lower motile force ($\mu_c < \mu < \mu_s$) by spontaneously forming intermittent streams. Essentially, when coordinating cell motion, cells can generate a larger mechanical force than individual cells.

Another remarkable feature of systems composed of motile and non-motile cells is their tendency to segregate according to their motile strength. This typically leads to specific morphogenetic patterns in which motile cells tend to stream around islands of non-motile tissue. Such a mechanism remains to be observed in Nature.

The main message of this model is that mechanical interactions between cells might be enough to drive a number of complex morphogenetic patterns in vitro and in vivo. This unified picture suggests simple mechanisms for the evolution of collective cell behaviours and allows us to reassess the need for biomolecular signalling in a broader context.

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A thin-film poroviscous flow model for cell motility

James Mark Oliver
(joint work with John R. King)

There is a rapidly growing field seeking to develop cell-scale models that capture the observed spatio-temporal distribution of the cell crawling cycle. The main focus has been on one- or two-dimensional travelling-wave configurations that are applicable to 'gliding' cells such as keratocytes. In contrast, the approach adopted here considers a cell whose configuration corresponds to a thin droplet partially wetting a substrate, which is the case for some mammalian cells, such as fibroblasts, at least during the final stages of spreading [2].

Our mathematical model is based on the two-phase poroviscous flow equations described in [1, 3, 4] and references therein. The two-phase mixture consists of a 'network' phase and a 'solution' phase. The network phase lumps together the constituents of the actin-myosin network, which generates actively the forces responsible for motion. The solution phase lumps together the aqueous solvent and G-actin complexes, which flow passively through the viscous porous network. The network is assumed to 'swell' at low and high concentrations, and to 'contract' at intermediate concentrations as in [1]. A novel feature is the introduction of a nonlocal pressure term modelling long range network compaction following [5]. The impermeable membrane is subject to a constant isotropic surface tension away from the contact set where the cell adheres closely to the substrate; adhesion is modelled by allowing the network phase to slip along the substrate according to a Navier slip law. The key model parameters characterizing the cell / surface interaction are the slip coefficient and the static microscopic contact angle, both of which are taken to be constant. The mesoscopic mechanisms of polymerization and depolymerization near the outer cell periphery are modelled by prescribing the rate of mass transfer between the phases at the contact line according to a law of mass action in terms of the network volume fraction; mass transfer between the phases in the bulk of the cell is neglected.

A novel thin-film poroviscous flow formulation is derived using lubrication theory. The resulting system of nonlinear degenerate fourth-order diffusion equations for the cell thickness and network volume fraction are subjected to physically relevant contact-line conditions at the outer cell periphery and analysed in the small-slip sub-limit using the method of matched asymptotic expansions (following [4]). In this strong- adhesion regime the cell thickness is governed by Poisson's equation, the network volume fraction by a Cahn-Hilliard-type equation and the location of the contact-line by a Tanner-type contact-line law. The contact-line law relates the macroscopic contact angle, the contact-line velocity and 'effective' microscopic contact angle. The effective microscopic contact angle decreases with the rate of mass transfer rate at the contact line in such a way that local polymerization (depolymerization) of the actin network promotes protrusion (retraction) of the contact line.

In the two-dimensional case a linear stability analysis shows that the homogenous steady-state solution is unstable over a finite band of wavenumbers for a sufficiently large contractile pressure, suggesting the formation of regions of high and low network density. The combination of this spatial pattern formation capability and the functional dependence of the contact-line velocity on the local network density provides a mechanism for the generation of asymmetry, and thereby a potential mechanism for cell polarization as an emergent property of the system associated with symmetry breaking behaviour, rather than imposing it *a priori*. Further evidence for this hypothesis is provided by numerical simulations in which physically relevant parameter values are taken from [3, 5] and the initial network density is a small random perturbation to the equilibrium density at the contact line. Figure 1 shows a typical result in which a symmetric mode is initially the most unstable one, leading to the formation of a high-density region at the centre of the cell. As the cell spreads this contraction weakens until the most unstable mode becomes an asymmetric one. This results in a rapid redistribution of network into an asymmetric configuration and locomotion in the direction of increasing network density. The cell appears to approach a travelling wave configuration.

