Higgs Centre Workshop: Fundamentals of Growing Active Matter (25-26 March 2021)

Book of Abstracts

Invited Talks

Julia Yeomans *(The Rudolf Peierls Centre for Theoretical Physics)*

Modelling confluent cell layers as active nematics

A lot is understood about the ways in which single cells move over a surface, but there are still many questions about the motion of confluent layers where cells coupled through intercellular junctions show a range of behaviours.

Several ways to model collective cell motility have been described in the literature. One of the most successful has been active nematic (a.k.a. active gel) continuum models. However these do not resolve individual cells and it is hard to distinguish the roles of intercellular and intracellular forces. Models which do resolve individual cells and the interactions between them include Potts, vertex and phase field models.

I shall describe recent results using continuum and phase field models of collective cell motility and show how the choices of the forces acting on the cells, in particular polar driving forces and dipolar intercellular activity, lead to different behaviours.

Jens Elgeti *(Foschungszentrum Jülich, Germany)*

Growth mechanics – Coexistence and Evolution

Cancer is in a way evolution on the micro scale. Cells aquier new geno- and phenotypes that result in excessive growth. Evolution is driven by competition – the fitter phenotype outcompetes the weaker one and overtakes the compartment.

For tissue competition, mechanics have been suggested to also play a significant role. Growth implies a change in volume. In physical terms, the conjugate force to a change in volume is a pressure. Thus, in order to grow, cells must exert mechanical pressure on the neighboring tissue. In turn, mechanical stress influences growth, and may play a role in cell competition. This insight has led to the notion of homeostatic pressure – the pressure exerted by a tissue in homeostasis [1]. This suggests that the tissue with higher homeostatic pressure, overwhelms the weaker one [1-6]. We use particle based computer simulations [4] to model growing tissues. Surprisingly we find, that when cross interactions are taken into account, tissues with different homeostatic pressure can coexist [5], and the evolution can favor the weaker tissue, or even result in tumor heterogeneity[6].

[1] Basan et al., 2009, HFSP 3, 265
[2] Montel et al., 2011, PRL 107, 188102
[3] Podewitz et al., 2016, EPL 109, 58005
[4] Basan et al, 2011., Phys. Biol. 8, 026014
[5] Ganai et al. 2019 N. J. Phys.21 063017
[6] Büscher et al., 2020 N. J. Phys. 22 033048

Luca Giomi *(Leiden University)*

The geometry of colonisation

When confined in a long channel, colonies of rod-shaped sessile bacteria are observed to form highly ordered structures, where the cells are aligned along the channel's longitudinal direction. By

contrast, freely expanding colonies on an open surface, give rise to a “mosaic” of microdomains consisting of mutually aligned cells, but whose average orientation does not propagate over the length scale of the entire colony. In this talk, I will describe our recent theoretical and experimental efforts toward understanding the origin of these fascinating examples of self-organisation in growing active matter.

Rosalind Allen *(University of Edinburgh)*

Simulating the growth of bacterial biofilms: spatial structure formation and genetic diversity

Biofilms, or aggregated assemblies of bacteria on surfaces, are believed to be the predominant form of bacterial growth in nature. The also cause significant problems when they form on medical implants or industrial devices. From a basic science point of view, the growth of a biofilm is a beautiful example of non-equilibrium spatial structure formation. I will discuss a simulation study of bacterial biofilm growth, that reveals a phase transition between different types of spatial structure, and highlights the crucial role of the dynamics of the active layer of growing bacteria. I will also discuss the generation, and loss, of genetic diversity within growing biofilms.

Rhoda Hawkins *(University of Sheffield)*

Growing actin networks

When driven out of equilibrium by the consumption of biochemical energy, cytoskeletal protein filaments alone and in combination with molecular motors are able to generate sufficient forces to deform and move cells. In particular the protein actin can polymerise into filamentous networks. Continued growth of actin filaments contributes to cell motility and deformation.
First I will discuss our work on polymerising branched actin, comparing in vitro data with simulations and analytical calculations. Then I will present stochastic simulations of polymerising branched actin exerting force to deform a model membrane in the context of phagocytosis, which is a process by which immune cells engulf pathogens.
I will conclude with some discussion of potential universal characteristics and general principles of growing active matter from the perspective of growing actin networks.

