BP 33: Focus session: Physics of organoids

Time: Thursday 15:00–17:30 Location: H 1028

Invited Talk BP 33.1 Thu 15:00 H 1028

Symmetry breaking in early embryonic organoids: bridging networks, mechanics and metabolism — •Vikas Trivedi — EMBL Barcelona, Spain — EMBL Heidelberg, Germany

How can tissue shapes and patterns emerge reproducibly and robustly in multicellular systems like animals? Despite more than 100 years of embryology, it still remains unclear how gene networks, forces and mechanical properties and the metabolic state of the cells integrate together to self-organize complex structures. This is due to our inability to disentangle the combined action of these factors (biophysical properties, gene networks and metabolic activity) within populations of genetically equivalent cells. We address this challenge within the context of the establishment of body axes in animals using aggregates of embryonic stem cells (ESCs) that recapitulate hallmarks of early embryonic development in vitro and probe the first symmetry breaking event that establishes anteroposterior polarity. By means of quantitative live imaging, mechanical measurements, molecular perturbations and mathematical modelling, we show how mechanochemical coupling between cells controls tissue rheology and metabolic activity controls the proportions of different cells types by acting upstream of signalling. Altogether, our results allow us to investigate how differentiation trajectories in vivo and in vitro can converge onto similar cell fates through coordinated changes in signaling, metabolic states and biophysical properties.

BP 33.2 Thu 15:30 H 1028

Mechanisms of pattern formation and self-organization in embryonic organoids — •Valentin Dunsing-Eichenauer, Alice Gros, Sham Tlili, Jules Vanaret, Leo Guignard, and Pierre-François Lenne — IBDM & CENTURI, Aix-Marseille University/ CNRS, Marseille, France

The emergence of asymmetries within a mass of equivalent cells is a key event in embryonic development, resulting in formation of the main body axes. We investigate symmetry breaking in gastruloids, an in vitro model of early mammalian embryogenesis. Upon Wnt activation, polarized gene expression patterns emerge from an initially homogenous state, followed by elongation and formation of germ-layer-like tissues. Interestingly, robust symmetry breaking occurs only in aggregates of a certain size, smaller or larger aggregates do not polarize. To understand this phenomenon, we investigate the underlying patterning mechanism. To this aim, we have developed a quantitative imaging pipeline using in toto 2-photon imaging and deep learning based cell segmentation. For aggregates of different size, we quantify i) overall shape, ii) coarse grained spatiotemporal distribution of differentiation, iii) relative proportions of emerging heterogenous cell populations. Our results indicate that cell differentiation emerges first in outer and subsequently propagates to inner cell layers. Concomitantly, the initially continuous adhesion protein network fragments and cells sort into different domains. We next plan to incorporate these findings into a cell-based model to test whether such propagation mechanism and fluctuations in aggregate shape are sufficient to break symmetry.

BP 33.3 Thu 15:45 H 1028

Dynamical systems theory of self-organized collective cell fate patterning — •David Brückner — Institute of Science and Technology, Am Campus 1, 3400 Klosterneuburg, Austria

A key feature of many developmental systems is their ability to self-organize spatial patterns of functionally distinct cell fates. A spectacular example of this ability are artificial stem cell assemblies, which are paving the way towards a quantifiable self-organization of biological systems. However, while the relevant molecular processes are increasingly well understood, we lack conceptual theoretical frameworks for the dynamics and statistics of self-organized patterning. Specifically, it is unclear how to generically quantify the patterning performance of biological self-organizing systems, and how to identify the dynamical systems motifs that optimize this performance. Here, we develop an information-theoretic framework and use it to analyze a wide range of models of self-organization. Our approach can be used to define and measure the information content of observed patterns, to functionally assess the importance of various patterning mechanisms, and to predict optimal operating regimes and parameters for self-organizing systems. I demonstrate the application of our framework using experimental gene expression data of gastruloid and intestinal organoid symmetry breaking. This framework represents a unifying mathematical language to describe biological self-organization across diverse systems.

BP 33.4 Thu 16:00 H 1028

Morphological instability at topological defects in spherical epithelial shells — •Oliver M. Drozdowski and Ulrich S. Schwarz — Institute for Theoretical Physics and BioQuant, Heidelberg University, 69120 Heidelberg, Germany

Spherical epithelial shells like cysts or intestinal organoids are model systems for developmental biology and have large potential for biomedical applications. They also lead to highly interesting physics questions: due to Euler's polyhedron theorem, they must contain at least 12 topological defects in the network of neighbor relations, similar to viral capsids. Topological defects have mainly been studied in a hydrodynamic context. Here we study them in the elastic context of spherical epithelial shells. We start from a three-dimensional vertex model and perform a rigorous coarse-graining procedure to a continuum model. We predict stretching and bending moduli in excellent agreement with computer simulations of the vertex model. For large spherical shells we find a generic morphological instability to an icosahedral shape at topological defects, at a length scale similar to budding events in organoids. This instability can be explained by our continuum theory and might be used by organoids to change shape during development.

