Active soft matter: cell biology in motion

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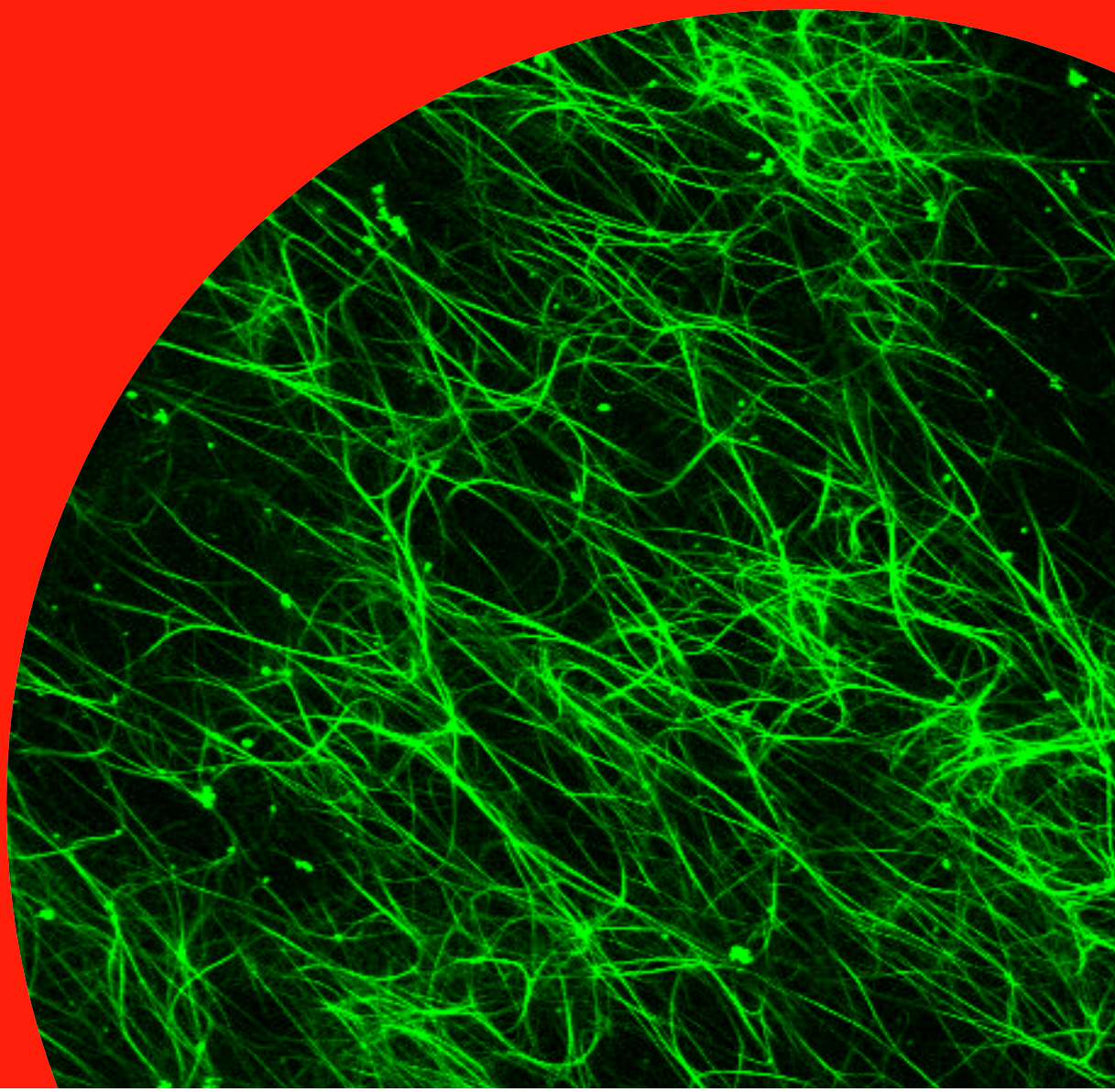

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Catalysis as a nonequilibrium regulator of enzyme-rich condensates

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We present a thermodynamically consistent model describing the dynamics of a multicomponent mixture where one enzyme component catalyzes a reaction between two other components. We find that the catalytic activity, when driven out of equilibrium by consumption of a fuel, is sufficient to induce phase separation into an enzyme-rich and an enzyme-poor phase, without any equilibrium interactions between enzymes. When equilibrium enzyme-enzyme interactions are additionally taken into account, equilibrium and catalysis-induced interactions can compete or cooperate, leading to a rich phase behaviour of the active system. All in all, we show that catalysis-induced interactions can act to regulate the enzymatic activity, which points at the biological relevance of this phenomenon.

