Novel Physics in Living Systems?

French-German WE-Heraeus-Seminar

02 - 06 September 2019
at the Station Biologique de Roscoff, France

WILHELM UND ELSE
HERAEUS-STIFTUNG

Abstracts of Talks

(in alphabetical order)

When neural systems tell us that we should respect their complexity

Demian Battaglia[1]

[1]*Aix-Marseille University, Institute for Systems Neurosciences UMR 1106, Marseille, France*

Perception, cognition and behaviour rely on flexible communication between microcircuits in distinct cortical regions. Based on both growing experimental evidence and modelling, it has been proposed that changing patterns of collective oscillatory synchrony support flexible information routing. The stochastic and transient nature of oscillations in vivo, however, is hard to reconcile with such a function. Recently, we advanced on this debate between “oscillo-partisans” and “oscillo-skeptics”, by showing that models of cortical circuits near the onset of oscillatory synchrony are well able to selectively route information streams. Indeed, gamma bursts arise stochastically but match their timing, frequency and phase across coupled regions in a self-organized manner, in such a way that selective and controllable communication is still feasible.

Moving to the analysis of actual electrophysiological recordings in hippocampus, enthorinal cortex and prefrontal cortex of anaesthetised and sleeping rats, we investigate whether dynamic changes between oscillatory modes, beyond inter-circuit routing, also affect ongoing computational manipulations of information within local circuits. Through an unsupervised algorithmic approach, we identify a multiplicity of internal “computing substates”, characterized by the flexible recruitment of alternative hub neurons, transiently specialising in different primitive operations of information processing (buffering and funneling). We find that different global oscillatory states give access to alternative “dictionaries" of computing substates. Furthermore, oscillatory states also affect the “syntax” of substate sequences, by modulating their relative complexity (measured by variations of Kolmogorov-Chaitin entropy). Global oscillatory states seem thus to set a “language” for information processing, beyond mere routing modes.

References

[1] Kirst, C., Timme, M. & Battaglia, D. Dynamic information routing in complex networks. *Nature Comms* **7,** 11061 (2016).

[2] Palmigiano, A., Geisel, T., Wolf, F. & Battaglia, D. Flexible information routing by transient synchrony. *Nature Neurosci* **20,** 1014–1022 (2017).

[3] Clawson, W. *et al.* Computing hubs in the hippocampus and cortex. *Science Adv* **5,** eaax4843 (2019).

Proteins: sequences and physics

Anne-Florence Bitbol[1]

[1]*Sorbonne Université, CNRS, Laboratoire Jean Perrin (UMR 8237), F-75005 Paris, France*

Proteins and multi-protein complexes play crucial roles in our cells. The amino-acid sequence of a protein encodes its function, including its structure and its possible interactions. In evolution, random mutations affect the sequence, while natural selection acts at the level of function. Hence, shedding light on the sequence-function mapping of proteins is central to a systems-level understanding of cells, and has far-reaching applications in synthetic biology and drug targeting. The current explosion of available sequence data has inspired data-driven approaches to discover the principles of protein operation. At the root of these approaches is the observation that amino-acid residues which possess related functional roles often evolve in a correlated way.

In the first part of my talk, I will present two novel statistical physics-inspired methods to predict protein-protein interactions from sequence data. One method [1] relies on the maximum-entropy inference approach that has already allowed to infer protein structures from sequences [2], and the other one [3] is based on information theory. I will show that these methods accurately identify interaction partners among the proteins of two families, starting from sequence data alone. I will also discuss the role of correlations arising from the shared evolutionary history of interacting partners in the success of these methods [4].

In the second part of my talk, I will propose a physical interpretation of the "sectors" of collectively correlated amino acids that have been discovered in several protein families through statistical analyses of sequence alignments [5]. I will show that selection acting on an additive physical property of a protein generically gives rise to a sector [6].

References

[1] Bitbol AF, Dwyer RS, Colwell LJ, Wingreen NS. Proc. Natl. Acad. Sci. U.S.A. **113**(43):12180–12185 (2016)
[2] Weigt M, White RA, Szurmant H, Hoch JA, Hwa T. Proc. Natl. Acad. Sci. U.S.A. **106**(1):67–72 (2009)
[3] Bitbol AF. PLoS Comput. Biol. **14**(11), e1006401 (2018)
[4] Marmier G, Weigt M, Bitbol AF. Preprint: ArXiv:1906.04266 (2019)
[5] Halabi N, Rivoire O, Leibler S, Ranganathan R. Cell **138**(4):774–786 (2009)
[6] Wang SW, Bitbol AF, Wingreen NS. PLoS Comput. Biol. **15**(4): e1007010 (2019)

Emergence and control of population dynamics and structure in bacterial microcolonies

P. Bittihn[1,3], S. R. Scott[2], A. Didovyk[1], M. O. Din[2], L. Xiong[1], L. S. Tsimring[1], J. Hasty[1,2]

[1]BioCircuits Institute • [2]Department of Bioengineering, University of California San Diego, La Jolla, California, USA
[3]Department of Living Matter Physics, MPI for Dynamics and Self-Organization, Göttingen, Germany

Emergent dynamics in living substrates are essential for biological systems as diverse as the brain, heart, development and bacterial biofilms. Synthetic biology seeks to engineer cellular behavior for biomedical and industrial applications by equipping cells with artificial gene regulatory networks. However, much of the development has taken place in cultures of continuously growing bacteria under homogeneous nutrient conditions, neglecting the mutual interaction between gene expression, colony growth and spatial confinement in potential target environments such as the gut, solid tumors, bioreactors and soil. This complexity remains a major conceptual challenge.

Here, I present two ways to achieve control of bacterial growth dynamics, combining biological processes – such as gene expression and metabolism – with physical coordination – through signal diffusion and growth-mediated mechanical interactions. One is a quorum-sensing circuit which autonomously limits population size. Our theoretical analysis shows that it can be tuned to a range of different population dynamics from steady states to oscillations and can stabilize co-cultures of strains with differing growth rates – consistent with experimental observations [1].

In the second one, we exploit the implicit spatial coupling through self-generated nutrient gradients. Using a reaction-diffusion-advection model, we show that the emergent growth pattern can be controlled by combining gene circuit elements which sense and modulate microbial growth. Experiments confirm that a feedback loop via nutrient transport leads to sustained spatiotemporal oscillations in growth and gene expression [2].

Our results lay the foundation for engineering defined bacterial population dynamics by viewing multicellular substrates as complex physical systems.

References

[1] S. R. Scott, M. O. Din, P. Bittihn, L. Xiong, L. S. Tsimring, J. Hasty, Nature Microbiology **2**, 17083 (2017)

[2] P. Bittihn, A. Didovyk, L. S. Tsimring, J. Hasty, bioRxiv 575068 (2019)

Microscale nonequilibria for the emergence of life

C. Mast and D. Braun

LMU Munich, Germany

The Origin of Life is one of the fundamental, unsolved riddles of modern science. Life is a stunningly complex non-equilibrium process that keeps its local entropy low to drive the Darwinian evolution of informational polymers. It is straightforward to argue that first living systems were jump-started in natural non-equilibrium settings.

In a cross-disciplinary, world-wide effort, we are assembling a chain of experimental evidence using non-equilibrium microsystems to drive Darwinian evolution autonomously. Our hypothesis focuses on geological temperature gradients across pores of rock. The most recent results explore physical mechanisms of self-amplification such as phase transitions[1], thermophoresis[2] to enhance polymerization[3], symmetry breaking in sequence space[4], capillary flow in microscale water cycles[5] and micro-convection[6] to support and sustain the replication of the first RNA or DNA.

Above experiments are part of the collaborative research center “Emergence of Life” and the Excellence Cluster “Origins” in Munich. Our mission is to combine the puzzle pieces from different disciplines into one experimental scenario to reconstruct the first steps of life in the lab.

References

[1] Morasch, Matthias, Dieter Braun, and Christof B. Mast. "Heat-Flow-Driven Oligonucleotide Gelation Separates Single-Base Differences." *Angewandte Chemie* 128.23 (2016): 6788-6791.

[2] Keil, Lorenz MR, et al. "Proton gradients and pH oscillations emerge from heat flow at the microscale." *Nature communications* 8.1 (2017): 1897.

[3] Mast, Christof B., et al. "Escalation of polymerization in a thermal gradient." *Proceedings of the National Academy of Sciences* 110.20 (2013): 8030-8035.

[4] Toyabe, Shoichi, and Dieter Braun. "Cooperative Ligation Breaks Sequence Symmetry and Stabilizes Early Molecular Replication." *Physical Review X* 9.1 (2019): 011056.

[5] *Nature chemistry* (2019), accepted

[6] Kreysing, Moritz, et al. "Heat flux across an open pore enables the continuous replication and selection of oligonucleotides towards increasing length." *Nature chemistry* 7.3 (2015): 203.

Collective motion in bacterial suspensions

C. Douarche[1], V.A. Martinez[2], E. Clément[3], P.-H. Delville[1], J. Schwarz-Linek[2], J. Arlt[2], A.K. Creppy[1], H. Auradou[1], A.N. Morozov[2], and W.C.K. Poon[2].

[1]Laboratoire FAST, Univ. Paris-Sud, CNRS, Univ. Paris-Saclay, 91405, Orsay, France.
[2] SUPA and School of Physics & Astronomy, The University of Edinburgh, Edinburgh EH9 3FD, United Kingdom
[3] Laboratoire PMMH, UMR 7636 ESPCI/CNRS/Université P.M. Curie/Université Paris-Diderot, 75005 Paris, France

Suspending highly motile *Escherichia coli* in a liquid lowers the viscosity of the solution at low shear rate [1]. At higher cell concentrations, a regime of near zero viscosity can be reached. In this work, we investigate the system-size dependence of the rheological response of an *E. coli* suspension as a function of shear rate and bacteria concentration using a low-shear Couette rheometer. Additionally, we image the suspensions in a cone-plate rheo-imaging setup allowing direct visualisation of the collective organisation under shear. We find the flow becomes banded and viscosity decreases to near zero at a bacterial concentration close to where collective motion appears in absence of flow.