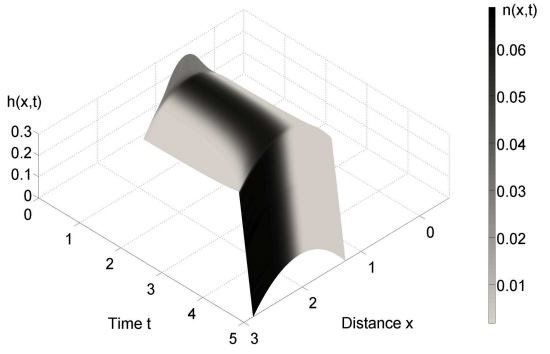

FIGURE 1. Dimensionless cell thickness $h(x,t)$ and network volume fraction $\theta(x,t)$.

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From individual to collective behavior without chemotaxis - transition to aggregation and large-scale patterns in myxobacteria

Fernando Peruani

(joint work with Markus Baer, Hugues Chate, Andreas Deutsch, Francesco Ginelli, Vladimir Jakovljevic, Lotte Sogaard-Andersen, Joern Starruss)

Collective behaviour of individual cells is often the first step in the transition from single cell behaviour to multicellularity. Generally, this transition is thought to rely on some specific intercellular communication between cells. Here we show that the transition from single cell behaviour to collective behaviour in a Myxococcus xanthus mutant can be understood as a dynamical self-assembly process where no biochemical communication is required [1]. Moreover, we show spatial organization of these mutants resembles that of self-propelled rods interacting by repulsive steric interactions.

Self-propelled rods interacting by volume exclusion - while moving on a dissipative surface - develop an effective velocity alignment. Such alignment allows the formation of polar clusters, which means that collective motion of groups of particles is observed [2]. Interestingly, volume exclusion effects do not induce ferromagnetic alignment of particles, but rather nematic ordering [3]. In addition to this, we known that fluctuations in self-propelled particles yield to non-classical effects [4]. Here, we explain how self-propelled particles interacting with nematic alignment - i.e., when interacting by volume exclusion - develop anomalous density fluctuations and long-range nematic order [5]. As observed in bacterial experiments, high density regions where particles are nematically oriented are formed.

We also show that there is a transition from a monodisperse phase to a self-assembly phase. The transition is characterized by a scale-free cluster size distribution with a cutoff, $p(m) \sim m^{-b} exp(-m/m_0)$, that emerges at a critical cell density. Above this critical density, the average cluster size exhibits a dramatic increase - a divergence with system size - while below, it is a well defined (microscopic) quantity [1]. Remarkably, the experiments with myxobacteria exhibit the same qualitative behavior.

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Mathematical models of the mechanics of cell motility and cell-substrate interaction

Magdalena Stolarska
(joint work with Hans G. Othmer)

Cell motility occurs in various biological processes such as immune function, wound healing, progression of cancer, and embryonic development, and as a result, understanding how cells integrate mechanical and biochemical signals to produce movement is important.

We approach cell movement from a mechanical point of view. In order to move a cell must polymerize actin at its leading edge, which in turn results in protrusion of the front of the cell. This protrusion is coordinated with contraction of actin filaments by myosin II, which typically occurs at the rear depending on cell type. This localized protrusion and contraction, coupled with dynamically overturning cell-substrate attachments, results in the forward translocation of the cell.

The mathematical model presented is based on a modification of the equations describing the motion of deformable continua. In the model, local extension (due to actin polymerization) and contraction is treated as a finite deformation field via a multiplicative decomposition of the deformation gradient, $\mathbf{F}$, such that $\mathbf{F} = \mathbf{F}_P\mathbf{F}_A$. Here, $\mathbf{F}_A$ is the active part of deformation gradient that describes local extension and contraction. It is assumed that $\mathbf{F}_A$ maps the cell from its original configuration to a fictitious, stress-free intermediate configuration. $\mathbf{F}_P$ is the passive part of the deformation gradient that describes deformation required to resolve incompatibilities that arise from the assumption of a stress-free intermediate configuration and this results in the formation of residual stresses internal to the cell. In addition, $\mathbf{F}_P$ accounts for deformation to body forces and external tractions.