Induced Integer Topological Defects Reveal the Importance of Nonlinear Forces in Cellular Active Nematics

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Sheets of confluent cells are often considered as extensile active nematics. When forming such a layer, neural progenitor cells (NPCs) are known to accumulate at +1/2 topological defects and to escape from -1/2 ones. Integer-charge defects, however, generally do not form spontaneously.

By using microfabricated patterns, we induced diverse +1 topological defects (asters, spirals, and targets) within monolayers of NPCs. Remarkably, cells are consistently attracted to the core of +1 defects regardless of their type, challenging existing theories and the conventional extensile/contractile dichotomy.

We trace back the origin of this accumulation behavior to previously overlooked `nonlinear active forces' using a combination of experiments and a continuous theory derived from a cell-level model. Our findings demonstrate that +1 topological defects reveal key features of active nematics and offer a new way to classify these systems.

Synthetic Cells: from Soft Matter to Cell-Like Behaviours

Contini C

My research group focuses on the development of artificial constructs that simulate the structure and functionality of biological cells, using a combination of synthetic and hybrid molecular frameworks engineered for precise manipulation. By mimicking the fundamental characteristics and behaviours of living cells, these cell-like systems offer insights into biological systems, paving the way for a variety of functional applications. A notable challenge in the field of bottom-up synthetic biology is the creation of these synthetic entities capable of dynamic behaviours, such as fusion, material uptake, and autonomous, directional movement in response to environmental stimuli, reflecting the intricate processes of biological communication and organization. The endeavour to construct life-like systems that are both manipulable and interpretable advances our comprehension of life's origins and drive scientific discovery. The fabrication of custom-designed, dynamic cell-like systems holds potential for extensive application in clinical and industrial settings. This rapidly advancing field promises to revolutionize the landscape with the introduction of artificial-cell devices powered by biological compounds. These artificial cell systems are poised to make significant contributions, from aiding in bioremediation efforts to facilitating the creation of biomimetic tissues and materials with controlled spatiotemporal self-organization, showcasing the potential for applications in both environmental and biomedical engineering.

Mesoscale Models of Biomolecular Motors

Harris S

Experimental tools such as cryo-electron microscopy and tomography (cryo-EM/ET) are revealing new regimes of biology at the mesoscale that have not yet been seen, such as the organization of protein complexes into subcellular architectures, and the action of molecular motors. We have developed the Fluctuating Finite Element Analysis (FFEA) software1 for modelling mesoscale biomolecular dynamics, which we are using to understand the walking mechanism of molecular machines such as dynein and myosin based on cryo-EM/ET images.

Using minimal systems to study mechanisms governing cell membrane organisation

Koester D

Cells in our body and in other organisms are constantly exposed to mechanical signals from their environment. The cell plasma membrane and its underlying actin cytoskeleton are the primary receiver of these signals and act as a processing platform for signalling as well as the uptake and release of cargo, to name a few processes. My research interest lies in the understanding of the molecular and physical principles that govern these processes at the plasma membrane. Particularly, by which mechanisms the force generating machinery of the cell cortex, structural filaments, and motor proteins, govern and regulate the mechanical properties of the cell membrane and dynamics of cell membrane components, and vice versa, how membrane organisation and signalling events feed-back to the regulation of the cortex machinery. These mechanisms, which in turn regulate cell motility and cell-cell interactions, underlie important, poorly understood human diseases that constitute global health problems.

Here, we use reconstituted minimal systems of the membrane – cortex interface to dissect and understand the interlinked contributions of cytoskeletal activity and membrane organisation. We use quantitative imaging approaches, controlled mechanical and biochemical manipulations and work with theoretical physicists to understand how cells might use the active cell cortex to generate local and temporal order in the plasma membrane. In a second part, I will present how studying cells adhering to functionalised lipid bilayers can offer new insights into the cell cortex dynamics during E-cadherin mediated cell-cell adhesion.