Indeed, dense suspensions of swimming bacteria display remarkable collective motion, *i.e.* local bacterial ordering associated with a characteristic correlation length, reminiscent of turbulent flow behaviour. Using video microscopy over large fields of view (up to 3 mm x 4 mm), and particle image velocimetry, we calculate the spatial correlation of the velocity vectors and extract a characteristic length scale. At sufficiently high bacterial concentrations, we find this length to be proportional to the smallest system size. However, the absence of saturation towards large system-sizes suggests there is no intrinsic length-scale in these dense populations of such 'pusher-like' swimmers.

References

[1] H.M. Lopez , J. Gachelin, C. Douarche, H. Auradou, E. Clément, *Phys. Rev. Lett*. **115**, 028301 (2015).

Dynamics of bacterial collective behavior

K. Drescher[1,2]

[1]*Max Planck Institute for Terrestrial Microbiology, Marburg, Germany*
[2]*Department of Physics, Philipps-Universität, Marburg, Germany*

In nature, bacteria often engage in a range of collective behaviors, which coordinate activities of communities. In this presentation, I will demonstrate how two bacterial behaviors, swarming and biofilm formation [1,2], are unified by physical interactions, chemical signaling, and dynamical transitions [3,4]. I will show how these collective behaviors arise from cell-cell interactions, and the physiological state of individual cells. Furthermore, I will introduce new experimental methods for investigating bacterial collective behaviors.

References

[1] Flemming & Wuertz, Nat. Rev. Microbiol. 17, 247 (2019)
[2] Kearns, Nat. Rev. Microbiol. 8, 634 (2010)
[3] Jeckel et al., PNAS **116**, 1489 (2019)
[4] Hartmann et al., Nature Physics **15**, 251 (2019)

New principles of material design – mechanics of the actin cortex

M. Mokbel[1] K. Hosseini[2] S. Aland[1] and E. Fischer-Friedrich[2]
[1]Faculty of Informatics/Mathematics, Hochschule für Technik und Wirtschaft, Dresden,Germany
[2]Biotechnology Center, Technische Universität Dresden, Dresden, Germany

Cell shape changes are vital for many physiological processes such as cell proliferation, cell migration and morphogenesis. They emerge from an orchestrated interplay of cellular force generation and cellular force response both crucially influenced by the actin cytoskeleton. To model cellular force response and deformation, cell mechanical models commonly describe the actin cytoskeleton as a contractile isotropic incompressible material. However, in particular at slow frequencies, there is no compelling reason to assume incompressibility as the water content of the cytoskeleton may change. Here we challenge the assumption of incompressibility by comparing computer simulations of an isotropic actin cortex with tunable Poisson ratio to measured cellular force response. Comparing simulation results and experimental data, we determine the Poisson ratio of the cortex in a frequency-dependent manner. Our results show that the Poisson ratio of the cortex depends on the frequency and may deviate from the incompressible case. In addition, our results suggest that the assumption of cortex isotropy is violated at large time scales likely due to anisotropic actin cortex repolymerization from the membrane.

Emergence and Self-Organization in Biological Systems

Erwin Frey,
Arnold-Sommerfeld-Center for Theoretical Physics
Ludwig-Maximilians-Universitaet Muenchen
Theresienstrasse 37
D-80333 Muenchen, Germany

Isolated systems tend to evolve towards thermal equilibrium, a special state that has been a research focus in physics for more than a century. By contrast, most processes studied in biological systems are far from equilibrium. A fundamental overarching hallmark of all these processes is the *emergence of structure, order, and information*, and we are facing the major challenge to identify the underlying physical principles. Two particular exciting problems are the self-organized formation of spatio-temporal patterns and the robust self-assembly of complex structures. In both fields there are recent advances in understanding the underlying physics that will be reviewed in this talk. In *reaction–diffusion systems*, it has been shown that the essential dynamics is the spatial redistribution of the conserved quantities which leads to moving equilibria [1,2]. Efficient *self-assembly* of macromolecules and protein clusters is a vital challenge for living organisms: Not only are resources limited but also are malfunctioning aggregates a substantial threat to the organism itself [3].

[1] Rethinking Pattern Formation in Reaction-Diffusion Systems, Jacob Halatek & Erwin Frey, Nature Physics 14, 507-514 (2018).

[2] Phase-space geometry of reaction--diffusion dynamics, Fridtjof Brauns*, Jacob Halatek* & Erwin Frey, submitted for publication [arXiv:1812.08684].

[3] Stochastic Yield Catastrophes and Robustness in Self-Assembly, Florian M. Gartner*, Isabella R. Graf*, Patrick Wilke*, Philipp M. Geiger & Erwin Frey, submitted for publication.

How living matter self-organizes while breaking action-reaction symmetry

Jaime Agudo-Canalejo[1] and Ramin Golestanian[1,2]

[1]Max Planck Institute for Dynamics and Self-Organization (MPIDS), D-37077 Göttingen, Germany
[2]Rudolf Peierls Centre for Theoretical Physics, University of Oxford, Oxford OX1 3PU, UK

Cells and microorganisms produce and consume all sorts of chemicals, from nutrients to signalling molecules. The same happens at the nanoscale inside cells themselves, where enzymes catalyze the production and consumption of the chemicals needed for life. In this work, we have found a generic mechanism by which such chemically-active particles, be it cells or enzymes or engineered synthetic colloids, can "sense" each other and ultimately self-organize in a multitude of ways. A peculiarity of these chemical-mediated interactions is that they break action-reaction symmetry: for example, one particle may be repelled from a second particle, which is in turn attracted to the first one, so that it ends up "chasing" it [1,2]. Such chasing interactions allow for the formation of large clusters of particles that "swim" autonomously. Regarding enzymes, we find that they can spontaneously aggregate into clusters with precisely the right composition, so that the product of one enzyme is passed on, without lack or excess, to the next enzyme in the metabolic cascade [3]. Such clusters, known as metabolons, have in fact been observed in cells but no generic mechanism for their formation was known so far.

References

[1] R. Soto and R. Golestanian, Phys. Rev. Lett. **112**, 068301 (2014)
[2] R. Soto and R. Golestanian, Phys. Rev. E **91**, 052304 (2015)
[3] J. Agudo-Canalejo and R. Golestanian, Phys. Rev. Lett. **123**, 018101 (2019)

From cell dynamics to epithelial tissue patterning

F. Graner[1]

[1]*Complex System and Matter, CNRS & Univ. Paris-Diderot, France*

Development, homeostasis and regeneration of tissues result from a complex combination of genetics and mechanics. Our model system is the Drosophila metamorphosis, during which the fly strikingly changes, within a few days, from a rather simple maggot shape to a refined adult shape with wings, legs, antennas, waist, neck, and compound eye.

To uncover mechanisms governing tissue development, a rigorous multiscale approach is required. The biologist and physicist jointly address several challenges : linking cell-cell interactions with tissue structure; linking cell-level dynamical processes such as divisions, apoptoses and rearrangements, with tissue-level morphogenetical changes; and most important, understanding the interplay between genetics and mechanics, which both contribute to regulate the morphogenesis.

Tremendous progress in experimental techniques now provide access to quantitative cell-scale information within tissues, whether on the cell shapes and shape changes, on cell-cell interaction forces, and on the genes being expressed. Key cell-level properties such as cell activity, fluctuations and heterogeneity induce tissue-level structural and dynamic properties which differ from what is observed for cellular materials in soft matter physics.

Insights into spatial genome organization using polymer physics

H. Chen[1], L. Barinov[1], V. Scolari[2], and T. Gregor[1,2]

[1]Princeton University, Princeton, USA
[2]Institut Pasteur, Paris, France

Finding new physics in biological systems is certainly a worthwhile endeavor, but it still remains a bold challenge. What distinguishes biological systems is their character of being "*alive*", a term that in itself is not clearly defined. From a physics perspective, the closest definition is perhaps that matter constituting biological systems is *active*, and thus working far from equilibrium, dissipating energy, while locally reducing entropy. One way to experimentally probe these attributes is by taking a molecular approach to directly examine the drivers of the smallest living unit, the cell. Here we present our work on the spatial organization of the DNA polymer in the cell nucleus, where we discovered three phenomena whose explanations might harbor insights into novel physics.

The eukaryotic cell nucleus is a micron-sized structure that accommodates the order one-meter long DNA polymer. It is well-established that the packing is organized in both space and time, however the rules that govern this organization and the sustained functionality of the polymer remain elusive. To address this problem, we designed a live imaging assay to simultaneously measure locations of multiple DNA foci and the functional transcriptional readout of a particular DNA locus. Analysis of the statistics of the spatiotemporal fluctuations of these foci in transcriptionally active and inactive contexts reveals stark deviations from simple polymer physics-based models and necessitates new theory to reconcile our experimental findings.

References

[1] H. Chen et al., Nature Genetics **50**, 1296–1303 (2018)
[2] T. Lampo, Biophysical Journal **110**, 338–347 (2016)

Synaptic domains and out-of-equilibrium phase coexistence.

V. Hakim[1]

[1]*Laboratoire de Physique de l'Ecole Normale Supérieure, Paris, France*

Synapses are important biological structures that serve to transmit information between neurons and are thought to be the sites of learning and memory. Yet, it is not well-understood how memory can be retained for years while synaptic components turnover over the course of hours. This is a strong motivation to search for a biophysics understanding of synapse formation and maintenance. In collaboration with A Triller's team (IBENS), we propose to view post-synaptic domains as out-of-equilibrium condensed structures. I will describe our preliminary work in this direction.

The balanced state: the standard model and beyond

David Hansel
Cerebral Dynamics, Plasticity and Learning Laboratory CNRS-UMR 8002,
Integrative Neuroscience and Cognition Center, Paris, France

Strong temporal irregularity and right-skewed, long-tailed distributions of firing rates are distinctive features of cortical spiking activity. Both features are quite puzzling upon consideration of the large number of synaptic inputs a cortical cell receives and the weak correlations among these inputs. A minimal theoretical framework accounting naturally for these features – the balance hypothesis – was proposed by van Vreeswijk and Sompolinsky in two seminal papers at the end of the 1990s. I will summarize the general phenomenology of the "standard" balanced network theory as well as its functional consequences for the selectivity of neuronal responses in primary visual cortex. In the second part of my talk I will address several limitations of the "standard model" and our recent works which extend the theory to resolve these limitations.

