Mechanism of signal propagation in Physarum polycephalum

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Complex behaviors are typically associated with animals, but the capacity to integrate information and function as a coordinated individual is also a ubiquitous but poorly understood feature of organisms like slime molds and fungi. Plasmodial slime molds grow as networks and use flexible, undifferentiated body plans to forage within and across substrates. How an individual communicates across its network to generate sophisticated behaviors remains a puzzle, but Physarum polycephalum has emerged as a novel model and is used to explore these emergent behaviors. Cytoplasm is shuttled throughout a P. polycephalum network in a peristaltic wave driven by the cross-sectional contractions of tubes. Here, we investigate the mechanism of signal propagation within a body by first following P. polycephalum's response to a localized nutrient stimulus. We observe a front of increased contraction amplitude that propagates with a velocity comparable to the dispersion of particles within the body advected by the cytoplasmic fluid flows. Data suggest the stimulus triggers advection of an unidentified signal that is also advected by the fluid flows and subsequently triggers changes in contraction amplitude which feed back and drive fluid flows. To test this hypothesis, we generate a theoretical model and not only find agreement with the observed front propagation, but also discover an explanation for the so far puzzling adaptation of the peristaltic wave to organism size. Finally we use our findings to explain how P. polycephalumis able to perform complex tasks, for example finding the shortest path between food sources. A simple feedback appears to give rise to P. polycephalum's complex behaviors, and the same mechanism is likely to function within the tens of thousands of additional species with behaviors like P. polycephalum.

3D Micro-Tissue dots

Bibette, Jérôme
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In the human body, each tissue has its own extracellular matrix composition and stiffness and its unique tri-dimensional cell arrangement which makes growing ex-vivo tissues a challenge. Here we show that long term culture (month) within the core of a few hundred microns diameter, porous and scaffold-free, capsules under physiological conditions provides a solution. As one example we show how primary human hepatocytes reorganize inside hydrogel capsules and create a tri-dimensional spheroid by self-assembling over the first week post-encapsulation. Establishment of cell-cell interactions and extracellular matrix deposition lead to formation of micro-tissues that mimic physiological in vivo phenotypes. One attribute are bile canaliculi, an interconnected network playing the role of elimination of bile secreted by hepatocytes, which is perfectly established in our system contrary to 2D cultures. This morphological conformity to liver architecture is also reflected in the high liver-specific metabolic functions detected in our micro-tissues such as high cell viability (up to 45 days) and preservation, as well as a high and stable level of gene expression and enzymatic activity of major liver-specific metabolizing enzymes. We will finally discuss the various potential applications and uses of such technology.

Applying controlled mechanical pressure on multicellular aggregates

Cappello, Giovanni
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Two key elements control the proliferation of tumors. On the one hand, cancer cells accumulate gene mutations. On the other hand, tumors have to interact with neighboring cells and to push on their surrounding in order to grow. Therefore, mechanical stress is one of the important parameters that have to be taken into account to understand the influence of the tumor microenvironment.

We developed a quantitative approach to apply a constant mechanical stress on spherical aggregates of cancer cells and to evaluate the effect of such a stress on their long term growth. Our results indicate that

the tumor growth rate strongly depends on the applied pressure. In particular, we show that a small mechanical pressure (500 Pa) reduces drastically the growth of a model tumor spheroid, whereas it has no impact on the growth of single cells. We also show that this pressure stops the cell cycle at the end of the G1 phase and preferentially in the core of the spheroid.

The reduction of cell proliferation is possibly linked to a mechanically-induced modification of the extracellular matrix.

Spreading epithelia as active polar fluids. Hydrodynamic instabilities, turbulence and wetting

Casademunt, Jaume
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Collective cell migration in freely spreading epithelia in controlled environments has become a landmark in our current understanding of fundamental biophysical processes in development, regeneration, wound healing or cancer. The possibility of measuring simultaneously both local forces and velocities in model epithelial monolayers has revealed a rich repertoire of dynamic behavior that is now amenable to quantitative modeling but still remains poorly understood. Here we propose a continuum approach that combines two sources of activity: traction forces on the substrate and contractile stresses in the tissue. This theoretical framework explains a variety of intriguing observations in spreading epithelia, such as the emergence of apparently elastic waves in a presumed liquid material. The model reveals a variety of activity-driven hydrodynamic instabilities and predicts a transition to weak turbulence. We also explain a variety of observations in terms of the concept of active wetting.

