Year of publication 2015

Vincent Nier, Maxime Deforet, Guillaume Duclos, Hannah G Yevick, Olivier Cochet-Escartin, Philippe Marcq, Pascal Silberzan (2015 Jul 21)

Tissue fusion over nonadhering surfaces.

Proceedings of the National Academy of Sciences of the United States of America : 9546-51 : DOI : 10.1073/pnas.1501278112

Summary

Tissue fusion eliminates physical voids in a tissue to form a continuous structure and is central to many processes in development and repair. Fusion events in vivo, particularly in embryonic development, often involve the purse-string contraction of a pluricellular actomyosin cable at the free edge. However, in vitro, adhesion of the cells to their substrate favors a closure mechanism mediated by lamellipodial protrusions, which has prevented a systematic study of the purse-string mechanism. Here, we show that monolayers can cover well-controlled mesoscopic nonadherent areas much larger than a cell size by purse-string closure and that active epithelial fluctuations are required for this process. We have formulated a simple stochastic model that includes purse-string contractility, tissue fluctuations, and effective friction to qualitatively and quantitatively account for the dynamics of closure. Our data suggest that, in vivo, tissue fusion adapts to the local environment by coordinating lamellipodial protrusions and purse-string contractions.

Floris Bosveld, Boris Guirao, Zhimin Wang, Mathieu Rivière, Isabelle Bonnet, François Graner, Yohanns Bellaïche (2015 Jul 5)

Modulation of junction tension by tumor suppressors and proto-oncogenes regulates cell-cell contacts.

Development (Cambridge, England) : 623-34 : DOI : 10.1242/dev.127993

Summary

Tumor suppressors and proto-oncogenes play crucial roles in tissue proliferation. Furthermore, de-regulation of their functions is deleterious to tissue architecture and can result in the sorting of somatic rounded clones minimizing their contact with surrounding wild-type (wt) cells. Defects in the shape of somatic clones correlate with defects in proliferation, cell affinity, cell-cell adhesion, oriented cell division and cortical contractility. Combining genetics, live-imaging, laser ablation and computer simulations, we aim to analyze whether distinct or similar mechanisms can account for the common role of tumor suppressors and proto-oncogenes in cell-cell contact regulation. In Drosophila epithelia, the tumor suppressors Fat (Ft) and Dachsous (Ds) regulate cell proliferation, tissue morphogenesis, planar cell polarity and junction tension. By analyzing the evolution over time of ft mutant cells and clones, we show that ft clones reduce their cell-cell contacts with the surrounding wt tissue in the absence of concomitant cell divisions and over-proliferation. This contact reduction depends on opposed changes of junction tensions in the clone bulk and its boundary with neighboring wt tissue. More generally, either clone bulk or boundary

junction tension is modulated by the activation of Yorkie, Myc and Ras, yielding similar contact reductions with wt cells. Together, our data highlight mechanical roles for proto-oncogene and tumor suppressor pathways in cell-cell interactions.

Simon de Beco, Jean-Baptiste Perney, Sylvie Coscoy, François Amblard (2015 Jun 6)
Mechanosensitive Adaptation of E-Cadherin Turnover across adherens Junctions.
PloS one : e0128281 : DOI : 10.1371/journal.pone.0128281

Summary

In the natural and technological world, multi-agent systems strongly depend on how the interactions are ruled between their individual components, and the proper control of time-scales and synchronization is a key issue. This certainly applies to living tissues when multicellular assemblies such as epithelial cells achieve complex morphogenetic processes. In epithelia, because cells are known to individually generate actomyosin contractile stress, each individual intercellular adhesive junction line is subjected to the opposed stresses independently generated by its two partner cells. Contact lines should thus move unless their two partner cells mechanically match. The geometric homeostasis of mature epithelia observed at short enough time-scale thus raises the problem to understand how cells, if considered as noisy individual actuators, do adapt across individual intercellular contacts to locally balance their time-average contractile stress. Structural components of adherens junctions, cytoskeleton (F-actin) and homophilic bonds (E-cadherin) are quickly renewed at steady-state. These turnovers, if they depend on forces exerted at contacts, may play a key role in the mechanical adaptation of epithelia. Here we focus on E-cadherin as a force transducer, and we study the local regulation and the mechanosensitivity of its turnover in junctions. We show that E-cadherin turnover rates match remarkably well on either side of mature intercellular contacts, despite the fact that they exhibit large fluctuations in time and variations from one junction to another. Using local mechanical and biochemical perturbations, we find faster turnover rates with increased tension, and asymmetric rates at unbalanced junctions. Together, the observations that E-cadherin turnover, and its local symmetry or asymmetry at each side of the junction, are mechanosensitive, support the hypothesis that E-cadherin turnover could be involved in mechanical homeostasis of epithelia.