Critically disordered cortical networks

M. Helias

[1]*Institute of neuroscience and Medicine (INM-6), Juelich, Germany*
[2] *Faculty of physics, RWTH Aachen University, Germany*
E-mail: m.helias@fz-juelich.de

Critical points are ubiquitous in physical systems, in thermodynamic equilibrium as well as beyond. A hallmark is the emergence of long-range correlations despite short-ranged interactions -- in space and time. The relevant control parameters are typically homogeneous in space; like the temperature or the mass term in a φ^4 theory.

Biological neuronal networks, on the other hand, are characterized by disorder: Connections between synapses are quasi random. We here show, by employing statistical field theory for disordered systems, that the amount of randomness controls the distance of the network dynamics to a critical point [1]. We find optimal sequential memory capacity of the network close to this phase transition [2].

Optimal performance is here due to a hitherto unreported dynamical regime that combines high amplification of signals on short time scales with asymptotically non-chaotic dynamics.

We show that heterogeneity of the network connectivity causes the critical dynamics to unfold in a low-dimensional subspace. The structure of correlations, predicted by a theory beyond the self-averaging assumption, is found in line with massively parallel recordings from motor cortex [1].

References

[1] D. Dahmen, S. Grün, M. Diesmann, M. Helias, PNAS, doi.org/10.1073/pnas.1818972116 (2019)
[2] J. Schuecker, S. Goedeke, M. Helias, Phys. Rev. X 8, 041029 (2018)

Active hydrodynamics of biological tissues

Jean-François Joanny,
Collège de France 11 place Marcelin Berthelot 75231 Paris, France

May 25, 2019

Active matter is a general class of systems that are not at thermodynamic equilibrium and that consume energy at the scale of their individual components. Many biological systems and in particular cells and tissues can be considered as active matter. At the theoretical level, hydrodynamic approaches have proved very useful for the study of active matter.

The first part of the presentation will give an introduction to the subject of active and spontaneous flows that appear in active materials. With high activity, these flows can become turbulent and define a new universality class of turbulence at low Reynolds number.

The second part of the presentation will be devoted to tissues considered as active materials. I will present experiments carried out in Pascal Silberzan's team at the Institut Curie on a monolayer of elongated cells that have nematic orientation and I will discuss the cell flow instability that might be important for some cancerous tissues.

The dynamics of internally generated brain activity

B. Hein[1,2], D. Bibichkov[1] and M. Kaschube[1,2]

[1]Frankfurt Institute for Advanced Studies, Frankfurt am Main, Germany
[2] Goethe University, Frankfurt am Main, Germany

Neural activity in the neocortex of primates and carnivores exhibits two fundamental characteristics: it is modular, comprising domains of coactive neurons with an approximately regular spacing on the order of 1mm, and spatially distributed, linking functional units that are spread across cortical space. In visual cortex, these two fundamental characteristics of cortical activity arise early in development, as evident from patterns of endogenous (spontaneous) activity, and remain present even after eliminating the feed-forward drive, suggesting a cortical origin [1]. Here I discuss theoretical models that have been proposed to explain how these two properties of neural activity in the neocortex can emerge from network interactions in its neural circuits. I will highlight important unresolved issues with the suggested mechanisms and propose potential solutions to overcome these limitations, pointing towards the importance of self-inhibition and network heterogeneities. Moreover, given that rigorous experimental tests of such models are still lacking, I will derive several critical predictions for the effects of manipulations of inhibitory network components and local circuit heterogeneities on modular and distributed cortical activity. I will discuss concrete possibilities to perform these manipulations in the visual cortex to test the validity of the proposed mechanisms. The work highlights the importance of an improved physical description for understanding the mechanisms underlying two of the most prominent features of cortical activity in the neocortex.

References

[1] G.B. Smith, B. Hein, D.E. Whitney, D. Fitzpatrick, M. Kaschube, Nat. Neurosci. **21**, 1600–1608 (2018)

Towards quantitative studies of post-embryonic development in *C. elegans*

Wolfgang Keil[1]

[1]*Institut Curie, Paris France*

The development of most metazoans can be divided in an early phase of embryogenesis and a subsequent phase of post-embryonic development. Developmental dynamics during the post-embryonic phase are generally much slower and often controlled by very different molecular mechanisms that, e.g., ensure tissue synchrony and integrate metabolic queues. However, obtaining long-term in-vivo quantitative imaging data post-embryonically with good statistical and cellular resolution has been highly challenging because animals must be allowed to grow, feed, and move in order to properly develop after embryogenesis. In this talk, I will discuss our recent progress in overcoming these challenges in the model organism *C. elegans*, using microfluidics technology [1,2]. I will then outline two of our recent studies, in which quantitative *in-vivo* imaging data of *C. elegans* post-embryonic development allows novel insights into mechanisms of cell-fate acquisition [3] and the regulation of oscillatory gene expression.

References

[1] Kutscher LM, Keil W, Shaham S *Dev Cell* 47 222-238 (2018)

[2] Keil W, Kutscher LM, Shaham S, Siggia ED *Dev Cell* 40 202-214 (2017)

[3] Attner & Keil et al., *in revision*

[4] Keil et al., *in prep.*

The dynamics of Life

Karsten Kruse

NCCR Chemical Biology, Departments of Biochemistry and Theoretical Physics, University of Geneva, 1211 Geneva, Switzerland

Life is dynamic. As no specific vital force has been identified up to now, the plethora of phenomena in the living world should be fully understandable in terms of physics. This notably holds for the formation of spatiotemporal patterns by protein ensembles, morphogenesis during organismal development, or the behavior of higher animals. In my talk, I will discuss a few examples, where the physical approach to Life has helped understanding biological dynamics. At the end, I will ask whether there still is a difference between the dynamics of living and non-living systems.

Survival of the simplest: the evolutionary cost of molecular complexity

T. Held[1], D. Klemmer[1], and M. Lässig[1]

[1]*Institute for Biological Physics*
University of Cologne, Germany

The evolution of microbial and viral organisms often generates clonal interference, a mode of competition between genetic clades within a population. Here we show how interference impacts systems biology by constraining genetic and phenotypic complexity. Our analysis uses biophysically grounded evolutionary models for molecular phenotypes, such as fold stability and enzymatic activity of genes. We find a generic mode of phenotypic interference that couples the function of individual genes and the population's global evolutionary dynamics. Biological implications of phenotypic interference include rapid collateral system degradation in adaptation experiments and long-term selection against genome complexity: each additional gene carries a cost proportional to the total number of genes. Recombination above a threshold rate can eliminate this cost, which establishes a universal, biophysically grounded scenario for the evolution of sex. In a broader context, our analysis suggests that the systems biology of microbes is strongly intertwined with their mode of evolution.

References

[1] T. Held, D. Klemmer, M. Lässig, Nature Communications **10**, 2472 (2019).

Modeling development and disease using neural organoids

J. J. Metzger[1,2], A. H. Brivanlou[2], E. D. Siggia[1]

[1]Center for Studies in Physics and Biology, Rockefeller University
[2] Laboratory of Stem Cell Biology and Molecular Embryology, Rockefeller University
New York, USA

The current generation of organoids generated from human stem cells is highly variable, which makes the identification of subtle phenotypes impossible. It is thus essential to derive more standardized organoids as well as to develop new methods to analyze such large multicellular aggregates. Here, we present a neural organoid derived from human embryonic stem cells grown on micropatterns that shows very reproducible patterning into the four ectodermal compartments of early development – neural precursors, neural crest, sensory placodes and epidermis. We have also developed an image-processing pipeline based on neural networks that can efficiently segment and classify features that allow for the detection of subtle phenotypes of the organoids. We have used this platform to identify phenotypic differences in the neural development of Huntington's disease, confirming earlier results of a developmental component of this late onset neurodegenerative disease [1,2].
Furthermore, since hundreds of these organoids can be grown on a single micropatterned chip, the platform can be used for drug screening. In preliminary results, we have identified a set of compounds that revert the phenotype of Huntington's disease to the wild type. Our work demonstrates the power of using quantitative methods to answer fundamental biological questions and for translational applications.

References

[1] Haremaki T, Metzger JJ, Rito T, Ozair Z, Etoc F, Brivanlou AH, *Nature Biotechnol.* in press (2019)

[2] Ruzo, A, Croft GF, Metzger JJ *et al. Development* **145***,* dev156844 (2018)

Abstract title (sample)

F. Author[1] and S. Author[2]

[1]Institute, Town, Country
[2] another Institute, another town, another country

Numerous experiments (1–7) suggest that a great variety of biomolecules already emerged during the prebiotic period of the early Earth. How abiogenesis occurred from such a prebiotic broth, however, has remained an open question. The idea of spontaneous molecular autocatalysis (8) as a first step of a molecular evolution towards Life has been at odds with the experimental difficulty of designing autocatalytic reactions. Here we show that a weakly driven prebiotic broth can spontaneously exhibit molecular autocatalysis. We perfom a Miller-Urey-type experiment (1) and monitor the composition of the evolving broth with real-time mass spectrometry. There is continuous emergence of a large number of substances during hours until we repeatedly observe autocatalytic oligomer formation followed by their disappearance. The oligomers consists of polyethylene glycols (PEGs) with aliphatic tails. PEGs are known as phase-transfer catalysts that circumvent hydrolysis, enabling biomolecular synthesis, the oligomerization of amino acids or nucleotides (9). At the same time NMR yields the presence of an NCC backbone polymer. We suspect that the emergence of both polymers is related and present a timid hypothesis on the functional mechanism.

References

[1] S. L. Miller, Science **117**, 528 (1953).
[2] Lowe, C. U., Rees, M. W., Markham, R., Nature **199**, 219 (1963)
[3] Or´o, J., Nature **191**, 1193 (1961)
[4] Gabel, N. W., Ponnamperuma, C., Nature **216**, 453 (1967).
[5] G. Schlesinger, S. L. Miller, J. Mol. Evol. **19**, 376 (1983)
[6] S. Miyakawa, H. Tamura, K. Kobayashi, A. Sawaoka, Jpn. J. Appl. Phys. **36**, 4481 (1997)
[7] S. Miyakawa, H. Yamanashi, K. Kobayashi, H. J. Cleaves, S. L. Miller, Proc. Natl. Acad. Sci. U.S.A. **99**, 14628 (2002)
[8] S. A. Kauffman, The Origins of Order: Self-Organization and Selection in Evolution, Oxford University Press, New York (1993)
[9] C.G. Blettner, Polymergestützte parallele Flüssigphasensynthese, Dissertation, Universität Hamburg, 1(999)

Master equation models for binding and transport problems in biological systems

U. S. Schwarz

Heidelberg University, Institute for Theoretical Physics, Heidelberg, Germany

Many essential biological processes can be conceptualized as a dynamic sequence of well-defined states. Because biological systems always work at body or room temperature, the corresponding transitions are usually stochastic, although not necessarily thermal. For these reasons, master equation modeling is a very appropriate and widely used method in theoretical biophysics. For complicated networks, few analytical tools exist and computer simulations are required. In marked contrast, for one-dimensional master equations most quantities of interest can be calculated analytically. In this contribution, I will discuss several instances where the one-step master equation could be used to comprehensively analyze an important biological systems, namely the binding dynamics in adhesion clusters [1], force generation by teams of molecular motors [2] and particle uptake by cells [3]. In particular, I will discuss the importance of stochastic fluctuations, which in this case can be easily assessed by comparing the full solutions with the solutions to the moment equations of the master equations.