Silke Henkes *(University of Bristol)*

Flow, fluctuate and freeze: Epithelial cell sheets as soft active matter

Epithelial cell sheets form a fundamental role in the developing embryo, and also in adult tissues including the gut and the cornea of the eye. Soft and active matter provides a theoretical and computational framework to understand the mechanics and dynamics of these tissues.
I will start by introducing the simplest useful class of models, active brownian particles (ABPs), which incorporate uncoordinated active crawling over a substrate and mechanical interactions. Using this model, I will show how the extended ’swirly’ velocity fluctuations seen in sheets on a substrate can be understood using a simple model that couples linear elasticity with disordered activity. We are able to quantitatively match experiments using in-vitro corneal epithelial cells. Adding a different source of activity, cell division and apoptosis, to such a model leads to a novel 'self-melting' dense fluid state. Finally, I will discuss a direct application of this simple particle-based model to the steady-state spiral flow pattern on the mouse cornea.

Contributed Talks

Robert Ross *(Okinawa Institute of Science and Technology)*

The emergent physics of growing active matter

I will present an example in which the competition outcome of a population model is controlled using growth. To explain this result required the derivation of equations describing the evolution of pairwise correlations between agents on the growing lattice, and the nature of these equations inadvertently led us to discover a number of additional results. For example, the evolution of population densities on a growing lattice can be made both scale and translationally invariant (or not) depending on how the lattice is grown. I will also suggest a number of biological systems in which I think this result can be applied.

Hannah Jeckel *(Philipps-University Marburg, Germany)*

Learning the space-time phase diagram of bacterial swarm expansion

Coordinated dynamics of individual components in active matter are an essential aspect of life on all scales. Establishing a comprehensive, causal connection between intracellular, intercellular, and macroscopic behaviors has remained a major challenge due to limitations in data acquisition and analysis techniques suitable for multiscale dynamics. Here, we combine a high-through-put adaptive microscopy approach with machine learning, to identify key biological and physical mechanisms that determine distinct microscopic and macroscopic collective behavior phases which develop as Bacillus subtilis swarms expand over five orders of magnitude in space. Our experiments, continuum modeling, and particle-based simulations reveal that macroscopic swarm expansion is primarily driven by cellular growth kinetics, whereas the microscopic swarming motility phases are dominated by physical cell–cell interactions. These results provide a unified understanding of bacterial multiscale behavioral complexity in swarms.

Erik Maikranz *(Saarland University - Center for Biophysics)*

Theoretical modelling of competitive microbial range expansion with heterogeneous mechanical interactions

Microbial range expansion experiments provide insight into the complex link between dynamic structure, pattern formation and evolutionary dynamics of growing populations. In order to investigate the interplay of growth statistics and mechanical interactions we implemented division driven pushing and swapping of cells into an Eden growth model. For the case of the competitive growth of a strongly and a weakly interacting strain we investigate the influence of different mean division times, as well as different mechanical interactions on the development of the colony. Our results show that the susceptibility to cell division induced pushing has a much stronger influence on the structure of the colony than cell sorting towards the colony's perimeter. Motivated by microbial range expansion experiments of Neisseria gonorrhoeae bacteria, we also consider the influence of mutating cells on the structure of the colony. We show that the outgrowth of the three different strains is strongly influenced by the relative strengths of their mechanical interaction. The experimentally observed patterns are reproduced for mechanical interactions of the mutants, which range between those of the strongly and weakly interacting strain.

Sujit Datta *(Princeton University)*

Escape from Flatland: Morphology of Three-Dimensional Bacterial Communities

Many fascinating phenomena arise from the interplay between activity---the consumption of energy---and growth in living systems; prominent examples include self-organization in intracellular polymer networks, the emergence of drug resistance in tumors, and the morphogenesis of bacterial colonies. The latter example is particularly well-studied. Experiments and simulations of 2D colonies have revealed that, when bacterial cells are constrained from individually moving, the interplay between nutrient availability and bacterial growth regulates the morphology of the overall colony. In particular, in a nutrient-rich environment, the colony perimeter is rough but quasi-circular ("Eden-like"); by stark contrast, when growth is nutrient-limited, the colony adopts a highly-branched diffusion-limited aggregation (DLA)-like pattern. While this nutrient-dependent morphological transition has been studied for decades, and is a cornerstone of present understanding of colony morphogenesis, here we demonstrate that it does not arise for 3D colonies of aerobic bacteria. Using experiments in transparent 3D media, we show that growing 3D colonies of E. coli exhibit highly-branched DLA-like patterns even in nutrient-rich conditions. This behavior reflects a key difference between 2D and 3D colonies: while 2D colonies are always exposed to oxygen, the growth of a 3D colony inevitably becomes oxygen-limited, driving a transition to branched growth. Because most bacteria inhabit 3D environments, we anticipate that our results will be relevant to describing the morphology of bacterial communities in real-world settings.