We treat the cell as an incompressible, viscoelastic solid and use classical mass balance and equilibrium equations to describe its motion. These two equations are coupled to a constitutive equation of the form

$$\boldsymbol{\sigma} + \boldsymbol{\sigma}^{\circ}\big(\mathbf{F}_P\big) \;=\; \gamma\boldsymbol{\epsilon}\big(\mathbf{F}_P\big) + \delta\boldsymbol{\epsilon}^{\diamond}\big(\mathbf{F}_P\big)$$

where $\boldsymbol{\sigma}$ is the Cauchy stress, $\boldsymbol{\epsilon}$ is the strain, and $\boldsymbol{\sigma}^{\circ}$ and $\boldsymbol{\sigma}^{\diamond}$ indicate frame invariant time derivatives. Note that the strain, strain rate, and stress rate all depend on $\mathbf{F}_P$. This incorporates the assumption that the mapping from the current to intermediate configuration is stress free.

We use the model to understand how localization of extension and contraction coupled to the location of cell-substrate attachments affects substrate traction patterns that have been observed experimentally in keratocytes [1]. In this application of the model, the computational domain consists of a three-dimensional keratocyte shaped region placed upon a deformable substrate, the deformation of which is governed by standard balance laws for an inactive, viscoelastic solid. At the predetermined cell-substrate attachment sites it is assumed that displacements and forces of the cell and substrate are equal, and all other surfaces (on the cell and substrate) are traction free. The rate of change of $\mathbf{F}_A$ is prescribed in accordance with experimental results [1, 2]. The model equations are solved using the finite element method, and traction patterns on the surface of the substrate are computed.

A sample of the results reported in [3] is illustrated in Figure 1. These traction patterns and magnitudes compare qualitatively and quantitatively to those observed in [1], We find that these traction patterns are obtained by attaching the cell to the substrate towards its leading edge as well as its back and by only allowing the cell to protrude at the front and contract only at the rear. A narrow contracting region following the region of protrusion at the leading edge results in forward oriented substrate surface tractions.

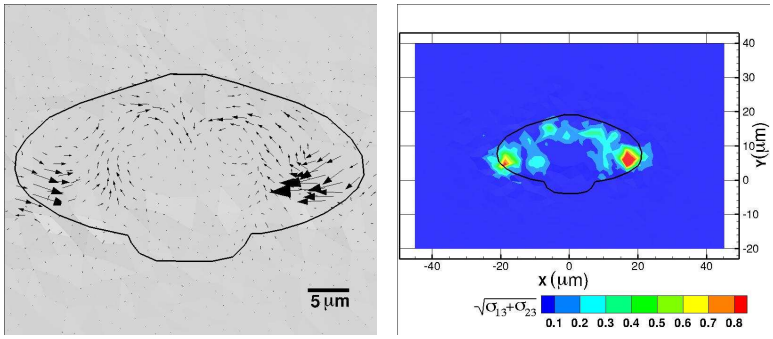

FIGURE 1. Left: Numerically computed substrate surface traction vectors. Right: Computed traction magnitudes.

The application of the model to cell-substrate interaction in keratocyte cell movement has provided some insight as to what types of local active deformations combined with locations of cell-substrate attachments are required to obtain observed traction patterns. A drawback of this model is that it currently allows for a fixed set of cell-substrate attachment regions, whereas in reality these regions change dynamically. Future work includes modifying the model so dynamic attachments are included and applying the model to other cell types. The overall goal of this type of modeling approach is to gain a better understanding of the processes that need to change in the underlying biomechanical principles to allow for the different types of movement (i.e. smooth vs. pulsatile) observed in various cell types.

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Cell polarity in plants and animals: an evolutionary conservation of developmental principles

Athanasius F. M. Maréé
(joint work with Verônica A. Grieneisen)

Animal cells display a fascinating ability to undergo cell shape changes and move. In contrast, plant cells are encased in a relatively rigid cellulose cell wall that impedes cell motility. Nevertheless, molecular and genetic studies reveal that even though plants and animals diverged 1.6 billion years ago, they still share a similar core machinery required for cell shape changes. A fascinating similarity between animal and plant cells with respect to the organisation of cytoskeletal elements in the regions of active protrusive growth and cell wall extension (the 'leading edges'), is parallelled by a striking conserved molecular mechanism responsible for the creation and organisation of those 'leading edges'. To unravel and understand the interplay and feedbacks which brings about animate cell motility, we have developed a multiscale model of a motile keratocyte, describing how the molecular players cause cell polarity and deformation[2]. We then contrast this to the cell shape changes that occur in pavement cells (PCs) in the leaves of plants, that form jigsaw-like patterns[1].