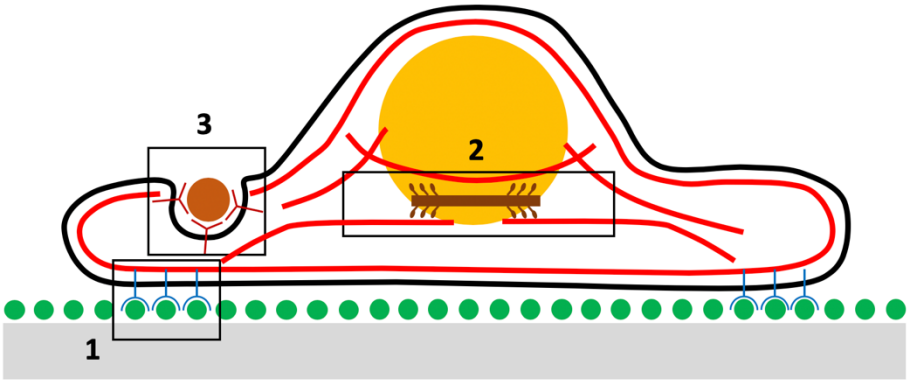


Figure: Three examples of sub-cellular stochastic processes that have been analyzed with one-step master equations: (1) stability of adhesion clusters, (2) force generations by small groups of myosin II molecular motors, and (3) particle uptake at the cell membrane.

References

[1] T. Erdmann and U.S. Schwarz, Phys. Rev. Lett. 92, 108102 (2004)
[2] T. Erdmann and U.S. Schwarz, Phys. Rev. Lett. 108, 188101 (2012)
[3] F. Frey, F. Ziebert and U.S. Schwarz, Phys. Rev. Lett. 122, 088102 (2019)

Physical models of crawling cell motility

M. Leoni and P. Sens[1]

[1]*Institut Curie - CNRS, Paris, France*

Living cells have the ability to generate forces by converting biochemical energy into mechanical energy, mostly through the hydrolysis of ATP. This allows cells to actively change their shape and to undergo autonomous movement both on 2D substrates and in 3D networks. As cells typically operate at small length scales, for which inertia can be neglected, the requirements for autonomous cell motion are very different than those applying to macroscopic bodies. In the case of swimming cells, the “scallop theorem” due to Ed. Purcell (1977) states that motion requires that cells undergo a series of shape changes that are non-reciprocal in time.

In the first part of this talk, I will discuss an extension of the scallop theorem for crawling cells, whose motion relies on the exchange of momentum with a rigid substrate. I will show in particular that, in addition to non-reciprocal shape change, crawling also requires a mechanical feedback between the traction force exerted by the cell on the substrate and the dynamics of cell-substrate adhesion [1].

In the second part of the talk, I will discuss a specific model of cell substrate interaction based on a stick-slip phenomenon that shows how the dynamics of cell adhesion can lead to spontaneous symmetry breaking and the initiation of directed motion in the absence of extrinsic directional cues from the environment. This model will illustrate the fundamental role of mechanics in regulating cell motility [2].

References

[1] M. Leoni and P. Sens, Phys. Rev. Let. **118** (2017), 228101
Model of cell crawling controlled by mechanosensitive molecular clutches

[2] P. Sens *In preparation*
Stick-slip controlled spontaneous polarisation and mouvement of crawling cells.

Bacterial Active Nematics

He Li [1], Xia-qing Shi[2,3], Hugues Chaté[3,4], and H. P. Zhang[1,5]

1. *School of Physics and Astronomy, Shanghai Jiao Tong University, Shanghai 200240, China; Institute of Natural Sciences, Shanghai Jiao Tong University, Shanghai 200240, China;*
2. *Center for Soft Condensed Matter Physics and Interdisciplinary Research & School of Physical Science and Technology, Soochow University, Suzhou 215006, China;*
3. *Service de Physique de l'Etat Condensé , Commissariat à l'Energie Atomique (CEA), CNRS, Université Paris-Saclay, CEA-Saclay, 91191 Gif-sur-Yvette, France;*
4. *Computational Science Research Center, Beijing 100094, China;*
5. *Collaborative Innovation Center of Advanced Microstructures, Nanjing 210093, China*

In many active matter system, such as bacterial systems and biofilament assays, constituent units are elongated and can give rise to local nematic orientational order. Such "active nematics" systems have attracted much attention from both theorists and experimentalists. However, despite intense research efforts, data-driven quantitative modeling has not been achieved, a situation mainly due to the lack of systematic experimental data and to the large number of parameters of current models. In this talk, we introduce an active nematics system made of swarming filamentous bacteria. We simultaneously measure orientation and velocity fields and show that the complex spatiotemporal dynamics of our system can be quantitatively reproduced by a type of microscopic model for active suspensions whose important parameters are all estimated from comprehensive experimental data. This provides unprecedented access to key effective parameters and mechanisms governing active nematics. Our approach is applicable to different types of dense suspensions and shows a path toward more quantitative active matter research.[1]

References:

[1] Li, H.; Shi, X.; Huang, M.; Chen, X.; Xiao, M.; Liu, C.; Chaté, H.; Zhang, H. P. Data-Driven Quantitative Modeling of Bacterial Active Nematics. *Proc Natl Acad Sci USA* **2019**, *116* (3), 777. https://doi.org/10.1073/pnas.1812570116.

How (biological) activity alters thermomechanics: from pressure to surface tension

R. Zakine[1], Y. Zhao[1], M. Knezevic[2], A. Daerr[1], Y. Kafri[3], J. Tailleur[1] and F. van Wijland[1]

[1]Laboratoire MSC, CNRS, Universite Paris Diderot, Paris, France
[2] Institut für Theoretische Physik, Technische Universität Berlin, Berlin, Germany
[3] Technion, Haifa, Israel

Motile cells dissipate energy to exert forces on their surroundings and self-propel. This microscopic mechanical drive out of equilibrium makes their thermodynamic properties unusual. Recently, a lot of attention has been brought to the mechanical properties of these momentum non-conserving, non-equilibrium systems. I will show how pressure and surface tension can still be defined in this context, but have a much richer phenomenology than in passive materials.

References

[1] A. P. Solon, Y. Fily, A. Baskaran, M. E. Cates, Y. Kafri, M. Kardar, J. Tailleur, "Pressure is not a state function for generic active fluids", Nature Physics 11, 673-678 (2015)

[2] A. P. Solon, J. Stenhammar, R. Wittkowski, M. Kardar, Y. Kafri, M. E. Cates, J. Tailleur, "Pressure and Phase Equilibria in Interacting Active Brownian Spheres", Phys. Rev. Lett. 114, 198301 (2015)

[3] N. Nikola, A. P. Solon, Y. Kafri, M. Kardar, J. Tailleur, R. Voituriez , "Active particles on curved surfaces: Equation of state, ratchets, and instabilities", Phys. Rev. Lett. 117, 098001 (2016)

[4] Y. Fily, Y. Kafri, A. Solon, J. Tailleur, A. Turner, "Mechanical pressure and momentum conservation in dry active matter", J. Phys. A 51, 044003 (2018)

[5] R. Zakine, Y. Zhao, M. Knezevic, A. Daerr, Y. Kafri, J. Tailleur, and F. van Wijland, in preparation

Control and localization of a stochastic particle in a flow-field

E. Tang[1] and R. Golestanian[1,2]

[1]Max Planck Institute for Dynamics and Self-Organization, Göttingen 37077, Germany

[2] The Rudolf Peierls Centre for Theoretical Physics, 1 Keble Road, Oxford, OX1 3NP, UK

We study the interplay between advection and diffusion in the general case of a moving fluid or current. Typically, diffusive particles spread throughout the system while advection flushes particles along a trajectory, and the interplay of these two processes in complex scenarios is not well understood. Using a path integral formalism, we solve for the dynamics in a finite region and examine how the behavior of a tracer particle changes with various flow-fields, geometries, and control parameters. We identify a mechanism to retain a particle for longer times than diffusion permits, as well as parameters that govern a sharp transition from localization around the origin to being expelled, which is unexpected for a stochastic particle. We show the information flow has two distinct contributions which characterize the particle delocalization compared to a purely diffusive particle. As our formalism is generic, this work has relevance for the control of particles in many scenarios: from applied electromagnetic currents such as in condensed matter or plasma physics, to fluid flows such as in biological systems or microfluidics.

Transition from asynchronous to oscillatory dynamics in balanced spiking networks

Alessandro Torcini[*(1)],Hongije Bi[(1)], Marco Segneri[(1)], Matteo di Volo[(1)]

(1) Laboratoire de Physique Théorique et Modélisation
Université de Cergy-Pontoise, UMR CNRS 8089 - 2 avenue Adolphe Chauvin, Pontoise
95302 Cergy-Pontoise cedex, Île-de-France, France

[*] Corresponding author, email: alessandro.torcini@u-cergy.fr

We report a transition from asynchronous to oscillatory behavior in balanced inhibitory networks for class I and II neurons with instantaneous synapses. Collective oscillations emerge for sufficiently connected networks. Their origin is understood in terms of a recently developed mean-field model, whose stable solution is a focus. Microscopic irregular firings, due to balance, trigger sustained oscillations by exciting the relaxation dynamics towards the macroscopic focus. The same mechanism induces in balanced excitatory-inhibitory networks quasi-periodic collective oscillations [1].