Yevick HG, Duclos G, Bonnet I, Silberzan P. (2015 May 12)
Architecture and migration of an epithelium on a cylindrical wire
Proc Natl Acad Sci USA112(19):5944-9 : DOI : 10.1073/pnas.1418857112

Summary

In a wide range of epithelial tissues such as kidney tubules or breast acini, cells organize into bidimensional monolayers experiencing an out-of-plane curvature. Cancer cells can also migrate collectively from epithelial tumors by wrapping around vessels or muscle fibers. However, in vitro experiments dealing with epithelia are mostly performed on flat substrates,

neglecting this out-of-plane component. In this paper, we study the development and migration of epithelial tissues on glass wires of well-defined radii varying from less than 1 µm up to 85 µm. To uncouple the effect of out-of-plane curvature from the lateral confinement experienced by the cells in these geometries, we compare our results to experiments performed on narrow adhesive tracks. Because of lateral confinement, the velocity of collective migration increases for radii smaller than typically 20 µm. The monolayer dynamics is then controlled by front-edge protrusions. Conversely, high curvature is identified as the inducer of frequent cell detachments at the front edge, a phenotype reminiscent of the Epithelial-Mesenchymal Transition. High curvature also induces a circumferential alignment of the actin cytoskeleton, stabilized by multiple focal adhesions. This organization of the cytoskeleton is reminiscent of in vivo situations such as the development of the trachea of the Drosophila embryo. Finally, submicron radii halt the monolayer, which then reconfigures into hollow cysts.

Marco Biondini, Guillaume Duclos, Nathalie Meyer-Schaller, Pascal Silberzan, Jacques Camonis, Maria Carla Parrini (2015 Mar 31)

Akirin specifies NF-κB selectivity of Drosophila innate immune response via chromatin remodeling

Scientific reports : 11759 : DOI : 10.1038/srep11759

Summary

RalA and RalB proteins are key mediators of oncogenic Ras signaling in human oncogenesis. Herein we investigated the mechanistic contribution of Ral proteins to invasion of lung cancer A549 cells after induction of epithelial-mesenchymal transition (EMT) with TGFβ. We show that TGFβ-induced EMT promotes dissemination of A549 cells in a 2/3D assay, independently of proteolysis, by activating the Rho/ROCK pathway which generates actomyosin-dependent contractility forces that actively remodel the extracellular matrix, as assessed by Traction Force microscopy. RalB, but not RalA, is required for matrix deformation and cell dissemination acting via the RhoGEF GEF-H1, which associates with the Exocyst complex, a major Ral effector. Indeed, uncoupling of the Exocyst subunit Sec5 from GEF-H1 impairs RhoA activation, generation of traction forces and cell dissemination. These results provide a novel molecular mechanism underlying the control of cell invasion by RalB via a cross-talk with the Rho pathway.

Year of publication 2014

Deforet M, Hakim V, Yevick HG, Duclos G, Silberzan P (2014 May 6)

Emergence of collective modes and tri-dimensional structures from epithelial confinement.

Nat Commun5:3747 : DOI : 10.1038/ncomms4747

Summary

Many in vivo processes, including morphogenesis or tumour maturation, involve small populations of cells within a spatially restricted region. However, the basic mechanisms underlying the dynamics of confined cell assemblies remain largely to be deciphered and would greatly benefit from well-controlled in vitro experiments. Here we show that confluent epithelial cells cultured on finite population-sized domains, exhibit collective low-frequency radial displacement modes as well as stochastic global rotation reversals. A simple mathematical model, in which cells are described as persistent random walkers that adapt their motion to that of their neighbours, captures the essential characteristics of these breathing oscillations. As these epithelia mature, a tri-dimensional peripheral cell cord develops at the domain edge by differential extrusion, as a result of the additional degrees of freedom of the border cells. These results demonstrate that epithelial confinement alone can induce morphogenesis-like processes including spontaneous collective pulsations and transition from 2D to 3D.

Reffay M, Parrini MC, Cochet-Escartin O, Ladoux B, Buguin A, Coscoy S, Amblard F, Camonis J, Silberzan P (2014 Apr 16)

Interplay of RhoA and mechanical forces in collective cell migration driven by leader cells

Nat Cell Biol16(4):382 : DOI : 10.1038/ncb2917

Summary

The leading front of a collectively migrating epithelium often destabilizes into multicellular migration fingers where a cell initially similar to the others becomes a leader cell while its neighbours do not alter. The determinants of these leader cells include mechanical and biochemical cues, often under the control of small GTPases. However, an accurate dynamic cartography of both mechanical and biochemical activities remains to be established. Here, by mapping the mechanical traction forces exerted on the surface by MDCK migration fingers, we show that these structures are mechanical global entities with the leader cells exerting a large traction force. Moreover, the spatial distribution of RhoA differential activity at the basal plane strikingly mirrors this force cartography. We propose that RhoA controls the development of these fingers through mechanical cues: the leader cell drags the structure and the peripheral pluricellular acto-myosin cable prevents the initiation of new leader cells.