Active turbulence in bacterial suspensions under the effect of an external chemical gradient

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Collective motion is an emergent phenomena observed in myriad biological systems across many length scales from birds to bacteria. The active constituents in the group provide energy to the system at the individual level via self-propulsion. An archetypal example of this is so-called “active turbulence” observed in dense suspensions of microscopic swimming bacteria such as Escherichia coli. This emerges due to hydrodynamic interactions between the microswimmers and takes the form of high-speed jets and large-scale vortices, shown in accompanying figure.

In isolation, an individual microswimmer travels ballistically (“runs”) until it randomly reorients (“tumbles”). In their typical environment, bacteria such as E. coli direct their movement by sensing their surroundings, specifically following chemical gradients, known as “chemotaxis”. This is done by extending the effective length of runs that happen to orient in the direction of the chemical gradient, which causes a net drift of the swimmer toward the chemoattractant.

Here we investigate the impact of chemotactic behaviour on the presence of the active turbulent state in a bacterial suspension using large-scale, particle-resolved, three-dimensional lattice Boltzmann simulations of model microswimmers. We find that chemotaxis is disrupted by the active turbulent state, inhibiting chemically directed motility at high densities, in agreement with previous experimental observations. Furthermore, we use the resultant understanding of the collective behaviour regime to construct a minimal model for the effective rotational dynamics of swimmers subjected to the fluid flow in this state. We show how this can be used to scrutinise the interplay of active turbulence with more complex, biologically relevant taxis models.

Deciphering the cellular mechanisms driving the structural organization of the skeletal muscle.

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Skeletal muscle formation involves major changes in both cell shape and position. Fast muscle precursors fuse and elongate to form contractile muscle fibres organised in a highly ordered tissue. Such organisation is crucial for the proper function of muscle in generating contractile forces able to propel movement. Yet, despite its physiological importance, it remains an open question as to how complex muscle architecture emerges during embryogenesis.
Here, we use high-resolution live 4D imaging in combination with quantitative analysis to elucidate how complex cell organisation emerges during skeletal muscle formation in zebrafish.
We observed that as future muscle fibres elongate and fuse, they form a highly polarised array parallel to the dorsal-ventral axis. The fibres also rearrange along the medial-lateral axis, with behaviour akin to a structural (topological) transition in the myotome. This change in topological order corresponds with the emergence of a characteristic helical organisation of the fibres by 36 hpf. In mutants lacking fusion or slow muscles, the cell packing and twisting are perturbed, consistent with a change in the local boundary constraints.
Overall, we find that robust muscle formation depends on cells undergoing topology transitions to ensure the emergence of a highly order architecture at the tissue scale.

Simple Chromosome Partitioning Mechanisms and a Mitotic Spindle.

Nedelec F

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We are using theory to explore simple mechanisms of chromosome partitioning with the aim of understanding the design principles of mitotic spindle assembly. Firstly, I will present how artificial evolution in a computer can uncover simple combinations of cytoskeletal elements that will self-organize to pull on a kinetochore pair symmetrically and reliably. I will then discuss the requirements to extend such elementary mechanisms to build a mitotic spindle that can handle multiple chromosomes. Secondly, I will present the characteristics of the mitotic spindles found in the roots of Arabidopsis thaliana, and argue that given these quantities, this plant spindle stands out as an ideal subject to build a quantitatively accurate 3D simulation. I will present our attempts to build such a model, detailing some key assumptions and using a simulation to illustrate the remarkable dynamics of metaphase mitotic spindles.