Philip Pearce *(Harvard Medical School)*

Emergent order and structure of growing biofilms

Bacterial biofilms are surface-attached multicellular communities encased in extracellular matrix. Biofilms represent a major form of microbial life on Earth and serve as a model active nematic system, in which activity results from growth of the rod-shaped bacterial cells. Here, we combine highly time-resolved single-cell live imaging with 3D multi-scale modeling to investigate the dynamics of all individual cells in growing biofilms. Our analysis implies that local cellular order and global biofilm architecture in these active bacterial communities arise from mechanical cell-cell interactions, and from the physical effects of the external environment.

Ilyas Djafer-Cherif *(Institute of Physical Chemistry, Warsaw)*

Tackling embryogenesis with an Active Junction Model

During gastrulation, and other development stages like germ band extension, epithelial cell sheets spontaneously organise to exert contractile mechanical forces, resulting in convergence-extension flow. Current models assume different types of chemical signalling-based pre-patterning of the junctions, leading to both tension and flow. Here we present a model of self-amplifying contractile cell sheets that posits a myosin-dependent junction contractility with a tension-dependent myosin kinetics leading to a positive feedback loop. This active mechanics model leads to the spontaneous formation of tension chains with both isotropic characteristics and directionality in the presence of an applied stress. We claim that active T1 transitions also known as cell intercalations are the main driver of convergent-extension flows. We show that for smallest active T1 unit possible, that is a patch of 4 cells, the model features spontaneous active T1 transitions when the surrounding passive matrix is stretched. Importantly these T1 transitions are resolved via the sole mechanical forces without enforcing cell-level symmetry breaking. We systematically studied our model with

parameters controlling both the myosin kinetics and the force magnitude, we quantify their effect on the cell and tissue level deformations and on the myosin response. Further, on a tissue when all cells are activated these T1 transition cooperatively lead to a tissue rearrangement and to biologically plausible convergence-extension flows.

Poster presentations

Jan Cammann *(Loughborough University)*

Boundary-interior principle for microbial navigation in geometric confinement

In recent years, biological microswimmers have attracted considerable interest due to the biological and ecological implications of understanding the mechanisms governing their dynamics. The possibility to harness their motion to power microdevices is a topic of exceptional importance for modern microtechnology. When the motion of a motile cell is observed closely, it appears erratic, and yet the combination of nonequilibrium forces and surfaces can produce striking examples of organization in microbial systems. While our current understanding is based on bulk systems or idealized geometries, it remains elusive how and at which length scale self-organization emerges in complex geometries. In this talk I will describe experiments, analytical and numerical calculations [1] to study the motion of motile cells under controlled microfluidic conditions, and demonstrate that a robust topology of probability flux loops organizes active motion even at the level of a single cell exploring an isolated habitat. By accounting for the interplay of activity and interfacial forces, we find that the boundary's curvature determines the nonequilibrium probability fluxes of the motion. We theoretically predict a universal relation between fluxes and global geometric properties that is directly confirmed by experiments. [1] J. Cammann, et al. "Boundary-interior principle for microbial navigation in geometric confinement." arXiv:2011.02811 (2020).

Mixon Faluweki *(Nottingham Trent University)*

Quantifying the flexural rigidity of cyanobacteria

The structural and mechanical properties of biofilms contribute to their successes in a wide variety of ecological niches; filamentous cyanobacteria show an increase in complexity from single cells towards multicellular structures. We study how the microscopic activity of these organisms gives rise to the macroscopic properties of their colonies, including biofilms and biomats. One of the most important mechanical properties is the flexural rigidity, also known as the bending modulus. Direct measurement of the flexural rigidity of filamentous cyanobacteria is a challenging task due to their small size. Here, we quantify the flexural rigidity of three cyanobacteria species via bending tests in a microfluidic flow device, where single cyanobacteria filaments are introduced into the microfluidic channel and deflected by fluid flow. This measurement is confirmed separately by measuring Young's modulus using atomic force microscopy and use it to calculate the cell wall thickness of the filaments. Our cell wall estimates are consistent with published values. These mechanical properties will control how individual filaments of cyanobacteria bend or curve when they interact with each other, or their environment, for example in their alignment into bundles, or with flows or physical boundaries.

Yuting (Irene) Li *(University of Cambridge)*

Non-equilibrium phase separation with reactions

Materials undergoing both phase separation and chemical reactions (defined here as all processes that change particle type or number) form an important class of non-equilibrium systems. Examples range from suspensions of self-propelled bacteria with birth-death dynamics, to bio-molecular condensates, or 'membraneless organelles', within cells. In contrast to their passive counterparts, such systems have conserved and non-conserved dynamics that do not, in general, derive from a shared free energy. This mismatch breaks time-reversal symmetry and leads to new types of dynamical competition that are absent in or near equilibrium. We construct a canonical scalar field theory to describe such systems, with conserved and non-conserved dynamics obeying Model B and Model A respectively (in the Hohenberg-Halperin classification), chosen such that the two free energies involved are incompatible. The resulting minimal model is shown to capture the various phenomenologies reported previously for more complicated models with the same physical ingredients, including microphase separation, limit cycles and droplet splitting. We find a low-dimensional subspace of parameters for which time-reversal symmetry is accidentally recovered, and show that here the dynamics of the order parameter field (but not its conserved current) is exactly the same as an equilibrium system in which microphase separation is caused by long-range attractive interactions.