Long and short time-scale rheology of living cell monolayers

Charras, Guillaume
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One-cell thick monolayers are the simplest tissues in multi-cellular organisms, yet they fulfil critical mechanical roles in development and normal physiology. To study their mechanics, we use an experimental system for tensile testing of freely suspended cultured monolayers that enables the examination of their mechanical behaviour at multi-, uni-, and sub-cellular scales. Using uniaxial stress relaxation experiments, we examined the rheology of cell monolayers on time-scales of seconds, minutes, and hours. At the shortest time-scales, ATP-independent processes dominated relaxation and appeared to result from intracellular water redistribution in response to the large imposed deformation. At minute time-scales, relaxation was ATP-dependent and due to junctional protein turnover. At hour time-scales, oriented cell divisions drove relaxation of tissue and the return to resting cell packing. As the application of a stretch naturally elongates cells within the monolayer along the stretch axis, oriented divisions in our system are a direct consequence of the propensity of cells to divide along their interphase long axis and does not require cells to detect mechanical cues other than their own shape.

Viscoelastic dissipation underlies irreversible cell-shape changes during morphogenesis

Clément, Raphaël
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Epithelial morphogenesis relies on the production of active cellular forces. Understanding how such forces are mechanically converted into irreversible cell shape changes is essential to our understanding of morphogenesis. We took advantage of Myosin II pulsatile activity during Drosophila embryogenesis to study how transient forces generate irreversible cell shape changes. Analysing the dynamics of junction shrinkage and extension resulting from Myosin II pulses, we found that long pulses yield less reversible deformations, typically a signature of dissipative mechanics. This is consistent with a viscoelastic

description, which we used to model individual shrinkage and extension events. The model predicts that dissipation occurs on the minute timescale, a timescale commensurate with that of force generation by Myosin II pulses. We confirmed this estimate by applying time-controlled forces on junctions with optical tweezers. Our results argue that active junctional deformation is stabilized by dissipation. Hence, tissue morphogenesis requires coordination between force generation and viscoelastic dissipation.

Ecdysone supports morphogenetic gene expression programs to promote and orient growth in the Drosophila wing

Dye, Natalie
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Growth of the Drosophila larval wing imaginal disc is anisotropic and contributes to the proximal-distal (PD) elongated shape of the adult wing. As it grows, wing epithelial cells at its periphery become enlarged and tangentially elongated while those in the center become smaller and remain isotropic. How these patterns of growth anisotropy and cell packing geometry emerge is unclear because we lack a full description of cell dynamics in the growing wing disc. Quantitative analysis based on long-term time-lapse imaging has been impeded by our incomplete knowledge of extrinsic signals required to maintain normal disc growth in explants. Insulin supports imaginal proliferation for several hours, but growth stops prematurely. Here, we show that low concentrations of the steroid hormone 20-hydroxyecdysone act directly on the larval wing to promote growth in vivo and in explants. 20-hydroxyecdysone supports growth for twice as long as insulin. Furthermore, 20E but not insulin maintains normal expression of the patterning systems that drive and orient wing growth. Consistent with this, quantifying and analysing cell dynamics reveals that insulin-cultured discs develop an abnormal growth pattern while discs cultured in 20E grow in an orientation predicted by clone shapes observed in vivo. Decomposing tissue shape change during growth into different cellular contributions confirms that oriented cell divisions contribute to PD growth anisotropy, but also uncover equivalent contributions from oriented cell rearrangements and shape changes. Unexpectedly, we observe a radially oriented pattern of cell rearrangements that exactly balances tangential cell elongation. Thus, radial rearrangements could account for the elongation and compression pattern in the growing wing disc.

Mechanical feedback on morphogenesis through geometry: the cephalic furrow and germ-band extension

Étienne, Jocelyn
(Université Grenoble Alpes, Laboratoire interdisciplinaire de Physique, Grenoble, France)

Morphogenesis is an eminently three-dimensional process, during which an organism undergoes complex deformations to acquire a given shape and organisation. The genetic patterning of Drosophila embryos and the way it regulates the expression of key molecules such as myosin, which can generate local mechanical action, has been well described. However, the way this integrates at the scale of the embryo to drive morphogenetic movements is still to be characterised. Understanding this requires us both to express locally the link between myosin activation and mechanical behaviour, and to calculate globally the resulting force balance and deformations. Axis extension in Drosophila is a good model system for this, since it involves a very large deformation of the whole of the embryo and is crucially dependent on a well characterised anisotropic myosin recruitement pattern. This paper specifically investigates whether this expression pattern causes the observed morphogenetic movement directly or only via the cell intercalation process.