15 min. break

BP 33.5 Thu 16:30 H 1028

Quantification of mechanical relaxation in retinal organoid tissues across scales — •Elijah Robinson Shelton[1], Michael Frischmann[1], Achim Theo Brinkop[1], Rebecca James[1], and Friedhelm Serwane[1,2] — [1]Faculty of Physics and Center for NanoScience, LMU Munich, Germany — [2]SyNergy, LMU Munich, Germany

Quantifying mechanical properties is critical for understanding how forces shape tissues during retinal development. Organoids recapitulate retina composition and morphology, providing physicists with a platform to study the mechanics underlying this self-organization. While retina mechanical properties have been investigated with various technologies, such probing has been restricted to timescales of seconds or less. Using retina organoids as in vitro models and ferrofluid droplets as force actuators, we probe retina rheology over a range of timescales. After we inject ferrofluid droplets (30 microns), we live-image organoids on a confocal microscope. We introduce homogenous magnetic fields to actuate the droplets and the tissue. Using linear viscoelastic models, we find a mean elastic modulus of 0.63 kPa when probed at a second timescale. We find viscosities of 4.5 to 15.1 kPa s for strain responses over 5 to 20 minutes, indicating stress relaxation over a range of timescales. To describe this rheology across scales, we employ fractional viscoelastic models and discuss their application to retinal organoid tissue mechanics. This modeling combined with our experimental observations provide mechanical insights for how the retina is shaped during development in vivo and in vitro.

BP 33.6 Thu 16:45 H 1028

DNA microbeads for spatio-temporally controlled morphogen release within organoids — •Tobias Walther[1,2], Cassian Afting[3], Joachim Wittbrodt[3], and Kerstin Göpfrich[1,2] — [1]Max-Planck-Institut für medizinische Forschung, Jahnstraße 29, 69120 Heidelberg — [2]Zentrum für Molekulare Biologie der Universität Heidelberg, INF 329, 69120 Heidelberg — [3]Centre for Organismal Studies Heidelberg, INF 230, 69120 Heidelberg

To this day, organoids across types and species fail to reach full maturity and function. A key reason for this is that current organoid culture methods lack spatial organization of the biochemical cues provided to guide organoids. Here, we introduce stiffness adaptable DNA microbeads as a novel tool for implementing spatio-temporally controllable sources of morphogen into organoids at any point in their life cycle. Employing medaka retinal organoids, we show that DNA microbeads can be integrated into organoids via microinjection and be non-invasively erased by light-triggered breakdown. Coupling a recom-

binant surrogate Wnt to the DNA microbeads nanostructure allowed its temporally controllable release from the microinjection site. We were thus able to bioengineer retinal organoids more closely mirroring the cell type diversity of in vivo retinas. While this work presents a first application, this technology is straightforward to adapt to other organoid applications and does not require specialized equipment for usage

BP 33.7 Thu 17:00 H 1028

Multi-cellular rosette formation guides cellular rearrangement initiating lumen opening in PDAC organoids — •Marion K. Raich[1], Tamara Müller[1], Fridtjof Brauns[3], Samuel J. Randriamanantsoa[1], Ann-Caroline Heiler[1], Maximilian Reichert[2], and Andreas R. Bausch[1] — [1]Chair for Cellular Biophysics, TUM, Garching, Germany — [2]Klinik und Poliklinik für Innere Medizin II, Klinikum rechts der Isar der TUM, Munich, Germany — [3]KITP, UCSB, Santa Barbara, California 93106, USA

Organ development and tissue growth is regulated by morphogenetic programs driven by molecular motors, such as non-muscle myosin II, acting on cytoskeletal crosslinked filaments, like F-actin as well as adherens junctions proteins, e.g E-cadherin. Pancreatic ductal adenocarcinoma (PDAC) organoids, forming branched structures, were used to investigate the contribution of these protein species during distinct morphogenetic growth phases, that result in the emergence of a lumen.

Live-cell imaging of PDAC organoids showed a transformation from an elongated cell shape to an epithelial-like structure. These alterations were marked by the presence of three-dimensional rosette formations, characterized by a wedge-like geometry of the cells, with a minimum of six cells converging at a single point. Rosettes appeared periodically within the branch, having a constant distance based on its diameter. The accumulation of non-muscle myosin II and F-actin at the center of the rosette indicated that stochastically distributed actomyosin dependent force generation was required for cellular rearrangement preceding lumen formation.

BP 33.8 Thu 17:15 H 1028

Rheology in 3D confined spaces: PANC-1 spheroids on polyHEMA-coated substrates using atomic force microscopy — •Isis do Vale Meira Lima, Shruti Kulkarni, Mènie Wiemer, and Manfred Radmacher — Institut für Biophysik, Universität Bremen, Bremen, Germany

Understanding biomechanical properties of living cells and tissues is a relevant foundation in advancing knowledge related to physiological and pathological processes, such as the effects of vascularization in tumor development and metastatic processes. In addition, considering that all types of biological tissues are viscoelastic materials, it becomes necessary to delve into the mechanical response of tissues at multiple time scales. From this point of view, in this work, we have developed a protocol to assemble PANC-1 cells in order to obtain spheroids and quantify their rheological properties using atomic force microscopy (AFM) technique. We used force curves to measure the relaxation response of cell aggregates, extracting the respective Young's modulus, storage and loss modulus from each force curve. PANC-1 cells are originated from a human pancreatic carcinoma. These cells are known to form aggregates, generating a structure which resembles a tumor. To achieve a three-dimensional structure which mimicks the tumor environment, we coated our supports with polyHEMA except at small depressions. Cells will not adhere to the support and aggregate in the depressions. Because of the three dimensional confinement of aggregates it is easy to investigate the tumor-like cell clusters by AFM.