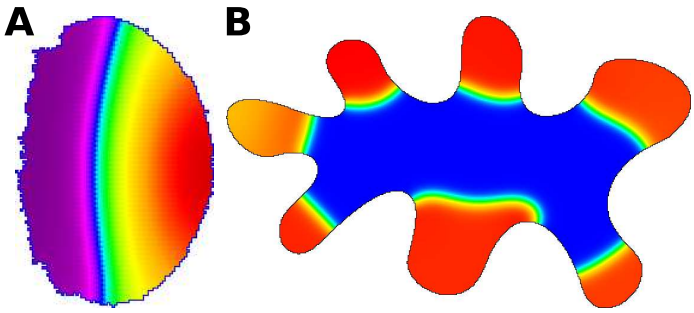

FIGURE 1. (A) Computer simulation of a migrating keratocyte, taking into account core subcellular processes such as actin cytoskeleton turnover, small G-protein dynamics and ARP2/3-regulated branching; (B) Computer simulation of ROP dynamics within a PC in the leaf epidermis of *Arabidopsis thaliana*.

One of the key determinants of cell polarity in both animal and plant systems are the small G-proteins. In motile cells, these proteins form a core mechanism of polarity generation by cycling between an active membrane-bound form and an inactive, both membrane-bound and cytoplasmic form, leading to spatial patterning of the active form. In plants, small G-proteins called ROPs (Rhos of Plants) have also been shown to play a key role in polarity organisation of many cell types, such as root hairs, pollen tubes and PCs, as well as to take up specific spatial distributions. Small G-proteins are switched between inactive and active forms by Guanine Exchange Factors (GEFs) and GTPase-Activating Proteins (GAPs) respectively, while Guanine Disassociation Inhibitors

(GDIs) bring the inactive forms into the cytosol. We mathematically show that these switches are crucial for intracellular pattern formation in both systems.
Rac, Rho and Cdc42 are spatially distributed within moving cells, with Rac and Cdc42 active in the front and Rho in the back, while ROPs are spatially distributed in plant PCs, with ROP2 and ROP4 active in the lobes, and ROP6 active in the indentations. Some of the cross-talk circuitry between these small G-proteins are known, both for the motile cells and for the plant PCs. Firstly, through mathematical exploration we pinpoint which elements of the proposed cross-talks are necessary and where knowledge is limiting, We developed a specific perturbation method to directly determine if polarisation is possible within the different interaction schemes without the need to explicitly take the spatial distribution of the chemicals into account, by reducing, for specific limiting cases, the system of Partial Differential Equations (PDEs) into a larger set of coupled Ordinary Differential Equations (ODEs). We use this method to show that keratocytes and PCs can acquire internal polarisation without a requirement for localised polarising signals (i.e. spatially inhomogeneous distributions can arise through an initially homogeneous activation of small G-proteins as opposed to local subcellular activation).
We then explore the effect of cell shape and its dynamics on the internal cell biochemistry and polarisation. PDE analysis serves as a powerful tool, supplemented by spatio-temporal computer simulations of the cell shape. Our simulations suggest that cell shape can strongly influence the internal biochemistry, and that GDIs are important in controlling polarisation, by regulating the effective diffusion of the inactive forms. In simulations of moving keratocytes, we use the Cellular Potts Model and go further, to study the interdependencies of the intracellular patterning on cell shape and movement, as well as how cell shape changes can actually enhance the intracellular response to external stimuli.
In short, through a combined study on cell polarity in two very distinct systems – keratocytes and PCs – our results converged to highlight the importance of intracellular patterning and cell shape dynamics. The fact that such core elements of the polarity-generating mechanism, as well as downstream activation components of the cytoskeleton, turn out to be shared points to an amazing evolutionarily conservation of underlying mechanisms for polarity establishment, which can finally be unravelled with mathematical and computational approaches.

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An individual cell–based model of the spatial organization of mesenchymal stem cell cultures in vitro

Joerg Galle
(joint work with Martin Hoffmann)

Over the past decade mesenchymal stem cells (MSC) derived from bone marrow, adipose, and many other tissues have intensively been investigated with respect to tissue regeneration prospects. Therapeutic applications of these cells require extensive in vitro expansion. MSC in cell culture grow to confluence within one or two weeks. They show characteristic spindle-shaped fibroblastoid morphology and align to each other in mesoscopic domains.