Our prediction of local mechanical behaviour is based on a rheological law which we have recently validated for cortical actomyosin and extend to the case when myosin generates an anisotropic prestress. In order to resolve the stresses and deformations that this produces at the scale of the whole embryo, we develop a novel finite element technique which allows us to solve the three-dimensional mechanical balance resulting from a given global distribution of myosin-generated prestress. Because axis extension is observed to involve in-plane tissue flows, the mechanical problem is expressed as a tangential flow of

an emergent fluid on the curved three-dimensional surface of the embryo.

Numerical simulations confirm that the planar-polarised arrangement of myosin in the germband can trigger embryo-scale flows which are qualitatively similar to those observed experimentally. Interestingly, this mechanical behaviour is shown not to rely necessarily on cell intercalation, but rather on the anisotropy of myosin action, which is known to be a major cause of intercalation in general but can also cause cell elongation. We also show that the mechanical balance that leads to axis extension towards posterior is crucially dependent on the geometry of the whole embryo, and specifically on the presence anteriorly of the cephalic furrow, which can act as a guide for morphogenetic movements. This is thus an instance when a prior morphogenetic event, cephalic furrow formation, can modify the mechanical feedback on actomyosin thanks to the geometric dependence of mechanical balance, thus having a cascading influence on further development.

Benefits of Particle Based Simulations

Elgeti, Jens
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Growth of solid tumors or metastasis requires, besides massive biomedical changes, also a spatial remodelling of the tissue. This remodelling, often including displacements of healthy tissue around, requires mechanical work to be done. These mechanics of growth has attracted a lot of attention in recent years, but still remains poorly understood.

Particle based simulation techniques offer a different perspective to study growth phenomena. Using a minimalistic approach, we predict results for some basic assumptions. These results are compared with experimental data and theoretical predictions. The combining simulations with experiments or analytic theory has lead to some surprising insights into the mechanics of growing tissues.
I will present an overview of the simulation technique, and provide examples how it contributed to recent developments in tissue growth and collective cell migration.

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Rheology of the active cell cortex in mitosis

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The cell cortex is a key structure for the regulation of cell shape and tissue organization. To reach a better understanding of the mechanics and dynamics of the cortex, we study here HeLa cells in mitosis as a simple model system. In our assay, cells are dynamically compressed between two parallel plates. Our measurements indicate that the cortical layer is the dominant mechanical element in mitosis as opposed to the cytoplasmic interior. To characterize the time-dependent rheological response, we extract a complex elastic modulus which characterizes the resistance of the cortex against area dilation. In this way, we present a rheological characterization of the cortical actomyosin network in the linear regime. Furthermore, we investigate the influence of actin crosslinkers and the impact of active prestress on rheological behavior. Notably, we find that cell mechanics in mitosis is captured by a simple rheological model characterized by a single time scale on the order of 10 seconds which marks the onset of fluidity in the system.

Bridging the gap between single cell migration and collective dynamics

Frey, Erwin
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Huge amounts of experimental data relating to the emergence of collective cell migration as one proceeds from the behavioral dynam- ics of small cohorts of cells to the coordinated migratory response of cells in extended tissues are now available. Integrating these findings into a mechanistic picture of cell migration which is appli- cable across such a broad range of system sizes constitutes a crucial step towards a better understanding of the basic factors that deter- mine the emergence of collective cell motion. Here we propose a cellular-automaton-based modeling framework, which focuses on the integration of high-level cell functions and their concerted effect on cellular migration patterns. In particular, we adopt a top-down ap- proach to incorporate a coarse-grained description of cell polarity and its response to mechanical cues, and address the impact of cell adhe- sion on collective migration in cell groups. We demonstrate that the model faithfully reproduces typical cell shapes and movements down to the level of single cells, and yet is computationally efficient enough to allow for the simulation of (currently) up to O(10^4) cells. To de- velop a mechanistic picture that illuminates the relationship between cell functions and collective migration, we present a detailed study of small groups of cells in confined circular geometries, and discuss the emerging patterns of collective motion in terms of specific cellular properties. Finally, we apply our computational model at the level of extended tissues, and investigate stress and velocity distributions as well as front morphologies in expanding cellular sheets.