Furthermore, we consider a balanced sparse inhibitory network of pulse coupled quadratic integrate-and-fire (QIF) neurons with finite synaptic decay time. We derive an effective mean-field (MF) description for this sparse spiking network by employing a recently developed reduction technique. The MF model exhibits the coexistence of a stable focus and a stable limit cycle. However, in direct simulations of the neural population the microscopic irregular dynamics, typical of the balanced state, turns the damped oscillations towards the stable focus in sustained collective oscillations (COs). Therefore in the spiking network we observe the coexistence of two oscillatory states corresponding to slow and fast gamma oscillations generated via two different mechanisms within the same inhibitory neural population. We show that almost instantaneous stimulations can switch the collective gamma oscillations from slow to fast and vice versa. Finally, in presence of an external theta driving we observe phase-phase coupling between the fast and slow gamma COs and the theta forcing, with the slow gamma occurring earlier during the theta cycle [2].

References

[1] M. di Volo, A. Torcini, "Transition from asynchronous to oscillatory dynamics in balanced spiking networks with instantaneous synapses", *Phys. Rev. Lett.* 121 , 128301 (2018).

[2] H. Bi, M. Segneri, M. di Volo, A. Torcini, “Coexistence of fast and slow gamma oscillations in one population of inhibitory spiking neurons”, preprint (2019).

Intrinsically motivated collective motion

H. J. Charlesworth and M. S. Turner

University of Warwick, Coventry, UK

We study moving, re-oreintable agents that seek to maximise their space of accessible (visual) environments, out to some time horizon [1]. The action of each agent is (re)established by exhaustive enumeration of its future decision tree at each time step - each agent chooses an action that leads to the branch of its tree leading from the present to the richest future state space. Swarm-like motion emerges that is similar to that observed in animal systems, such as bird flocks despite the fact that *neither coalignment nor cohesion are explicitly encoded into the model*. We develop heuristics that mimic this computationally intensive process but that could operate in real time under animal cognition. These heuristics include a neural network that can be trained to mimic (any) trajectory data, such as that produced by our future state-space maximization algorithm. I will argue that future state maximisation may confer fitness for rather general reasons and offers a philosophically attractive, bottom-up mechanism for the emergence of swarming in nature.

References

[1] H. J. Charlesworth and M. S. Turner, PNAS, in press (2019)

First-passage statistics of non Markovian random walks and random search processes

R. Voituriez[1]

[1]*CNRS/Sorbonne Université, Laboratoire Jean Perrin, Paris*

The first-passage time is a key quantity for evaluating the kinetics of various processes, such as chemical reactions involving "small" numbers of particles, where the limiting step is the search for reaction partners, or the search for resources by living organisms.
I will present asymptotic results that enable the determination of first-passage time statistics to a target site for a wide range of random processes. I will show how these results can be extended to non Markovian processes (i-e processes with memory), which are often needed to model transport in biological systems, and how they permit to revisit the question of optimality of random search processes [1,2].

References

[1] T. Guerin, N. Levernier, O. Benichou, and R. Voituriez. Mean first-passage times of non-markovian random walkers in confinement. Nature, 534(7607) (2016)

[2] N. Levernier, O. B enichou, T. Guerin, and R. Voituriez. Universal first-passage statistics in aging media. Physical Review E, 98(2):022125 (2018)

Abstracts of Posters

(in alphabetical order)

Shear-driven instabilities on membrane tubes

Sami C. Al-Izzi[1,2], Pierre Sens[2], Matthew S. Turner[1]

[1] *University of Warwick, Coventry, UK*
[2] *Institut Curie, Paris, France*

The scission of membrane tubes is a process vital to many pathways of intercellular transport, including endocytosis and mitochondrial fission. Motivated by the mechanics of Dynamin-mediated membrane tube fission we analyse the stability of fluid membrane tubes subjected to shear flow in azimuthal direction, driven by some active torque at the boundary. We find a novel helical instability driven by the membrane shear flow which has its onset at shear rates that are physiologically accessible under the action of Dynamin and could also be probed using in-vitro experiments on GUVs using magnetic tweezers. We discuss how such an instability may play a role in the mechanism for Dynamin-mediated membrane tube fission.

How do colonial algae swim towards light?

H. de Maleprade[1], F. Moisy[2], T. Ishikawa[3] and R. E. Goldstein[1]

[1] DAMTP, CMS, Wilberforce Road, CB3 0WA Cambridge, UK
[2] Laboratoire FAST, Université Paris-Sud, 91405 Orsay, France
[3] Department of Finemechanics, Tohoku University, Japan

Microscopic algae are commonly found in mud, puddles or lakes, and show great diversity in structural complexity. One of the simplest algae encountered is the unicellular *Chlamydomonas*, exhibiting two flagella whose beating enables them to swim in a breast stroke. One also finds *Gonium pectorale*, a colony made of 16 *Chlamydomonas*-like cells arranged in two concentric squares, with all flagella on one side of the plate (figure a). These colonies, already showing cell differentiation, are among the first multicellular algae. Therefore, their study offers an insight into understanding the evolution from unicellular to collective and coherent multicellular behaviour.

Algae, like plants, get energy from photosynthesis: *Gonium* colonies take advantage of their motility to swim towards light, efficiently reorienting within a couple of seconds. However, the mechanism of this phototactic behaviour is not yet understood: how do all 16 cells individually produce a coherent collective response? How are the flagella modulated to create an asymmetry in the swimming pattern, and how does that lead to reorientation?

We experimentally investigate the phototaxis of *Gonium*, analysing their reorientation trajectory towards light. We analyse the reaction of isolated colonies held with a micropipette (figure a), enabling access to the flagella waveform and frequency, as well as the flow around colonies, dramatically affected by light (figure b). Therefore, we develop a model, together with numerical simulations, linking individual cell reaction to the trajectory of a colony during reorientation.

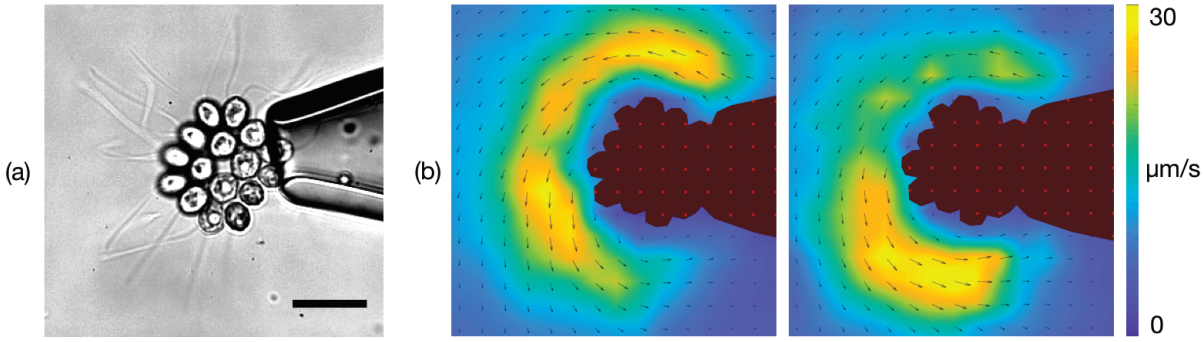


Figure a: *Gonium Pectorale* colony held on a micropipette. Each of the 16 cells exhibits 2 flagella. The scale bar shows 20 μm. **b** (left) Homogeneous circular flow around a colony held in the dark. (right) Asymmetrical flow just after light is shone from the bottom of the picture. (Same colour scale).

Model of lamellipodium initiation during cell spreading

M. Dedenon[1] and P. Sens[1]

[1]Institut Curie, Paris, France

Many cells possess a dense and highly crosslinked layer of actin filament underneath their plasma membrane, called the actomyosin cell cortex. During spreading on solid substrates, cells often generate an isotropic thin protrusion called lamellipodium at the leading edge of their surface in contact with the substrate. This involves a major reorganisation of the cortex, with filaments mostly oriented parallel to the substrate. Little is known about the way cytoskeleton mechanics influences the transition between the cortical actin network of round detached cells and the lamellipodial architecture seen at the edge of late spreading cells.

We propose a model coupling actin mechanics, filaments orientation, and the local curvature of the cell membrane, inspired by the physics of nematic liquid crystals and fluid membranes [1]. This model naturally yields the collective orientation of actin filaments in regions of high membrane curvature, such as the one found at the contact line of a spreading cell. The coupling between filament orientation and the traction force exerted by the flow of actin treadmilling on the substrate generates a positive feedback loop by which high curvature increases the traction force and cell spreading, which increases again membrane curvature.

We establish the condition under which this feedback leads to a full wetting transition, which we interpret as the initiation of a lamellipodium. We also show that in certain conditions, this transition is characterised by the appearance of bi-stability regime which could trigger spontaneous cell polarization or generate local lamellipodial protrusions at the cell periphery as can be observed in so-called anisotropic spreading.

Reference

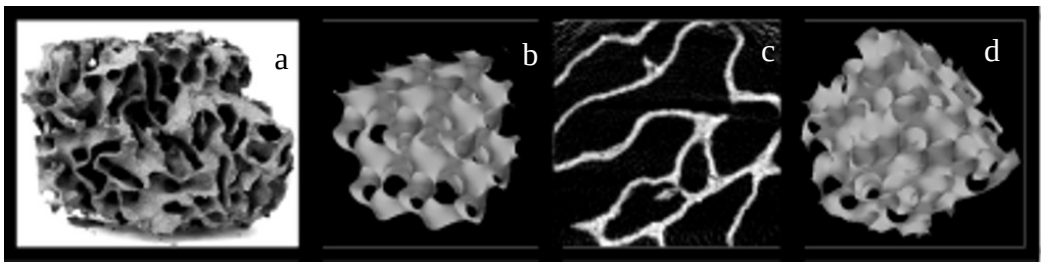
[1] arXiv:1906.02559

Interaction between form and growth in a remarkable self-organised biological structure: the arboreal nests of nasute termites

G. Facchini[1], A.Lazarescu[2], A. Perna[1], and S. Douady[3]

[1]Life Sciences Department, University of Roehampton, London, UK
[2]Centre de Physique Théorique (CPHT), École Polytechnique, Paris , France
[3]Laboratoire Matière et Systèmes Complexe, Université Paris Diderot, Paris, France

Termite nests are among the most complex structures built by animal groups. While their building results from local interactions and self-organised processes, their form has a coherent global organisation and serves important biological functions such thermoregulation and protection from predators. Here, we focus on the arboreal nests (a) built by termites of the genus Nasutitermes, which are particularly interesting because beside complexity (an intricate network of corridors made of fecal carton) and variability (expressed by different species of the genus), they show a strong similarity in the way corridors are saddle-shaped and highly connected forming what resembles a minimal surface called gyroid (b). If an underlying pattern is shared across species, the nest building strategy might also be shared across the genus, but this contrasts with nests built by species which live in different continents and likely developed independently. Our hypothesis is that very few shared features of the building behaviour of termites could be sufficient to account for many of the general features of Nasutitermes nests. In this frame we model the nest growth with a single non-linear equation driven by the surface curvature, exploring the tendency for termites to concentrate building activity in areas where this quantity is large. Simulating this equation we succeed to reproduce growth and branching, obtaining objects which asymptotically tend to minimal surfaces (d). In parallel we collect nest samples from three continents and five different species which are scanned with a micro-CT scanner (c) and compared to simulations. The curvature distribution is qualitatively similar and support the hypothesis of a curvature-driven growth. We infer that, similar to pheromones in other social insects, here curvature is the local information that allow thousands of insects to collectively build a complex structure which is hundreds of times their own body.