Helen Pringle *(University of Sheffield)*

Pattern formation in the axon: Self-Assembly of Actin Rings

Neuronal axons are crucial to the connectivity of the nervous system; however, they are vulnerable to damage through injury and neurodegenerative diseases which can disrupt the internal cell cytoskeleton, resulting in cell death or loss of function. Recent advances in super-resolution microscopy have exposed a highly organised cytoskeletal structure within the axon, referred to as the membrane-associated periodic skeleton (MPS). This structure consists of rings of actin filaments, spaced periodically at approximately 190 nm intervals, and connected laterally by spectrin tetramers. The mechanism by which this structure forms, and the benefits derived from its organisation, are currently unknown. We use in-silico models to investigate the factors driving self-assembly of the MPS structure in axons. Cytoskeletal filaments and their accessory proteins are modelled within a viscous, axon-like environment. The system is simulated using the Cytosim software, employing a combined approach of Langevin dynamics to simulate Brownian motion of filaments, along with a subset of stochastic protein-level events such as binding and polymerisation, which are evaluated at every timestep. We search parameter space and show that self-assembly of an MPS-like structure is possible under specific parameter values.

Jan Kirschbaum *(Max Planck Institute for Dynamics and Self Organization)*

Controlling biomolecular condensates via chemical reactions

Biomolecular condensates are small droplets forming spontaneously in biological cells through phase separation. They play a role in many cellular processes, but it is unclear how cells control their size and growth. Cellular regulation often relies on post-translational modifications of proteins. For biomolecular condensates, such chemical modifications could alter the molecular interaction of key condensate components. We here test this idea using a theoretical model based on non-equilibrium thermodynamics. We identify that control of dissolution or formation is only

fast when external energy input drives the reaction out of equilibrium. In particular, a non-equilibrium flux balance leads to stable droplets of fixed size if the reactions differ between the droplet and the solvent phase. We quantify the energetic cost of size control and find that smaller droplets consume more energy. The necessary imbalance in the reaction could be created by enzymes localizing to the droplet. Since this situation is typical inside cells, we speculate that our proposed mechanism stabilizes multiple droplets with independently controlled size and count. Our model provides a novel and thermodynamically consistent framework for describing droplets subject to non-equilibrium chemical reactions.

Liam Ruske *(University of Oxford)*

Three-dimensional organisation and morphology of active droplets

It is increasingly becoming apparent that the physical concepts of forces and flows play an important role in understanding biological processes, from the spread of cancers to morphogenesis, the development of organisms. One important source of activity in biological systems is cell divisions which generate extensile forces and drive dynamical patterns in cell assemblies. Indeed, even in the absence of division events individual cells can generate strong extensile or contractile forces to move and self-organise. Such a continuous influx of energy leads to striking collective behaviour like the chaotic flow patterns of active turbulence seen in cell-monolayers and self-propelled topological defects which are now thought to be relevant to some modes of biofilm formation. This talk presents a numerical investigation of three-dimensional droplets composed of active matter and the ways in which their shapes change in response to the continuous input of energy. The unprecedented range of complex morphologies of 3D active droplets is reminiscent of many processes seen in biology, ranging from the continuous formation of finger-like protrusions, similar to the collective motion of invading cancer cells, to wrinkling of the droplet surface or invagination leading to cup-shaped droplets, suggestive of patterns seen during morphogenesis. These results provide a starting point for establishing a link between 3D active nematics and the tissue-scale organisation of biological systems.

Roshan Shrestha *(Central Department of Physics, Tribhuvan University)*

Molecular Dynamics Simulations of Nanoparticles in Model Bilayers: Lipid Phase Separation and Membrane Protein Interaction

The unique and adjustable properties of nanoparticles present enormous opportunities for their use as targeted drug delivery vectors. For example, nanoparticles functionalized with key surface ligands have been shown to pass through phospholipid bilayers without causing localised disruption. However, the further effects nanoparticles have on multi-component phospholipid bilayers remain unclear. We investigate the effects nanoparticles have on lipid phase separation and we also include models of our most recent work on the interaction between nanoparticles and transmembrane proteins in model bilayers.

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