Année de publication : 2019

Moitrier Sarah, Pricoupenko Nastassia, Kerjouan Adèle, Oddou Christiane, Destaing Olivier, Battistella Aude, Silberzan Pascal, Bonnet Isabelle (2019 Sep 3)

Local light-activation of the Src oncoprotein in an epithelial monolayer promotes collective extrusion

Communications Physics : 2 : 98 : DOI : 10.1038/s42005-019-0198-5

Résumé

Transformed isolated cells are usually extruded from normal epithelia and subsequently eliminated. However, multicellular tumors outcompete healthy cells, highlighting the importance of collective effects. Here, we investigate this situation in vitro by controlling in space and time the activity of the Src oncoprotein within a normal Madin–Darby Canine Kidney (MDCK) epithelial cell monolayer. Using an optogenetics approach with cells expressing a synthetic light-sensitive version of Src (optoSrc), we reversibly trigger the oncogenic activity by exposing monolayers to well-defined light patterns. We show that small populations of activated optoSrc cells embedded in the non-transformed monolayer collectively extrude as a tridimensional aggregate and remain alive, while the surrounding normal cells migrate towards the exposed area. This phenomenon requires an interface between normal and transformed cells and is partially reversible. Traction forces show that Src- activated cells either actively extrude or are pushed out by the surrounding cells in a non- autonomous way.

Sarah Moitrier, Carles Blanch-Mercader, Simon Garcia, Kristina Sliogeryte,abc Tobias Martin, Jacques Camonis, Philippe Marcq, Pascal Silberzan and Isabelle Bonnet (2019 Feb 4)

Collective stresses drive competition between monolayers of normal and Ras-transformed cells

Soft Matter : 15 : DOI : 10.1039/C8SM01523F

Résumé

We study the competition for space between two cell lines that differ only in the expression of the Ras oncogene. The two cell populations are initially separated and set to migrate antagonistically towards an in-between stripe of free substrate. After contact, their interface moves towards the population of normal cells. We interpret the velocity and traction force data taken before and after contact thanks to a hydrodynamic description of collectively migrating cohesive cell sheets. The kinematics of cells, before and after contact, allows us to estimate the relative material parameters for both cell lines. As predicted by the model, the transformed cell population with larger collective stresses pushes the wild type cell population.

Année de publication : 2018

Coscoy S, Baiz S, Octon J, Rhoné B, Perquis L, Tseng Q, Amblard F, Semetey V. (2018 Oct 16)
Microtopographies control the development of basal protrusions in epithelial sheets
Biointerphases : 13 : 041003 : DOI : 10.1116/1.5024601

Résumé

Venzac B, Madoun R, Benarab T, Monnier S, Cayrac F, Myram S, Leconte L, Amblard F, Viovy JL, Descroix S, Coscoy S (2018 Oct 16)
Engineering small tubes with changes in diameter for the study of kidney cell organization
Biomicrofluidics : 12 : 024114 : DOI : 10.1063/1.5025027

Résumé

Blanch-Mercader C., Yashunsky V., Garcia S., Duclos G., Giomi L., Silberzan P. (2018 Oct 9)
Turbulent dynamics of epithelial cell cultures
Phys. Rev. Lett. : 120 : 208001 : DOI : 10.1103/PhysRevLett.120.208101

Résumé

We investigate the large length and long time scales collective flows and structural rearrangements within in vitro human bronchial epithelial cell (HBEC) cultures. Activity-driven collective flows result in ensembles of vortices randomly positioned in space. By analyzing a large population of vortices, we show that their area follows an exponential law with a constant mean value and their rotational frequency is size independent, both being characteristic features of the chaotic dynamics of active nematic suspensions. Indeed, we find that HBECs self- organize in nematic domains of several cell lengths. Nematic defects are found at the interface between domains with a total number that remains constant due to the dynamical balance of nucleation and annihilation events. The mean velocity fields in the vicinity of defects are well described by a hydrodynamic theory of extensile active nematics.