Emergent spatiotemporal (multistable) patterning enabled by the bio-mechanical underpinnings of different gene regulatory network motifs

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Spatiotemporal pattern formation plays a key role in various biological phenomena including Epithelial Mesenchymal Transition (during cellular differentiation and cancer initiation). Though the reaction-diffusion systems enabling pattern formation in different biological contexts have been studied, the bio-mechanical underpinnings of these processes have not been modeled in detail. Here, we present the emergence of multistable spatiotemporal patterns due to transcriptional/cooperative gene regulation, host-circuit interaction, and protein dimerization. We investigate the patterns formed due to the coupling of inherent multistable behavior of transcriptional toggle switches (bistability), and toggle triads (tristability), coupled with their molecular diffusion, with varying diffusion coefficients, across a two-dimensional tissue. In another setup of a diffusible cellular environment, we investigate emergent spatiotemporal bistability by a motif with non-cooperative positive feedback, that imposes a metabolic burden on its host. Spatiotemporal diffusion coupled with competitive protein dimerization and autoregulatory feedback induces higher-order spatiotemporal multistability — quadra-, hexa-, and septastability. These analyses offer valuable insights into the design principles of synthetic bio-circuits and suggest mechanistic underpinnings of biological pattern formation

Migration of active fluid droplets through interstices

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Active fluid droplets are a fashinting example of bio-mimetic self-propelled system whose motion is triggered by a self-assembled active gel [1,2]. Examples of active gels include actomyosin solutions and networks of extensile microtubule bundles plus kinesin, often modeled as orientationally-ordered soft fluids comprising force dipoles. These droplets can be of interest for the design of artificial microswimmers and in material science, for engineered tissues. In this work, we study, by lattice Boltzmann simulations, the physics of an active fluid droplet migrating across a microchannel hosting a constriction with adhesive properties, whose design resembles realistic conditions (such as a capillary vessel). Droplet and interstice are modeled using a phase field method, where the pillars of the interstice are fluid-free static fields incorporating adhesive effects and the droplet is a dynamic phase field comprising an active liquid crystal. Our simulations show of a variety of dynamic regimes whose properties depend on droplet speed, elasticity of the active gel, degree of confinement and adhesiveness to the pore [3]. Our results suggest that non-uniform adhesion forces between droplet and constriction are crucial in enabling the crossing, in contrast to larger pores where a careful balance between speed and elasticity ensures the transition.

[1] Marchetti, M. C. et al., Hydrodynamics of soft active matter , Rev. Mod. Phys. 85 , 1143, 2013.
[2] T. Sanchez et al., Spontaneous motion in hierarchically assembled active matter, Nature 491, 431-434, 2012.
[3] Tiribocchi, A. et al., The crucial role of adhesion in the transmigration of active droplets through interstitial orifices , Nature Commun. 14 , 1096, 2023.

Optimizing Four-Way DNA Branch Migration Kinetics by Introducing Bulges in Toeholds

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In dynamic DNA nanotechnology, DNA strands are employed to design programmable reaction networks and nanodevices. The key reaction in this technology involves the swapping of DNA strands among different molecular species, achieved through three-way and four-way DNA exchange reactions. Traditionally, the four-way exchange reaction has been slower than the three-way reaction, although both are widely used in constructing reaction circuits. This study presents a novel strategy to enhance the kinetics of the four-way DNA exchange reaction by incorporating bulges into the toeholds of the DNA complexes involved.

We extensively tested the four-way DNA exchange with and without bulges in the toeholds, examining toehold lengths ranging from 3 to 6 nucleotides, concentration levels from 20 nM to 1000 nM, and the inclusion of one or two bulges in the toeholds. The presence of bulges was found to improve the reaction by facilitating an alternative branch migration mechanism and weakening the four-way DNA junction, thereby accelerating both branch migration and binding rates, making them more comparable to those of the three-way reaction. This innovative approach could expand the potential of dynamic DNA nanotechnology, enabling more efficient four-way DNA exchange processes for in vivo applications.

Engineering a Protocell system using in situ RNA gates

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The emergence of RNA nanotechnology has paved the way for innovative applications in synthetic biology, allowing for the design of novel in vitro and in vivo RNA reaction circuits for efficient control of biological systems. By leveraging previous work by Bae et al (1) our technique allows implementation of RNA toehold mediated strand displacment reaction (TMSD) within a giant unilamellar vesicle (GUV) to create a protocell system, that emulates the cellular characteristics of separation from environment and information processing. By encapsulating a DNA template and transcribing an RNA circuit inside of a GUV the possibility to produce higher functioning cellular mimics is possible. We have successfully optimized the high throughput formation of 1 to 20 µm protocells util- ising the inverted emulsion method. GUVs were generated using 1-palmitoyl-2-oleoyl-glycero-3-phosphocholine (POPC) lipids and characterized under an optical microscope. DNA templates encoding the RNA gate complexes can be encapsulated inside the vesicles and transcribed for toehold-mediated strand displacement reactions to take place inside of a GUV (Figure 1). The functionality of the transcribed gates can be assessed by fluorescent DNA reporters.
In summary, this research showcases the potential of RNA nanotechnology in developing in vitro transcribed gates for protocell systems. RNA gate complexes can be used as minimal components to mimic complex genetic circuits. We aim to build more advanced protocell systems that can interact with the external environment by utilising microfluidics and DNA-based synthetic nanopores.