Asymmetric segregation of endosomes in an asymmetric spindle

Gonzalez-Gaitan, Marcos
(University of Geneva, Biochemistry Department, Geneva 4, Switzerland)

During asymmetric division, fate determinants at the cell cortex segregate unequally into the two daughter cells. We have recently showed that Sara signaling endosomes in the cytoplasm also segregate asymmetrically during asymmetric division. Biased dispatch of Sara endosomes mediates asymmetric Notch/Delta signaling during the asymmetric division of sensory organ precursors in Drosophila. In flies, this has been generalized to stem cells in the gut and the central nervous system. We also showed that, in zebrafish, Sara endosomes are implicated in asymmetric cell fate assignation during division of the neural precursors of the spinal cord. However, the mechanism of asymmetric endosome segregation is not known. We unravelled now this mechanism. The plus-end kinesin motor Klp98A targets Sara endosomes to the central spindle. At the central spindle, endosomes move bidirectionally on an antiparallel array of microtubules. The microtubule depolymerising kinesin Klp10A and its antagonist Patronin generate central spindle asymmetry. The asymmetric spindle, in turn, polarizes endosome motility, ultimately causing asymmetric endosome dispatch into one daughter cell. Spindle inversion targets the endosomes to the wrong cell. Our data uncovers the molecular and physical mechanism by which organelles localized away from the cellular cortex can be dispatched asymmetrically during asymmetric division.

Microbes under pressure

Hallatschek, Oskar
(University of California, Berkeley, Physics and Integrative Biology, Berkeley, USA)

In natural settings, microbes tend to grow in dense populations where they need to push against their surroundings to accommodate space for new cells. The associated contact forces play a critical role in a variety of population-level processes, including biofilm formation, the colonization of porous media, and the invasion of biological tissues. Although mechanical forces have been characterized at the single cell level, it remains elusive how collective pushing forces result from the combination of single cell forces. Here, we reveal a collective mechanism of confinement, which we call self-driven jamming, that promotes the build-up of large mechanical pressures in microbial populations. Microfluidic experiments on budding yeast populations in space-limited environments show that self-driven jamming arises from the gradual formation and sudden collapse of force chains driven by microbial proliferation, extending the

framework of driven granular matter. The resulting contact pressures can become large enough to slow down cell growth, to delay the cell cycle in the G1 phase, and to strain or even destroy the microenvironment through crack propagation. Finally, we discuss how discuss how collective pushing dynamics can promote the emergence of mutational jackpot events. Our results suggest that self-driven jamming and build-up of large mechanical pressures is a natural tendency of microbes growing in confined spaces, contributing to microbial pathogenesis and biofouling.

Bioimaging across scales with light sheets

Hufnagel, Lars
(European Molecular Biology Laboratory Heidelberg, Cell Biology and Biophysics Unit, Heidelberg, Germany)

Selective-plane illumination microscopy has proven to be a powerful imaging technique due to its unsurpassed acquisition speed and gentle optical sectioning. We present a multiview selective-plane illumination microscope (MuVi-SPIM), comprising two detection and illumination objective lenses, that allows rapid in toto fluorescence imaging of biological specimens with subcellular resolution. However, even in the case of multi-view imaging techniques that illuminate and image the sample from multiple directions, light scattering inside tissues often severely impairs image contrast. Here we combine multi-view light-sheet imaging with electronic confocal slit detection (eCSD) on modern sCMOS sensors. In addition to improved imaging contrast, eCSD doubles the acquisition speed in multi-view setups with two opposing illumination directions as it allows for simultaneous dual-sided illumination without the otherwise inherent loss in image quality. This eliminates the need for specimen-specific data fusion algorithms and thus greatly reduces image post-processing, eases data handling and storage. We will demonstrate application of light sheet imaging for probing large scale tissue interaction and embryonic development in fly and early mouse.

Biomechanical regulation of organ growth through Hippo signaling

Irvine, Kenneth D.
(Rutgers, The State University of New Jersey, Waksman Institute of Microbiology, Molecular Biology and Biochemistry, USA)

Normal health and physiology is dependent upon formation of organs of appropriate size. Cells in a developing organ are exposed to multiple growth factors, which provide information about their location, developmental stage, and nutritional status. In addition to this biochemical environment, cells in a developing organ also experience a mechanical environment, in which they are subject to forces through their contact with neighboring cells and the extracellular matrix. The mechanical environment has also been proposed to modulate organ growth, yet how this occurs and what it contributes to in vivo growth regulation remains largely unknown. We recently discovered a biomechanical signaling pathway, which we refer to as the Jub biomechanical pathway, that regulates organ growth through modulation of the conserved Hippo signaling network. I will discuss evidence that this pathway carries out a mechanical feedback response that modulates growth rates in developing organs.