G Duclos, S Garcia, H G Yevick, P Silberzan (2014 Mar 14)

Perfect nematic order in confined monolayers of spindle-shaped cells.

Soft matter : 10 : 2346-53 : DOI : 10.1039/c3sm52323c

Summary

Elongated, weakly interacting, apolar, fibroblast cells (mouse fibroblasts NIH-3T3) cultured at confluence align together, forming large domains (correlation length ~ 500 μm) where they are perfectly ordered. We study the emergence of this mesoscopic nematic order by

quantifying the ordering dynamics in a two-dimensional tissue. Cells are initially very motile and the monolayer is characterized by anomalous density fluctuations, a signature of far-from-equilibrium systems. As the cell density increases because of proliferation, the cells align with each other forming these large oriented domains while, at the same time, the cellular movements and the density fluctuations freeze. Topological defects that are characteristic of nematic phases remain trapped at long times thereby preventing the development of infinite domains. When confined within adhesive stripes of given widths (from 30 μm to 1.5 mm) cells spontaneously align with the domain edges. This orientation then propagates toward the pattern center. For widths smaller than the orientation correlation length, cells perfectly align in the direction of the stripe. Experiments performed in cross-shaped patterns show that in the situation of two competing populations, both the number of cells and the degree of alignment impact the final orientation.

Olivier Cochet-Escartin, Jonas Ranft, Pascal Silberzan, Philippe Marcq (2013 Jul 20)
Border forces and friction control epithelial closure dynamics.
Biophysical journal : 65-73 : DOI : 10.1016/j.bpj.2013.11.015

Summary

We study the closure dynamics of a large number of well-controlled circular apertures within an epithelial monolayer, where the collective cell migration responsible for epithelization is triggered by the removal of a spatial constraint rather than by scratching. Based on experimental observations, we propose a physical model that takes into account border forces, friction with the substrate, and tissue rheology. Border protrusive activity drives epithelization despite the presence of a contractile actomyosin cable at the periphery of the wound. The closure dynamics is quantified by an epithelization coefficient, defined as the ratio of protrusive stress to tissue-substrate friction, that allows classification of different phenotypes. The same analysis demonstrates a distinct signature for human cells bearing the oncogenic RasV12 mutation, demonstrating the potential of the approach to quantitatively characterize metastatic transformations.

Year of publication 2013

Zi Liang Wu, Renbo Wei, Axel Buguin, Jean-Marie Taulemesse, Nicolas Le Moigne, Anne Bergeret, Xiaogong Wang, Patrick Keller (2013 Jul 16)
Stimuli-responsive topological change of microstructured surfaces and the resultant variations of wetting properties.
ACS applied materials & interfaces : 7485-91 : DOI : 10.1021/am4017957

Summary

It is now well established that topological microstructures play a key role in the physical properties of surfaces. Stimulus-induced variations of topological microstructure should therefore lead to a change in the physical properties of microstructured responsive surfaces.

In this paper, we demonstrate that roughness changes alter the wetting properties of responsive organic surfaces. Oriented nematic liquid crystalline elastomers (LCEs) are used to construct the microstructured surfaces via a replica molding technique. The topological microstructure of the surfaces covered with micropillars changes with temperature, due to the reversible contraction of the LCE pillars along the long axis at the nematic-to-isotropic phase transition. This is directly observed for the first time under environmental scanning electron microscopy (E-SEM). A high boiling point liquid, glycerol, is used to continuously monitor the contact angle change with temperature. The glycerol contact angle of the microstructured surfaces covered with small pillars decreases from 118° at room temperature to 80° at 140 °C, corresponding to a transition from Cassie state to Wenzel state.

Néstor Sepúlveda, Laurence Petitjean, Olivier Cochet, Erwan Grasland-Mongrain, Pascal Silberzan, Vincent Hakim (2013 Mar 7)

Collective cell motion in an epithelial sheet can be quantitatively described by a stochastic interacting particle model.