From the left: fragment of a real nest, gyroid, slice of a CT-Scan, 3D simulation

Effect of the three-dimensional cell neighbourhood on cellular behaviour

S.C. Fischer[1]

[1]*Center for Computational and Theoretical Biology (CCTB), Faculty of Biology, University of Würzburg, Würzburg, Germany*

Tissue development and maintenance rely on coordinated interactions of individual cells. The correct composition of the three-dimensional cell neighbourhood is essential. However, often the details of the spatial arrangement of the cells are unknown and the processes underlying its establishment and maintenance are understudied. We quantitatively analyse the three-dimensional spatial arrangement of cells in mammalian tissues and tissue-like structures by applying a combination of microscopy, cell graph analyses and agent-based modelling. Our biophysical approach elucidates how adhesion molecules and cytoskeletal components drive tissue integrity and reveals patterns of cell differentiation based on the expression of the transcription factors NANOG and GATA. These results link the setup of the three-dimensional cell neighbourhood to the properties of subcellular components.

References

[1] B. Mathew, S. Muñoz-Descalzo, E. Corujo-Simon, C. Schröter, E.H.K. Stelzer, S.C. Fischer, Mouse ICM Organoids Reveal Three-Dimensional Cell Fate Clustering. Biophys. J. **116**, 127–141 (2019)

[2] I. Smyrek, B. Mathew, S.C. Fischer, S.M. Lissek, S.Becker, E.H.K. Stelzer, E-cadherin, actin, microtubules and FAK dominate different spheroid formation phases and important elements of tissue integrity. Biol. Open 10.1242/bio.037051 (2018)

[3] S. Garg, S.C. Fischer, E.M. Schuman, E.H.K. Stelzer, Lateral assembly of N-cadherin drives tissue integrity by stabilizing adherens junctions. J. Roy. Soc. Interface **12**, 20141055 (2015)

Dynamical states of a living network

P. Fleig[1], M. Kramar[1], M. Wilczek[1], and K. Alim[1]

[1]Max Planck Institute for Dynamics and Self-Organization,Göttingen, Germany

Understanding the emergence of behaviour in living systems from underlying physical mechanisms is a major goal of biophysics. Even very simple, non-neural organisms like the slime mould Physarum polycephalum show remarkably complex behaviour including growth, adaptation of the network morphology and foraging for food - despite only being a single, giant, network-shaped cell. Behavioural dynamics, here, emerge directly from living matter, namely the coordinated contractions of the cell's tubular shaped actomyosin cortex undergoing rhythmic contraction every 100 seconds. We decompose this spatiotemporal dynamics into principal components and identify a reduced set of characteristic large-scale contraction patterns spanning the network. Based on this dictionary of patterns we are able to determine the typical sequence of the network's response patterns to a controlled stimulus, mimicking a natural response scenario. Further we find spontaneously occurring breaking of coherent contraction dynamics into decoherent patterns over shorter time scales. We show how variations in the type of contraction dynamics impact on the growth behaviour of the organism. Our findings connect behaviour with characteristic states of living matter.

Mechano-sensitive ion channels mediate the coordination of epithelial cells during morphogenesis

Matthias Häring[1,2], Prachi Richa[3], Jörg Großhans[3] and Fred Wolf[1,2]

[1]*Campus Insitute for Dynamics of Biological Network, Göttingen, Germany*
[2] *MPI for Dynamics and Self-Organization, Göttingen, Germany*
[3]*University Medical Center, Göttingen, Germany*

Epithelial cells are capable of sensing and reacting to the forces and movements of their neighbors. These forces are transmitted by multi-protein complexes at the cell-cell adhesion sites. During Drosophila morphogenesis, Ca^{2+} acts as an upstream regulator of acto-myosin dynamics. This can for example be exploited to induce cell contraction in the living embryo via calicum uncaging.
Mechano-sensititve ion channels, and in particular the putative ion channel TMC, are expressed in the Amnioserosa of Drosophila. We therefore hypothesized that mechano-sensitive ion channels behave as molecular transducers responding to changes in force at the cell-cell junctions and generate intracellular Ca^{2+} signals. In particular, Ca^{2+} currents through mechano-sensitive ion channels would be well positioned to synchronize contractions of neighbouring cells, enabling coordinated force generation across the tissue.

We thus assessed the coordination of epithelial cells in the Amnioserosa comparing wild type embryos and mutants with an ion-channel knock-down (TMC^{Gal4}). Using a novel high-throughput image analysis pipeline based on deep neural networks we achieved near-complete segmentation, for entire ensembles of embryos [1]. Cell synchronization was studied by decomposing cell-cell interactions into three distinct coupling types: positively coupled, negatively coupled and neutral cell pairs. With this approach, each epithelium is represented by a planar graph of cell couplings allowing us to analyse cell coordination in an ensemble of embryos for each mutant. Using this approach we found that while wild type embryos in cells can synchronize their contraction in spatially coherent groups this type of synchronization is disrupted in TMC^{Gal4} mutants. *TMC* forms complexes with other molecular components of adherence junctions and its knock-down is associated with an anisotropy of junction tension in the Amnioserosa, confirming a function of Ca^{2+} signals in actomyosin regulation.

References

[1] Häring, Großhans, Wolf, Eule, “Automated Segmentation of Epithelial Tissue Using Cycle-Consistent Generative Adversarial Networks”, bioRxiv 2018, https://doi.org/10.1101/311373

Control of droplet kinetics in active emulsions

Jacqueline Janssen[1,2] and Christoph A. Weber[1,2]

[1]Max Planck Institute for the Physics of Complex Systems,
Nöthnitzer Straße 38, 01187 Dresden, Germany
[2] Center for Systems Biology Dresden,
Pfotenhauerstraße 108, 01307 Dresden, Germany

Living cells host many membrane-less compartments which originate via liquid-liquid phase separation in both the cytoplasm and the nucleoplasm. Liquid phase separated droplets are crucial in living cells to spatially control chemical reactions and thereby also facilitate temporal regulation of cellular functions. Recent experimental work revealed a new class of active emulsions where the lifetime and the rate of droplet growth can be controlled. This class of active emulsions involves a fuel that drives a chemical reaction from thermodynamically stable precursor molecules to metastable building blocks. At large enough concentration of building block material the liquid droplets can form and undergo an anomalously fast ripening towards fewer droplets of larger size. Up to date there is no theoretical model which would describe such anomalous ripening kinetics of active emulsions. I will present a model which quantitively coincides with the experimental measurements conducted by the Boekhoven Laboratory. Additionally, we find new scaling laws for the average droplet volume where the scaling exponent is increased compared to the Ostwald ripening growth law derived by Lifschitz and Slyozov. Our theory allows to understand how the metastable building blocks determine the lifetime or accelerate the droplet kinetics in this new class of phase separated systems. The control of growth speed and lifetime might represent a selection mechanism of molecular components relevant at the origin of life.

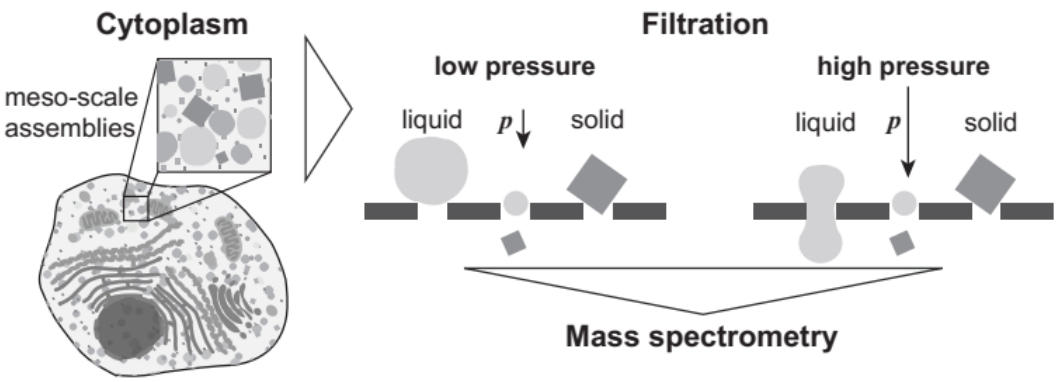
Proteome-Wide Analysis of Cytoplasmic Meso-Scale Organization

F. Keber[1], C. Brangwynne[1] and M. Wühr[1]

[1]Lewis-Sigler Institute for Integrative Genomics, Princeton University, USA

While we now possess a nearly complete parts list of our cells, we still lack knowledge about how these nanoscale molecules organize into larger structures. Key organization principles in eukaryotes are the formation of stable protein complexes and membrane-bound organelles. About a decade ago, liquid-liquid-phase separation (LLPS) was shown to provide another mechanism that enables the spontaneous formation of protein droplets without any membrane. While in the meantime many of these membrane-less organelles have been discovered, it is still unclear what fraction of proteins in the cytoplasm organizes via this principle, how many different of these organelles exist, or at what size these assemblies form.