Reference:
(1)Bae, W., Stan, G.-B.V. and Ouldridge, T.E. (2020) ‘in situ generation of RNA complexes for synthetic molecular strand-displacement circuits in Autonomous Systems’, Nano Letters, 21(1), pp. 265–271.

Understanding macrophage-ECM interaction in the endometriosis niche.

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Endometriosis is an inflammatory and gynaecological disease that occurs in 10% of menstruating individuals. It is characterised by the endometrium (inner lining of uterus/womb) growing outside of the uterus, leading to the formation of lesions. Macrophages are important in the pathophysiology of endometriosis.
They are highly adaptive cells and have a variety of phenotypes in lesions,
which is largely governed by local signals within their niche. Therefore, the microenvironment may play a key role in dictating the phenotype and behaviour of these macrophages in lesions.
However, the precise involvement of the microenvironment in the behaviour of these macrophages is not fully understood. This project focusses on the role of collagen and macrophages in the disease progression of endometriosis.
We observed a difference in collagen staining across lesions from weeks 2-6, with a significant increase between weeks 4 and 6 when compared to collagen in the uterus of a mouse model of experimental endometriosis. By combining biophysical and computational methods, this project aims to study macrophage-ECM interactions and how this influences macrophage phenotype in the disease advancement in endometriosis.

Effect of actin-modulating proteins on actin filament mechanics

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The plasma membrane wraps around animal cells to delimit it from the environment, and the underlying thin actin cortex regulates the membrane morphology. Force generation by a dynamic network of actin filaments and actin-modulating proteins (AMPs) induces deformation in lipid membranes, and vice versa, membrane geometry promotes specific actin filament organisations. Examples of such an interplay are filopodia (membrane-surrounded bundles of formin generated, linear actin filaments) or lamellipodia (membrane sheets formed by Arp2/3 generated, branched actin filament networks) formation, where each structure is associated with distinct actin organization and membrane composition. In addition to the well-established actin filament geometries, we recently reported on the formation of highly bent actin filaments and actin rings by the interaction with the N-terminal part of IQGAP proteins, such as curly (S.pombe Rng2(1-189)) [1]. Here, we present a semi-automated computational analysis to extract actin geometry and mechanical properties from microscope images of fluorescently labelled actin filaments.

We compare the curvature distribution of actin filaments associated with 2D membrane-tethered curly in the presence of various AMPs. The curvature distribution of actin filament in the presence of actin-polymerization regulator formin showed a shift towards high curvature when compared to the actin-stabilizing protein tropomyosin and control conditions. We derive mechanical properties of actin filaments, such as the bending modulus and persistence length for each experimental condition, which informs our theoretical model of the curly-induced actin bending. In future, we will expand the analysis to 3D data sets to study features and mechanisms involved in morpho dynamics of lipid membrane spheres (giant unilamellar vesicles) linked to dynamic actin networks.

Dynamic curvature of microtubules in a 2D assay

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In this study, we analyse the conformation of microtubules deformed by the active stress exerted by kinesin-1 motor proteins. To achieve this, we mixed the filaments with motor proteins and applied the solution to a functionalized substrate designed to minimize non-specific protein absorption. This setup allows kinesin-1 to bind to the substrate and move the microtubules by walking on them. The spatial motor distribution is not homogeneous. Under these conditions, the microtubules glide over the motors, similar to a traditional gliding assay. However, the uneven motor concentration generates a force distribution that curves and curls the microtubules, leading to the formation of complex structures, including knots. The concentration of motors is crucial, as demonstrated by experiments conducted with both reduced and increased levels of motor proteins.