Duclos G., Blanch-Mercader C., Yashunsky V., Salbreux G., Joanny J.-F., Prost J., Silberzan P. (2018 Oct 3)
Spontaneous shear flow in confined cellular nematics
Nature Physics : DOI : 10.1038/s41567-018-0099-7

Résumé

In embryonic development or tumour evolution, cells often migrate collectively within confining tracks defined by their microenvironment[1,2]. In some of these situations, the displacements within a cell strand are antiparallel[3], giving rise to shear flows. However, the mechanisms underlying these spontaneous flows remain poorly understood. Here, we show that an ensemble of spindle-shaped cells plated in a well-defined stripe spontaneously develops a shear flow whose characteristics depend on the width of the stripe. On wide stripes, the cells self-organize in a nematic phase with a director at a well-defined angle with the stripe's direction, and develop a shear flow close to the stripe's edges. However, on stripes narrower than a critical width, the cells perfectly align with the stripe's direction and the net flow vanishes. A hydrodynamic active gel theory provides an understanding of these observations and identifies the transition between the non-flowing phase oriented along the stripe and the tilted phase exhibiting shear flow as a Fréedericksz transition driven by the activity of the cells. This physical theory is grounded in the active nature of the cells and based on symmetries and conservation laws, providing a generic mechanism to interpret in vivo antiparallel cell displacements.

Duclos G., Deforet M., Yevick H.G., Cochet-Escartin O., Ascione F., Moitrier S., Sarkar T., Yashunsky V., Bonnet I., Buguin A., Silberzan P. (2018 Jun 11)
Controlling confinement and topology to study collective cell behaviors
Methods in Molecular Biology"Cell Migration: Methods and Protocols" : 1749 : 387-399 : DOI : 10.1007/978-1-4939-7701-7_28

Résumé

Confinement and substrate topology strongly affect the behavior of cell populations and, in particular, their collective migration. In vitro experiments dealing with these aspects require strategies of surface patterning that remain effective over long times (typically several days) and ways to control the surface topology in three dimensions. Here, we describe protocols addressing these two aspects. High-resolution patterning of a robust cell-repellent coating is achieved by etching the coating through a photoresist mask patterned directly on the coated surface. Out-of-plane curvature can be controlled using glass wires or corrugated « wavy » surfaces.

Année de publication : 2017

Breau M, Bonnet I, Stoufflet J, Xie J, De Castro S, Schneider-Maunoury S (2017 Aug 21)
Extrinsic mechanical forces mediate retrograde axon extension in a developing neuronal circuit
Nature Communications : 8 : 282 : DOI : 10.1038/s41467-017-00283-3

Résumé

To form functional neural circuits, neurons migrate to their final destination and extend axons towards their targets. Whether and how these two processes are coordinated in vivo

remains elusive. We use the zebrafish olfactory placode as a system to address the underlying mechanisms. Quantitative live imaging uncovers a choreography of directed cell movements that shapes the placode neuronal cluster: convergence of cells towards the centre of the placodal domain and lateral cell movements away from the brain. Axon formation is concomitant with lateral movements and occurs through an unexpected, retrograde mode of extension, where cell bodies move away from axon tips attached to the brain surface. Convergence movements are active, whereas cell body lateral displacements are of mainly passive nature, likely triggered by compression forces from converging neighbouring cells. These findings unravel a previously unknown mechanism of neuronal circuit formation, whereby extrinsic mechanical forces drive the retrograde extension of axons.

Vincent Hakim, Pascal Silberzan (2017 Mar 11)
Collective cell migration : a physics perspective.
Reports on progress in physics. Physical Society (Great Britain) : 80 : 076601 : DOI : 10.1088/1361-6633/aa65ef

Résumé

Cells have traditionally been viewed either as independently moving entities or as somewhat static parts of tissues. However, it is now clear that in many cases, multiple cells coordinate their motions and move as collective entities. Well-studied examples comprise development events, as well as physiological and pathological situations. Different ex vivo model systems have also been investigated. Several recent advances have taken place at the interface between biology and physics and have benefitted from the progress in imaging and microscopy, the use of microfabrication techniques, as well as the introduction of quantitative tools and models. We review these interesting developments in quantitative cell biology that also provide rich examples of collective out-of-equilibrium motion.