Here, we assay organization of proteins into meso-scale assemblies on a proteome-wide scale and reveal the underlying organization principles with molecular resolution. To this end, we filtered undiluted cytoplasm from frog eggs through pore sizes ranging from the nano- to micrometer scale. We measured the ability of thousands of proteins to pass these filters via quantitative multiplexed proteomics. This allows assigning an apparent assembly-bound size to each protein. Furthermore, we interrogate the character of assemblies by application of differential pressure during filtration. Protein complexes will not permeate pores smaller than their assembly size regardless of used pressure. In contrast, liquid assemblies will also not permeate small pores under low pressure but will squeeze through these small pores under high pressure. We find that a remarkable number of well-known LLPS proteins showed the predicted differential behavior. Furthermore, we identified hundreds of novel proteins with similar characteristics, some of which we are now following up on. Thus, we present new methods to assay the meso-scale organization of cytoplasm. Our preliminary data indicate that a significant fraction of the proteome organize into so-far undiscovered membrane less organelles via LLPS. Our data paves the way for identifying these organelles and might enable us to identify the molecular features underlying this self-organizati



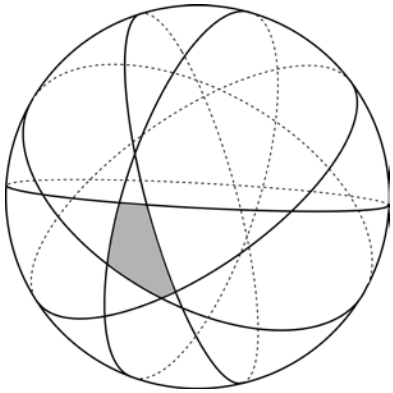
on of the cytoplasm.

On non-negative solutions to large systems of random linear equations

S. Landmann[1] and A. Engel[1]

[1]Institute of Physics, Carl von Ossietzky Universität Oldenburg, 26111 Oldenburg,Germany

Systems of random linear equations may or may not have solutions with all components being non-negative. The question is, e.g., of relevance when the unknowns are concentrations or population sizes. Here we show that if such systems are large the transition between these two possibilities occurs at a sharp value of the ratio between the number of unknowns and the number of equations. We analytically determine this threshold as a function of the statistical properties of the random parameters and show its agreement with numerical simulations. We also make contact with two special cases that have been studied before: the storage problem of a perceptron and the resource competition model of MacArthur.



The solution space of the problem (shaded) is part of a high-dimensional sphere defined by the constraints set by the considered system of linear equations.

References

[1] Landmann, S. and Engel, A., 2018. Systems of random linear equations and the phase transition in MacArthur's resource-competition model. Europhysics Letters, **124**(1), p.18004.

[2] Landmann, S. Engel, A., 2019. On non-negative solutions to large systems of random linear equations. arXiv: 1904.06977.

Reverse-time inference of biological dynamics evolving towards target-states

N.Lenner[1], D.Kong[2] , J.Großhans[2] , S.Eule[1] and F.Wolf[1,3,4]

[1]Max-Planck-Institute for Dynamics and Self-Organization, Göttingen, Germany;
[2] Institute of Developmental Biochemistry, University Göttingen, Germany;
[3]Bernstein-Center for Computational Neuroscience, Göttingen, Germany;
[4] German Primate Center, Göttingen, Germany

Mesoscopic bio-systems typically evolve towards functionally important target-states, such as cell cycle checkpoints or decision boundaries for the release of a specific behavior. To infer the underlying directional out-of-equilibrium dynamics from such data, we develop a theory of target-state-aligned (TSA) ensembles that reveals whether and when the system can be represented by a single, effective stochastic equation of motion. We show how, in this equation, genuine biological forces can be separated from spurious forces, which, invariably arise from target-state-alignment. We apply our inference scheme to canonical biological examples, such as cytokinetic ring constriction and derive the universal low-noise and short-term behavior of TSA ensembles. Our theory establishes a transparent mathematical foundation for analysis and inference of directed biological dynamics by target-state-alignment.

Quantitative assessment of the Toner and Tu theory of Polar Flocks

B. Mahault[1,2], F. Ginelli[3], and H. Chaté[1,4,5]

[1]Service de Physique de l'Etat Condensé, CEA-Saclay, Gif-sur-Yvette, France
[2]Max Planck Institute for Dynamics and Self-Organization, Göttingen, Germany
[3]Dept. of Physics, Kings College, University of Aberdeen, Aberdeen, United Kingdom
[4]Beijing Computational Science Research Center, Beijing, China
[5]LPTMC, CNRS, Univ. Pierre et Marie Curie, Paris, France

We propose a quantitative assessment of the Toner and Tu theory [1,2] describing the universal scaling of fluctuations in dry active matter polarly-ordered phases. Using large scale simulations of the Vicsek model [3] in two and three dimensions, we show that while the overall phenomenology and generic algebraic scaling predicted by Toner and Tu are qualitatively correct, the values of the associated exponents differ significantly from the ones they conjectured. In particular, we identify a large crossover scale beyond which flocks are only weakly anisotropic. We discuss the meaning and consequences of these results, and contextualize them with respect to previous studies.

References

[1] J. Toner and Y. Tu, Phys. Rev. Lett. 75, 4326 (1995)
[2] J. Toner and Y. Tu, Phys. Rev. E 58, 4828 (1998)
[3] T. Vicsek, A. Czirók, E. Ben-Jacob, I. Cohen and O.Sochet, Phys. Rev. Lett. 75, 1226 (1995)

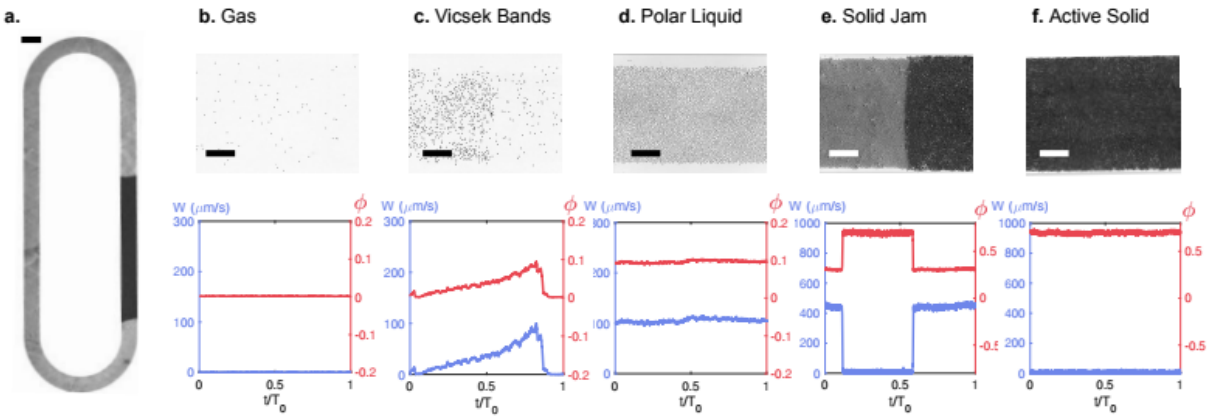
Motility-Induced Solidification in roller Flocks

G. Delphine[1], D. Martin[2], J. Tailleur[2], D. Bartolo[1]

[1]ENS Lyon, 69342 Lyon, France
[2] Université Paris Diderot , 75013 Paris, France

The emergence of collective motion is a well-established phenomenon in living systems, be it among developed organisms such as fish swarms or starling flocks, or among simpler ones such as bacteria. Although the microscopic mechanisms entailing the transition toward collective motion typically depend on the system, some features are universal, and, as such, can be captured by simple microscopic models. The vicsek model has proven itself such a minimal description, able to predict important features of flocks. Unfortunately, it does not encompass steric effects and hence fails to describe assemblies at higher densities.

A new physics is however expected in such cases, since repulsive forces, by themselves, can trigger phase transitions such as motility-induced phase separation (MIPS). I will present theoretical and experimental results on how the flocking transition interplays with steric interactions at high density. In particular, I will show how active solids emerge in flocking states made by Quincke colloidal rollers. Particles in the solid are effectively arrested, but the solid collectively propagates upstream due to its rich boundary dynamics.



a*- active solid propagating upstream in an experimental racetrack* ***b to f****- close-up pictures of the different phases observed in the racetrack. The graphs below represent the density Φ and order parameter W as a function of the curvilinear coordinate for each corresponding phase.*

References

[1] D. Geyer, D. Martin, J. Tailleur, D. Bartolo, arXiv:1903.01134 (2019)

[2] D. Geyer, A. Morin, D. Bartolo, Nature materials **17**, 789 (2018)

Hydraulic control of Oocyte size selection

Arghyadip Mukherjee[1,2,3,4], Nicolas T. Chartier[4], Sebastian Fürthauer[6], Julia Pfanzelter[4], Frank Jülicher[2,3,5], Stephan W.Grill[1,3,4,5]

1) Max Planck Institute of Molecular Cell Biology and Genetics, 2)Max Planck Institute for the Physics of Complex Systems, 3)Center for Systems Biology Dresden, 4) BIOTEC, TU-Dresden, 5) Physics of Life, Excellence Cluster TU-Dresden, 6) Flatiron Institute, NY

The process of making an oocyte starting from a germline tissue is a fundamental cellular process. Oogenesis demonstrates remarkable mechanical as well as hydrodynamic phenomena across organisms. Dynamic size regulation and mechanical symmetry breaking in germ cell population (within a syncytia) leads to heterogeneous growth leading to cell fate decisions. The roundworm *C. elegans* has a tubular syncytial (tissue architecture with connected cytoplasm) germline, which achieves germ-cell growth by hydrodynamic flows that range across 400 microns. By quantitative analysis and theoretical modeling, we discover that germ cells actively generate long-range hydrodynamic flows along the germline, while also locally maintaining their homogenous size. The coupling of cell mechanics and hydrodynamic fields lead to active pressure-tuning, which yields a hydraulic instability setting a critical size for the germ-cells in the absence of active sources. This mechanism ensures selection and growth of germ cells beyond a critical size at the expense of smaller cells and is independent of the apoptotic machinery. We unravel the physical basis of oogenesis and cell elimination by combining cellular mechanics and active hydrodynamics. Our findings elucidate a novel connection of cell fate and mechanics of volume regulation, and proposes a cell death mechanism that is emergent out of cellular competition rather than programmed

Integrin-mediated attachment of the blastoderm to the vitelline envelope impacts gastrulation of insects

S. Münster[1,2,3], A. Mietke[2], A. Jain[1], P. Tomančák[1] and S.W. Grill[1,3]

[1]MPI of Cell Biology and Genetics, Dresden, Germany
[2] MPI for Physics of Complex Systems, Dresden, Germany
[3] TU Dresden, Biotec, Dresden, Germany

Gastrulation is a critical step during the development of multicellular organisms in which a single-layered tissue folds into a multi-layered germband. This shape change is characterized by tissue folding and large-scale tissue flow. The myosin-dependent forces that underlie this process have been increasingly investigated; however, thus far, the possible interaction between the moving tissue and the rigid shell surrounding the embryo has been neglected. Here, we present our quantitative findings on the physical mechanisms governing gastrulation in the red flour beetle *(Tribolium castaneum)*. We investigated the forces expected within the tissue given the myosin distribution observed by multi-view light-sheet microscopy and discovered that an additional external force must be counteracting this tissue-intrinsic contractility. We then identified that a specific part of the tissue tightly adheres to the outer rigid shell. This attachment is mediated by a specific integrin *(Inflated)* whose knock-down leads to a complete loss of the counter-force. Moreover, in the fruit fly *(Drosophila melanogaster)* knock-down of another integrin *(Scab)* leads to a severe twist of the germband, suggesting that the integrin-mediated interaction between tissue and vitelline envelope may be conserved in insects.