PLoS computational biology : e1002944 : DOI : 10.1371/journal.pcbi.1002944

Summary

Modelling the displacement of thousands of cells that move in a collective way is required for the simulation and the theoretical analysis of various biological processes. Here, we tackle this question in the controlled setting where the motion of Madin-Darby Canine Kidney (MDCK) cells in a confluent epithelium is triggered by the unmasking of free surface. We develop a simple model in which cells are described as point particles with a dynamic based on the two premises that, first, cells move in a stochastic manner and, second, tend to adapt their motion to that of their neighbors. Detailed comparison to experimental data show that the model provides a quantitatively accurate description of cell motion in the epithelium bulk at early times. In addition, inclusion of model “leader” cells with modified characteristics, accounts for the digitated shape of the interface which develops over the subsequent hours, providing that leader cells invade free surface more easily than other cells and coordinate their motion with their followers. The previously-described progression of the epithelium border is reproduced by the model and quantitatively explained.

Year of publication 2012

Jonathan Saragosti, Pascal Silberzan, Axel Buguin (2012 Jan 30)

Modeling E. coli tumbles by rotational diffusion. Implications for chemotaxis.

PloS one : e35412 : DOI : 10.1371/journal.pone.0035412

Summary

The bacterium Escherichia coli in suspension in a liquid medium swims by a succession of runs and tumbles, effectively describing a random walk. The tumbles randomize

incompletely, i.e. with a directional persistence, the orientation taken by the bacterium. Here, we model these tumbles by an active rotational diffusion process characterized by a diffusion coefficient and a diffusion time. In homogeneous media, this description accounts well for the experimental reorientations. In shallow gradients of nutrients, tumbles are still described by a unique rotational diffusion coefficient. Together with an increase in the run length, these tumbles significantly contribute to the net chemotactic drift via a modulation of their duration as a function of the direction of the preceding run. Finally, we discuss the limits of this model in propagating concentration waves characterized by steep gradients. In that case, the effective rotational diffusion coefficient itself varies with the direction of the preceding run. We propose that this effect is related to the number of flagella involved in the reorientation process.

Maxime Deforet, Maria Carla Parrini, Laurence Petitjean, Marco Biondini, Axel Buguin, Jacques Camonis, Pascal Silberzan (2012 Jan 20)
Automated velocity mapping of migrating cell populations (AVeMap).
Nature methods : 1081-3 : DOI : 10.1038/nmeth.2209

Summary

Characterizing the migration of a population of cells remains laborious and somewhat subjective. Advances in genetics and robotics allow researchers to perform many experiments in parallel, but analyzing the large sets of data remains a bottleneck. Here we describe a rapid, fully automated correlation-based method for cell migration analysis, compatible with standard video microscopy. This method allows for the computation of quantitative migration parameters via an extensive dynamic mapping of cell displacements.

Year of publication 2011

J Saragosti, V Calvez, N Bournaveas, B Perthame, A Buguin, P Silberzan (2011 Sep 14)
Directional persistence of chemotactic bacteria in a traveling concentration wave.
Proceedings of the National Academy of Sciences of the United States of America : 16235-40 : DOI : 10.1073/pnas.1101996108

Summary

Chemotactic bacteria are known to collectively migrate towards sources of attractants. In confined convectionless geometries, concentration “waves” of swimming Escherichia coli can form and propagate through a self-organized process involving hundreds of thousands of these microorganisms. These waves are observed in particular in microcapillaries or microchannels; they result from the interaction between individual chemotactic bacteria and the macroscopic chemical gradients dynamically generated by the migrating population. By studying individual trajectories within the propagating wave, we show that, not only the mean run length is longer in the direction of propagation, but also that the directional

persistence is larger compared to the opposite direction. This modulation of the reorientations significantly improves the efficiency of the collective migration. Moreover, these two quantities are spatially modulated along the concentration profile. We recover quantitatively these microscopic and macroscopic observations with a dedicated kinetic model.

Yusuke T Maeda, Axel Buguin, Albert Libchaber (2011 Aug 16)

Thermal separation: interplay between the Soret effect and entropic force gradient.

Physical review letters : 038301 : DOI : 10.1103/PhysRevLett.107.038301

Summary

Thermophoresis, the Soret effect, depletes a high concentration of a polyethylene glycol polymer solution from the hot region and builds a concentration gradient. In such a solution, solutes of small concentration experience thermophoresis and polyethylene glycol concentration-dependent restoring forces. We report that by using focused laser heating and varying the polyethylene glycol concentration one observes geometrical localizations of solutes like DNA and RNA into patterns such as a ring. For DNA up to 5.6 kbp, the ring size decreases following a behavior analogous to a gel electrophoresis separation. Above 5.6 kbp, the ring diameter increases with the DNA length. Mixtures of DNA and RNA can be separated as well as different RNA lengths. Separation of colloids is also observed. The experiments might be relevant for the separation of small RNA ribozymes in an early stage of life.