Ayako Yamada, Renaud Renault, Aleksandra Chikina, Bastien Venzac, Iago Pereiro, Sylvie Coscoy, Marine Verhulsel, Maria Carla Parrini, Catherine Villard, Jean-Louis Viovy, Stéphanie Descroix (2016 Nov 1)
Transient microfluidic compartmentalization using actionable microfilaments for biochemical assays, cell culture and organs-on-chip.
Lab on a chip : DOI : 10.1039/C6LC01143H

Résumé

We report here a simple yet robust transient compartmentalization system for microfluidic platforms. Cylindrical microfilaments made of commercially available fishing lines are embedded in a microfluidic chamber and employed as removable walls, dividing the chamber into several compartments. These partitions allow tight sealing for hours, and can be removed at any time by longitudinal sliding with minimal hydrodynamic perturbation. This allows the easy implementation of various functions, previously impossible or requiring more

complex instrumentation. In this study, we demonstrate the applications of our strategy, firstly to trigger chemical diffusion, then to make surface co-coating or cell co-culture on a two-dimensional substrate, and finally to form multiple cell-laden hydrogel compartments for three-dimensional cell co-culture in a microfluidic device. This technology provides easy and low-cost solutions, without the use of pneumatic valves or external equipment, for constructing well-controlled microenvironments for biochemical and cellular assays.

Duclos G., Erlenkämper C., Joanny J.-F., Silberzan P. (2016 Sep 12)
Topological defects in confined populations of spindle-shaped cells
Nature Physics : 13 : 58-62 : DOI : 10.1038/nphys3876

Résumé

Most spindle-shaped cells (including smooth muscles and sarcomas) organize in vivo into well-aligned 'nematic' domains, creating intrinsic topological defects that may be used to probe the behaviour of these active nematic systems. Active non-cellular nematics have been shown to be dominated by activity, yielding complex chaotic flows. However, the regime in which live spindle-shaped cells operate, and the importance of cell–substrate friction in particular, remains largely unexplored. Using in vitro experiments, we show that these active cellular nematics operate in a regime in which activity is effectively damped by friction, and that the interaction between defects is controlled by the system's elastic nematic energy. Due to the activity of the cells, these defects behave as self-propelled particles and pairwise annihilate until all displacements freeze as cell crowding increases. When confined in mesoscopic circular domains, the system evolves towards two identical +1/2 disclinations facing each other. The most likely reduced positions of these defects are independent of the size of the disk,the cells' activity or even the cell type, but are well described by equilibrium liquid crystal theory. These cell-based systems thus operate in a regime more stable than other active nematics, which may be necessary for their biological function.

Année de publication : 2016

Laxsoomee Bhoonderowa, Fatima Hameurlaine, Atousa Arbabian, Fahima Faqir, François Amblard, Sylvie Coscoy (2016 Aug 31)
Polycystins and intercellular mechanotransduction: A precise dosage of polycystin 2 is necessary for alpha-actinin reinforcement of junctions upon mechanical stimulation.
Experimental cell research : 348 : 23-35 : DOI : 10.1016/j.yexcr.2016.08.021

Résumé

Polycystins 1 and 2, which are mutated in Autosomal Polycystic Kidney Disease, are involved in mechanotransduction through various mechanisms. In renal cells, polycystins not only have an important mechanotransductive role in primary cilia but are also present in

intercellular contacts but their role there remains unclear. Here, we address the hypothesis that polycystins are involved in mechanotransduction via intercellular junctions, which would be expected to have consequences on tissue organization. We focused on the role of polycystin 2, which could be involved in mechanical organization at junctions either by its channel activity or by the direct recruitment of cytoskeleton components such as the F-actin cross-linker α-actinin. After mechanical stimulation of intercellular junctions in MDCK renal epithelial cells, α-actinin is rapidly recruited but this is inhibited upon overexpression of PC2 or the D509V mutant that lacks channel activity, and is also decreased upon PC2 silencing. This suggests that a precise dosage of PC2 is necessary for an adequate mechanosensitive α-actinin recruitment at junctions. At the multicellular level, a change in PC2 expression was associated with changes in velocity in confluent epithelia and during wound healing together with a loss of orientation. This study suggests that the mechanosensitive regulation of cytoskeleton by polycystins in intercellular contacts may be important in the context of ADPKD.