Tissue ecology: Recognition and response of cells to local differences in fitness

Johnston, Laura
(Columbia University, Medical Center, Department of Genetics & Development, New York, USA)

Stochastic fate choice and cell-to-cell interactions in tissue homeostasis

Kawaguchi, Kyogo
(Harvard Medical School, USA)

Many adult tissues are dynamically sustained by the rapid turnover of cells. Previous works have addressed the validity of stochastic fate models in adult tissues by comparing the predicted statistical properties with long-term clonal tracing experiments[1]. However, the mechanism of tissue homeostasis - how cell division and differentiation are precisely balanced in stochastic fate choice - is still unknown. Regulation mechanisms can involve intrinsic fate choice tuned at the single-cell level, or include extrinsic

feedback from neighboring cells or signaling molecules. Since different mechanisms, intrinsic or extrinsic, will result in different universality classes at the level of abstract models, predictions from simplified models can be useful in discriminating the underlying rules in real tissues. Here we will start by discussing a stochastic interacting particle model that includes the different mechanisms, intrinsic and extrinsic, as the two extreme cases of homeostasis regulation[2]. After describing some of the recent data obtained from live imaging of mouse skin[3], we will show our recent attempts to reconstitute tissue homeostasis in a cultured system.

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Coordination of organ growth during Drosophila development

Léopold, Pierre
(Univ. Nice / CNRS / Inserm, IBV, Nice, France)

Mechanical feedback driven epithelial remodeling

Mani, Madhav
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Ou quantitative analysis of germ band extension in the early Drosophila embryo motivates exploring the consequence of mechanical feedback at cell-cell junction in the remodeling epithelia. In particular, we will present consequences of myosin bistability driven by junctional tension-dependent recruitment, and junctional shear stress dependent enhancement of cadherin detachment. Together the two effects support the spontaneous emergence of stress cables, as well as a secondary instability responsible for the formation of four-fold vertices and their resolution through rosette-like structures. We comment on the potential generality of the mechanism and phenomena investigated, and experiments that are motivated by our quantitative analysis and modeling of the extending germ band.

Inference of internal stress in a cell monolayer

Marcq, Philippe
(Université Pierre et Marie Curie - Paris VI, Institut Curie, Physico-Chimie Curie, Paris, France)

The mechanical behavior of living tissues is deeply connected with many important biological questions, yet little is known about internal tissue mechanics. Since the traction forces exerted by cells on a planar, deformable substrate can be measured, we propose to combine traction force data with Bayesian inversion to estimate the internal stress field of a cell monolayer. The method is validated using numerical simulations performed in a wide range of conditions. It is robust to changes in each ingredient of the underlying statistical model. Importantly, its accuracy does not depend on the rheology of the tissue. Combining Bayesian inversion with Kalman filtering allows to process time-lapse movies of the traction force field. Examples of applications to epithelial cell monolayers include experimental evidence for stress waves in confined geometries and an estimate of the tissue stress field close to cell delaminations.

Coordinating growth and tissue organization

McNeill, Helen
(Samuel Lunenfeld Research Institute, Mount Sinai Hospital, TORONTO, Canada)

Coordinating Tissue Growth and Tissue organization

Period and Pattern in the Embryo

Oates, Andrew
(The Francis Crick Institute, University College London, London, United Kingdom)

The segmentation clock is a multi-cellular patterning system of genetic oscillators thought to control the rhythmic and sequential formation of the vertebrate embryo's body segments. Individual oscillating cells are synchronised with their neighbours, forming a coherent wave pattern of gene expression. How these wave patterns arise and how they are regulated during embryogenesis is not clear. I will discuss recent progress in understanding the behaviour of individual cells as they slow their oscillations and differentiate during segmentation.