On the Existence of Generalized Free Energies to Describe Non-equilibrium Phase Transitions in Motile Populations of Chemotactic and Quorum Sensing Bacteria

J. O'Byrne[1] and J. Tailleur[1]

[1]Université Paris Diderot, Paris, France

Irreversible energy consumption drives biological systems out of thermal equilibrium, hence endowing them with a much richer phenomenology than their passive counterparts. This however comes at a cost: no general framework exists to account for their statistical properties. A natural question is then whether some methods of equilibrium statistical mechanics can be generalized to describe non-equilibrium systems and their phase transitions[1]. In the context of motile populations of cells, we show[2] how the existence of a generalized free energy can be systematically addressed at the coarse-grained, hydrodynamic level. We show[2] that there is a large class of systems whose phase transitions can indeed be mapped onto that of interacting particle systems in equilibrium, hence allowing us to account for their phenomenologies. In particular, this includes large classes of run-and-tumble bacteria interacting via chemotaxis or quorum-sensing as well as a wide range of active systems.

References

1. A. Solon et al.,Physical Review E, 2018
2. Still in writing process

Generic Long-Range Interactions Between Passive Bodies in an Active Fluid

Yongjoo Baek[1,2], Alexandre Solon[3], Xinpeng Xu[1,4], Nikolai Nikola[1] and Yariv Kafri[1]

[1]Department of Physics, Technion—Israel Institute of Technology, Haifa 32000, Israel
[2]DAMTP, Centre for Mathematical Sciences, University of Cambridge, Cambridge CB3 0WA, United Kingdom
[3]Sorbonne Université, CNRS, Laboratoire de Physique Théorique de la Matière Condensée, LPTMC, F-75005 Paris, France
[4]Department of Physics, Guangdong Technion—Israel Institute of Technology, Shantou, Guangdong 515063, People's Republic of China

A single nonspherical body placed in an active fluid generates currents via breaking of time-reversal symmetry. We show that, when two or more passive bodies are placed in an active fluid, these currents lead to long-range interactions. Using a multipole expansion, we characterize their leading-order behaviors in terms of single-body properties and show that they decay as a power law with the distance between the bodies, are anisotropic, and do not obey an action-reaction principle. The interactions lead to rich dynamics of the bodies, illustrated by the spontaneous synchronized rotation of pinned nonchiral bodies and the formation of traveling bound pairs. The occurrence of these phenomena depends on tunable properties of the bodies, thus opening new possibilities for self-assembly mediated by active fluids.

References

[1] Y. Baek, A. P. Solon, X. Xu, N. Nikola, and Y. Kafri, Phys. Rev. Lett. 120, 058002 (2018)

Feature selectivity in a synthetic neuronal network

J. Vogel[1,2,3], M. Schottdorf[2,3], A. Neef[1,2], W. Stühmer[3] and F. Wolf[1,2]

[1]Campus Institute for Dynamics of Biological Networks, Göttingen, Germany
[2] Max-Planck Institute for Dynamics and Self-Organization, Göttingen, Germany
[3] Max-Planck Institute for Experimtental Medicine, Göttingen, Germany
Email: vogel@nld.ds.mpg.de

Feature selectivity in the primary visual cortex is arguably the most studied aspect of sensory processing in the brain. The arrangement of orientation selective neurons follows two different designs: highly structured maps as found in primates, carnivores, ungulates and tree shrew on the one hand, and unstructured 'salt-and-pepper' layouts as found in rodents and lagomorphs on the other hand. However, it is unknown which mechanisms constitute the emergence of these cortical architectures.

In order to probe different realizations of the thalamo-cortical connectome and disentangle the contributions of feed-forward input and recurrent intracortical connections we developed a synthetic biology approach. A computational model of thalamic projections is combined with living neural tissue as a model for the cortical input layer. We built an optogenetic interface for the in-silico and in-vitro components using holography and the light-gated ion channel Channelrhodopsin-2 [1]. Neural activity can be read out electrophysiologically or optically using a genetically-encoded calcium indicator [2].

We find that even in the absence of specific feed-forward input a basic level of orientation selectivity is generated by self-organization in the recurrent neuronal circuit. The spatial arrangement of orientation selective cells in this model resembles a sparse salt-and-pepper layout.

References

[1] G. Nagel et al., Current Biology **15**, 2279-2284 (2005)
[2] H. Dana et al., ELife **5**, 1-24 (2016)

Activated Escape of a Self-Propelled Particle from a Metastable State

E. Woillez[1] , Y. Zhao[2], Y. Kafri[1], V. Lecomte[3], and J. Tailleur[4]

[1]Department of Physics, Technion, Haifa 32000, Israel
[2] School of Physics and Astronomy and Institute of Natural Sciences, Shanghai Jiao Tong University, Shanghai 200240, China
[3]Université Grenoble Alpes, CNRS, LIPhy, F-38000 Grenoble, France
[4]Université Paris Diderot, Sorbonne Paris Cité, MSC, UMR 7057 CNRS, 75205 Paris, France

The problem of the activated escape of a physical system over a barrier plays an important role in physical, biological, and chemical systems. At the heart of our understanding of this problem lies a simple picture, first derived by Kramers, of a Brownian particle escaping over a potential barrier. The classical result states that the escape rate over the barrier depends, to leading order, only on the height of the barrier.
We recently found an analytical solution to the escape problem of a self-propelled active particle over a confining potential barrier. In the present poster, I show that the physics of this process is very different from the corresponding equilibrium one. More precisely, I explain why the activation process depends on the full shape of the potential barrier, and not solely on its height. This leads to several striking phenomena. For example, the escape rate of active particles over a high potential barrier may be faster than over a lower one, as illustrated on the figure below. Moreover, which barrier is quicker depends in a subtle way on the self-propelling force and varying the latter can lead to corresponding dynamical phase transitions.

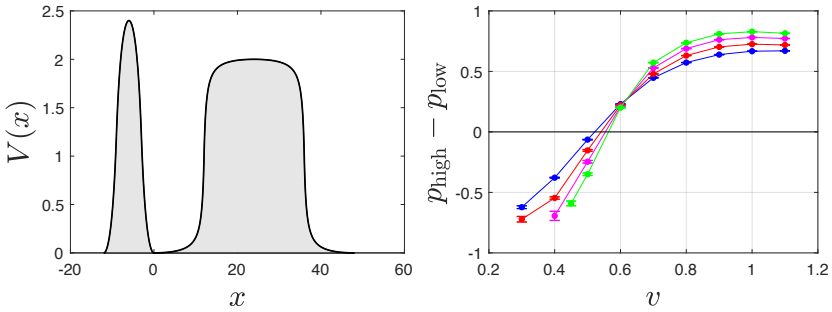


FIG: Active escape from a metastable well confined by two barriers of different heights (left). We measured the fraction of particles escaping over the higher barrier, p_{high}, and over the lower one, p_{low}, depending on the value of the particles' velocity.

Reference

1. E. Woillez, Y. Zhao, Y. Kafri, V. Lecomte, and J. Tailleur, Activated Escape of a self-propelled particle from a metastable state, arXiv:1904.00599, coming soon in Phys. Rev. Lett. (2019)

Spreading of run-and-tumble bacteria in complex environments

Yongfeng Zhao[1, 7], Thibault Bertrand[2], Nan Zhou[3], Olivier Bénichou[4]

Jiandong Huang [3, 5, 6], Julien Tailleur[1], and Raphaël Voituriez[2, 4],

[1]*Laboratoire Matière et Systèmes Complexes, Université Paris Diderot, Paris, France*

[2]*Laboratoire Jean Perrin, Sorbonne Université, Paris, France*

[3]*School of Biomedical Sciences, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, PR China*

[4]*Laboratoire de Physique Théorique de la Matière Condensée, Sorbonne Université, Paris, France*

[5]*Institute of Synthetic Biology Shenzhen, Institutes of Advanced Technology, Shenzhen, PR China*

[6]*Shenzhen Institute of Research and Innovation, University of Hong Kong, Shenzhen, PR China*

[7]*Institute of Natural Sciences, Department of Physics, Shanghai Jiaotong University, Shanghai, China*

The spreading of bacterial colonies typically relies on both cell division and motility. The simplest of models for such behaviours is the so-called FKPP equation, which predicts ballistic propagation of the colony front. This model however neglects the nonequilibrium nature of cellular motion and fails to capture the influence of complex environments, such as porous media, on the latter [1]. In this poster, starting from a simple lattice model of run-and-tumble bacteria, I will show how to obtain a FKPP-like equation for a proliferating colony and derive the speed of the corresponding Fisher wave.

Then I will show how random obstacles impact the speed of the wave in a non-trivial way, without altering the ballistic spreading of the colony. In particular, I will show how our results allow us to account for experiments in which colonies of *E. coli* spread in soft agar gel.

References

[1] T Bertrand, Y Zhao, O Bénichou, J Tailleur, R Voituriez, Optimized Diffusion of Run-and-Tumble Particles in Crowded Environments, Physical Review Letters **120**, 198103 (2018).