Laura Wagstaff, Maja Goschorska, Kasia Kozyrska, Guillaume Duclos, Iwo Kucinski, Anatole Chessel, Lea Hampton-O'Neil, Charles R Bradshaw, George E Allen, Emma L Rawlins, Pascal Silberzan, Rafael E Carazo Salas, Eugenia Piddini (2016 Apr 26)
Mechanical cell competition kills cells via induction of lethal p53 levels.
Nature communications : 11373 : DOI : 10.1038/ncomms11373

Résumé

Cell competition is a quality control mechanism that eliminates unfit cells. How cells compete is poorly understood, but it is generally accepted that molecular exchange between cells signals elimination of unfit cells. Here we report an orthogonal mechanism of cell competition, whereby cells compete through mechanical insults. We show that MDCK cells silenced for the polarity gene scribble (scrib(KD)) are hypersensitive to compaction, that interaction with wild-type cells causes their compaction and that crowding is sufficient for scrib(KD) cell elimination. Importantly, we show that elevation of the tumour suppressor p53 is necessary and sufficient for crowding hypersensitivity. Compaction, via activation of Rho-associated kinase (ROCK) and the stress kinase p38, leads to further p53 elevation, causing cell death. Thus, in addition to molecules, cells use mechanical means to compete. Given the involvement of p53, compaction hypersensitivity may be widespread among damaged cells and offers an additional route to eliminate unfit cells.

Casimir Emako, Charlène Gayrard, Axel Buguin, Luís Neves de Almeida, Nicolas Vauchelet (2016 Apr 13)
Traveling Pulses for a Two-Species Chemotaxis Model.
PLoS computational biology : e1004843 : DOI : 10.1371/journal.pcbi.1004843

Résumé

Mathematical models have been widely used to describe the collective movement of bacteria

by chemotaxis. In particular, bacterial concentration waves traveling in a narrow channel have been experimentally observed and can be precisely described thanks to a mathematical model at the macroscopic scale. Such model was derived in [1] using a kinetic model based on an accurate description of the mesoscopic run-and-tumble process. We extend this approach to study the behavior of the interaction between two populations of E. Coli. Separately, each population travels with its own speed in the channel. When put together, a synchronization of the speed of the traveling pulses can be observed. We show that this synchronization depends on the fraction of the fast population. Our approach is based on mathematical analysis of a macroscopic model of partial differential equations. Numerical simulations in comparison with experimental observations show qualitative agreement.

Année de publication : 2015

Simon Garcia, Edouard Hannezo, Jens Elgeti, Jean-François Joanny, Pascal Silberzan, Nir S Gov (2015 Dec 1)

Physics of active jamming during collective cellular motion in a monolayer.

Proceedings of the National Academy of Sciences of the United States of America : 15314-9 : DOI : 10.1073/pnas.1510973112

Résumé

Although collective cell motion plays an important role, for example during wound healing, embryogenesis, or cancer progression, the fundamental rules governing this motion are still not well understood, in particular at high cell density. We study here the motion of human bronchial epithelial cells within a monolayer, over long times. We observe that, as the monolayer ages, the cells slow down monotonously, while the velocity correlation length first increases as the cells slow down but eventually decreases at the slowest motions. By comparing experiments, analytic model, and detailed particle-based simulations, we shed light on this biological amorphous solidification process, demonstrating that the observed dynamics can be explained as a consequence of the combined maturation and strengthening of cell-cell and cell-substrate adhesions. Surprisingly, the increase of cell surface density due to proliferation is only secondary in this process. This analysis is confirmed with two other cell types. The very general relations between the mean cell velocity and velocity correlation lengths, which apply for aggregates of self-propelled particles, as well as motile cells, can possibly be used to discriminate between various parameter changes in vivo, from noninvasive microscopy data.