Warburg-like metabolism regulates vertebrate somitogenesis

Oginuma, Masayuki
(Brigham and Women's Hospital/Harvard Medical School, Boston, USA)

Vertebrate somitogenesis occurs by the elongation of the embryo from posterior region known as the tail bud and the periodic segmentation of the presomitic mesoderm (PSM) controlled by genetic signaling such as Fgf, Wnt and Notch. It is unknown whether metabolism also regulates this process. In this study, we examined metabolic activity during somitogenesis with metabolome and transcriptome analysis, and found dynamics of energy metabolism, posterior gradients of glycolysis and increase of mitochondira respiration activity during PSM differentiation. Using time-lapse imaging of developing chicken embryo, we found that glycolysis and respiration have different functions. Glycolysis inhibition blocks elongation but not segmentation, whereas respiration inhibition blocks segmentation but not elongation. Strikingly, metabolism in the tail bud shows several features of cancer cells, that we call “Warburg-like metabolic gradient”, which allows embryo elongation in cooperation with Fgf and Wnt signaling. These results indicate that metabolism has key functions during development: not only energy and biomass production, but also embryo patterning by modulation of signaling pathways.

Mechanical and cell biological control of cell competition

Piddini, Eugenia
(University of Cambridge, Gurdon Institute, Cambridge, United Kingdom)

Cell competition is a fundamental quality control mechanism that helps fit cells to eliminate unfit cells from tissues, thereby acting as a quality control mechanism to help maintain overall tissue health. My group investigates the mechanisms and implications of cell competition for tissue biology. Our strategy is to combine genetics and in vivo studies in Drosophila and cell biological approaches using mammalian cell culture models of cell competition. In my talk I will give an overview of some of our recent work investigating the mechanisms of cell competition and I will highlight that there are several pathways that can earmark cells as losers, which lead to mechanistically distinct modes of cell competition.

Planarian growth and de-growth: A scaling challenge

Rink, Jochen
(Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany)

Planarian flatworms are amazing animals. Probably best known for their ability to regenerate complete and perfectly proportioned animals from arbitrary tissue pieces, they also do not have a fixed body size. Planarians grow when fed and literally shrink when starving, continuously adjusting their body size between 0.5 mm and 20 mm in length or between 15 000 or 7 Millions of constituent cells. Abundant pluripotent stem cells are at the core of such astonishing body plan plasticity and their division progeny continuously replaces all organismal cell types and tissues. Planarians therefore provide a unique experimental system for exploring the establishment, maintenance and scaling of body plan proportions. I will present recent results on the patterning systems specifying the cardinal body axes and the regulation of total cell numbers during growth and de-growth.

Universality in the clonal dynamics in developing tissues

Rulands, Steffen
(University of Cambridge, Cavendish Laboratory, Deparmtent of Physics, Cambridge, United Kingdom)

Lineage tracing studies using transgenic animal models have advanced our understanding of cellular identity, hierarchy and function, providing insights into the mechanisms that support the development, maintenance and regeneration of tissues, as well as the factors leading to their dysregulation in diseased states. However, large-scale cell rearrangements, particularly in development, can lead to the merger and fragmentation of marked cells and their progeny – clones – which may render the retrospective analysis of lineages highly problematic. Giving the example of mouse heart development, we show how such effects lead to emergence of universal scaling distributions of clone size, in which information on the underlying cell dynamics becomes obscured or erased. By mapping the problem of clonal evolution onto the classical theory of aerosols, we elucidate the origin and range of scaling behaviors. In generalizing our studies to other tissue types, we show how biological information on cell fate behavior can be distilled from short-term non-universal clone size dependences.

Physics of epithelial folding

Salbreux, Guillaume
(The Francis Crick Institute, London, United Kingdom)

Three-dimensional deformations of epithelia play a fundamental role in tissue morphogenesis. The shape of an epithelium is determined by mechanical stresses acting within the tissue cells and from the outside environment. In this work, we introduce a three-dimensional vertex model which allows to represent the shape of a tissue in three dimensions by a set of vertices. In the model, the motion of vertices is set by apical, lateral and basal surface and line tensions, as well as intracellular pressures and external forces. Using this framework, we discuss how patterned force generation in an epithelium can drive biological tissue folding.