In a recent study we simulated the expansion and chondrogenic differentiation behavior of MSCs using an individual cell-based model (IBM) approach (Krinner et al. 2009). However, assuming spherical model cells the applied model was not capable of describing the directional cell-cell alignment of the cells in vitro. Considering this experimentally observed feature of MSC culture required the development of a novel model for migrating cells with podia. Here, we present the resulting, extended IBM that is able to quantitatively describe the spatio-temporal organization of MSC in culture including the alignment feature which is, at the same time, simple enough to simulate thousands of cells with reasonable computational effort. Applying this model to MSC growth on micro-structured surfaces, we demonstrate how it can be used to optimize MSC culture protocols.

The extended IBM explicitly represents cell podia. It accounts for individual cell-cell and cell-substrate interactions and employs podia-generated forces for cell movement. Accordingly, cell migration depends on the protrusion and traction forces exerted by the podia, the friction between the cells and the substrate, and the podium inactivation probabilities. The migration phenotype largely differs between cells with only one active podium (mostly ballistic cell movement with random turns) and cells with two or more active podia (stretched out, mostly resting cells with random reorientation moves). The cross-over between ballistic and diffusive cell movement occurs at short time (10 min) and length (10m) scales.

Experimental findings obtained by automated image analysis of ovine MSC cultures under standard conditions were used in order to adjust the parameter set of the model. In simulation series we quantitatively reproduced the observed growth dynamics and cell-cell alignment of these cells assuming cell density-dependent cell shape, migration, and proliferation (Fig. 1). In a further step we used the model to simulate MSC alignment to substrate micro-structures. Thereby, the experimental observed effects of parallel substrate micro-structuring on the growth of MSC populations obtained by Ricci and co-workers (Ricci et al. 2008) were faithfully reproduced. This allowed us to propose a hexagonal lattice of star-like micro-structured plating units that according to our simulations can significantly increase the cell culture harvest compared to culture on flat surfaces. We predict an at least two-fold increase in cell number after eight days of cultivation for this type of surface structure design.

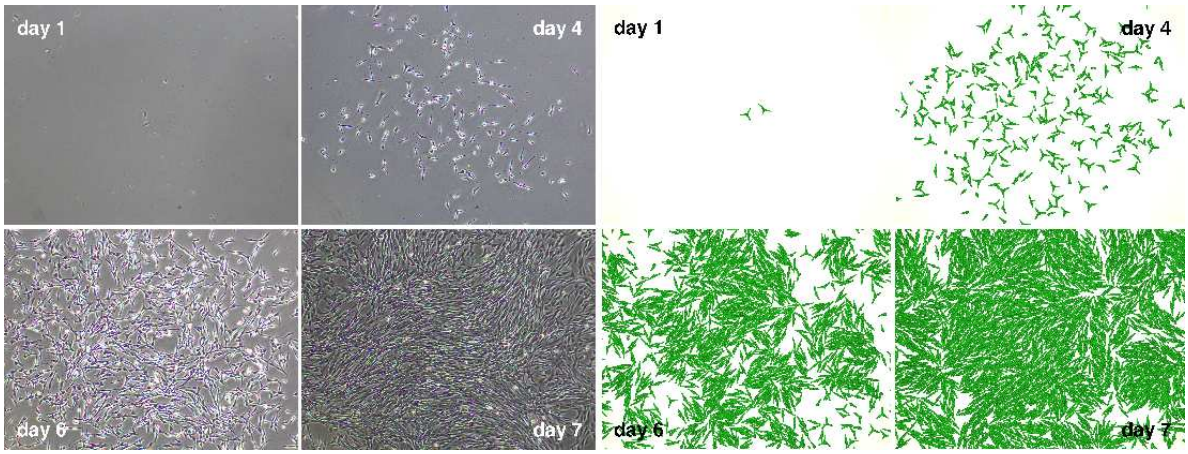

FIGURE 1. MSC culture in vitro and in vivo. Images of an growing MSC population at day 1, 4, 6, and 7 of culture. Experimental (left) and simulation (right) results match qualitatively regarding cellular phenotype and quantitatively regarding spatial distribution and cell number.

In general, our results underline the importance of cell-cell interactions in tissue formation. While additional sophisticated cell-cell interaction and cell-developmental modules can readily be integrated into the presented modeling framework our model can easily be applied to simulate MSC behavior under fare more complex culture conditions. Moreover, we expect our model to be also useful for the simulation and understanding of the behavior of a variety of other fibroblast-like cell types.

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