Mechanical cues for skeletal morphogenesis

Smit, Theodoor
(VU University Medical Center, Amsterdam Institute of Movement, Orthopaedic Surgery, Amsterdam, Netherlands)

Transitions between the mesenchymal and the epithelial cell state are essential to vertebrate organogenesis and they are key to understanding of cancer metastasis and wound healing. Mesenchymal-to-epithelial transition (MET) is not a cell-autonomous process, but is triggered by micro-environmental cues. They can originate from the extracellular matrix and molecular morphogens, but mechanical strain has been suggested as another.
Here we investigate if externally applied tension might function as a micro-environmental cue for MET. We use chick somitogenesis as an in vivo model for MET and observe that a strong axial deformation slowly reorganizes somites into smaller daughter somites. During this reorganization, mesenchymal cells from the somite core undergo MET and get incorporated into the existing somitic epithelia. In silico Cellular Potts modeling supports a contact-induced recruitment mechanism for this incorporation. We conclude that mechanical strain can function as a micro-environmental cue for MET, possibly by lateral induction by epithelial cells.

Tumor Angiogenesis: a mathematical model in three dimensions.

Soares, Maurício
(University of Coimbra, Department of Physics, Coimbra, Portugal)

Cancer is among the leading causes of death worldwide. Sprouting angiogenesis, the process by which new blood vessels grow from existing ones, is crucial in the growth of solid tumors and is also present in more than seventy diseases. In response to a chemotactic stimulus (Vascular Endothelial Growth Factor), endothelial cells of the vessel sprout can adopt either a migratory or a proliferating phenotype. In this

work we use a multi-scale phase field model of vesssel growth in 3D coupled with the blood flow hydrodynamics and we discuss the role of the irrigation, endothelial cells' chemotactic response and proliferation rate as key factors in determining the morphology of vascular networks. Preliminary results show a significant difference in the morphology of the vascular network for the case where the blood flow is taken into account and otherwise. Overall, these results indicate the essential role of the blood flow in angiogenesis.

Development of multiciliated ependymal cells in mammals

Spassky, Nathalie
(École Normale Supérieure, Institut de Biologie, PARIS, France)

Multiciliated cells are epithelial cells that line the airways, the oviduct, the paranasal sinuses and the brain ventricles. Each of these cells extend multiple (more than 50) long beating cilia producing a constant extracellular flow that clears mucus from the airways, moves ova from the oviducts toward the uterus and propels cerebrospinal fluid (CSF) through the cerebral ventricles. Each beating cilium grows from a modified centriole, also called a basal body. In the brain, proper circulation of CSF is crucial for brain functioning, because defects in ependymal cilia lead to hydrocephalus. Hydrocephalus is a common neurological disorder that leads to the expansion of cerebral ventricles and is frequently associated with morbidity and mortality. Neurogenesis persists in the adult brain in two discreet regions, one of which is the subventricular zone (SVZ) of the lateral ventricles, which generates the neurons that migrate to the olfactory bulb. Ependymal cells provide trophic support that creates a permissive neurogenic environment for the adult SVZ, and favor the migration of new neurons thanks to the oriented beating of their cilia. Remarkably, ependymal and neural stem cells adopt a unique organization in the neurogenic region, described as “pinwheels”. Apical processes of NSC form the core of the pinwheel, which is surrounded by ependymal cells. The origin and functions of this peculiar architecture is still mysterious, but it is tempting to speculate that it is necessary for correct neurogenesis, for example through hydrodynamic interactions among these cells. I will present our recent work using multidisciplinary approaches to understand how multiciliated ependymal cells develop in the mouse brain.

Polarity remodelling in asymmetric cell division

Tapon, Nic
(The Francis Crick Institute, London, United Kingdom)

The RASSF family of proteins (RASSF1-RASSF10) has been implicated in both growth control and tissue architecture. Several family members are candidate tumour suppressors linked with Hippo signalling. Our work has identified Drosophila RASSF8 as a modulator of cell junction dynamics and a putative Hippo pathway downstream effector [1]. In mammals, RASSF8 is part of the ASPP/PP1 complex, which has been reported to promote YAP activity by reversing its inhibitory phosphorylation by the Hippo core kinase cascade. We have also shown that Drosophila RASSF (the RASSF1-6 ortholog) antagonises Hippo signalling via the STRIPAK PP2A phosphatase complex, which directly dephosphorylates Hippo kinase [2]. We are currently exploring the function of Drosophila RASSF8, 9 and 10 as components of PP1 phosphatase complexes that controls tissue architecture via the apico-basal and planar cell polarity pathways. In particular, we have shown that RASSF10 is expressed exclusively in Sensory Organ precursor cells, where it serves to link the Fz/Dsh planar cell polarity complex with Bazooka. This allows Bazooka planar polarisation and ultimately ensures proper spindle orientation and segregation of cell fate determinants such as Numb.