XXVIII International Summer School "Nicolás Cabrera"

Physics of Biological Systems:

From Emergent Collective behaviors to Functional Materials

"La Cristalera"

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Madrid (Spain)

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Physics of Biological Systems: From emergent Collective behaviors to Functional Materials

XXVIII International Summer School "Nicolas Cabrera"

September 2, 2022

Motivation

Natural selection has engineered sophisticated nano- and microscopic machines able to perform vital and complex biological processes such as directed transport of molecules, energy storage, tissue remodeling, wound healing and immune responses. To perform these processes, active systems transform energy into mechanical forces, thereby operating out-of-equilibrium. It is precisely the non-equilibrium nature of biological systems, which makes fascinating behaviors emerge, ranging from self-propulsion to collective behaviors, and including patterning formation. However, these behaviors strongly depend on their interaction with the environment, where the forces generated by these active systems can either stressed the environment or where the environment can serve as an energy sink. These environment-mediated interactions, which can be either physical or chemical, may result into coordinated behaviors. For example, the characteristic elements of these systems may be able to coordinate their movements or even their metabolic status through the environment. Therefore, understanding the physical principles that determine the interaction between active elements and their environment is crucial to develop functional materials that take advantage of these behaviors.

The development of functional materials capable of actively responding to external stimuli is thus an open frontier in material science. The dynamical properties of these responsive materials to deformations or sustained movements exhibit striking similarities to those exhibited by living systems. Therefore, the materials science community could be inspired by the behaviors of living matter to develop synthetic and versatile platforms that generate and control dynamically complex individual and collective behaviors. Can we thus use active matter systems to engineer novel responsive materials? Can we link the non-equilibrium physics inherent to living systems to material science in an attempt to apply dynamics and fluctuations to the design of smart materials?

This Summer School seeks bringing together researchers from the fields of biological physics, soft matter physics and material science to open a new avenue of biophysical soft matter research built on the knowledge gained over these years on both the building blocks and the fundamental interactions that drive the behavior of active systems. Understanding the dynamics of these elements enables the development of synthetic materials that either mimic behaviors found in living matter or exploit the elements to improve materials properties.

Contents

Motivation **iii**

Poster's Sessions **1**

(*Session on Monday*) 1

(*Session on Tuesday*) 2

Abstracts **3**

Active buckling of pressurized spherical shells : Monte Carlo Simulation (*Vipin Agrawal, Vikash Pandey, Dhrubaditya Mitra*) 3

Preparation and characterization of stearic acid nanoparticles through rapid expansion of supercritical solution (RESS) (*Zahra Akbari, Javad Karimi-Sabet, Mojtaba Shariati Niasar, Masoud Amanloo, Abolfazl Golestani and Alice Supper*) 4

Artificial transcription in lipid containers (*Ane Arroyo, Macarena Calero, Alicia del Prado, Francisco Monroy and Margarita Salas*) 5

Quasi-Laminar Active Nematic Flows Under Confinement (*O. Bantysh, J. Ignés-Mullol and F. Sagués Mestre1,2*) 6

B. subtilis and *E. coli* swimming motility in structured media (*Richard A. Campusano, Laura R. Arriaga, Juan L. Aragones, Pablo Llombart, Paula Magrinya and Berta Tinao*) 7

Optofluidic platform for the manipulation of water droplets on engineered $LiNbO_3$ surfaces (*Sebastian Cremaschini, Annamaria Zaltron, Davide Ferraro, Alessio Meggiolaro, Mattia Carneri, Enrico Chiarello, Paolo Sartori, Matteo Pierno, Cinzia Sada and Giampaolo Mistura*) 8

Uncovering Rules for Collective Multicellular Behavior in Developmental Biology (*Ramya Deshpande*) 9

Converting energy into work using coupled colloidal clusters (*Andreas Ehrmann*) 10

Artificial organelles encapsulating autocatalytic enzyme reactions for application in controlled release and chemotactic transport (*Oliver Fance*) 11

Programming the transport of colloidal particles in arrays of obstacles (*Galor Geva, Alfredo Alexander-Katz, Laura R. Arriga and Juan L. Aragones*) 12

Modelling Motility in Confined Epithelia: From Single-Cell to Collective Behaviours (*James Graham*) 13

Mechano-signaling waves in epithelial tissues (*Léna Guitou and Javier Buceta*) 14

Design rules for highly selective multivalent DNA-nanostars (*Jain Swareena*) 15
Self-buckling of filamentous cyanobacteria reveals gliding forces (*Maximilian Kurjahn*) 16
Run-and-tumble motion in a nonvibrating 1D-granular-magnetic-system (*Mónica Ledesma-Motolinía, José Luis Carrillo-Estrada, Ángeles Escobar, Fernando Donado, Pavel Castro-Villarreal*) 17
Chlorophyll aggregates for light-harvesting antennas (*Pablo Llombart and Juan L. Aragonés*) 18
Force-dependent mechanical properties of nucleic acids (*Juan Luengo-Márqueza and Salvatore Assenza*) 19
Towards understanding out-of-equilibrium thermodynamics in biological systems (*Clara Luque-Rioja, Diego Herráez, Niccolò Casselia, Macarena Caleroa, Elías Faroa, Juan Pedro García-Villaluenga Horacio López-Menéndez and Francisco Monroy*) 20
Membrane mechanics as a regulator of motion in externally-driven spinning vesicles (*Paula Magrinya, Pablo Llombart, Juan L. Aragones, and Laura R. Arriaga,*) 21
Quantitative Dynamics of the Zebrafish Retinogenesis. The role of Shh and Wnt in cell diferentiation (*Pablo Martínez Martínez*) 22
Rheology of Pseudomonas fluorescens biofilms: from experiments to DPD mesoscopic modelling (*José Martín-Roca*) 23
Droplet microfluidic device based on magnetic microbeads handling for extracellular vesicle purification (*Alessio Meggiolaro, Valentina Moccia, Paola Brun, Alessando Sammarco, Giampaolo Mistura, Matteo Pierno, Valentina Zappulli, Davide Ferraro*) 24
Collective behavior of energy depot repulsive particles (*Juan Pablo Miranda, Demian Levis , Chantal Valeriani*) 25
Characterization of the TGF-β signalling cascade using FLIM-FRET (*Mikel Ocio*) 26
Mechanical interaction of bacterial colonies inside a matrix (*Samaneh Rahbar*) 27
Artificial cells with biochemical clocks: oscillatory enzyme reactions in confinement (*Darcey Ridway Brown*) 28
Topology controls the emergent dynamics in nonlinear flow networks: towards an excitable fluidic system (*Miguel Ruiz-Garcia, Alejandro Martinez-Calvo, Matthew D Biviano, Kaare H. Jensen, and Eleni Katifori*) 29
Perovskite@metal-organic framework for bioimaging applications (*Isabella Sandak-Lewin*) 30
Transport properties and phase behavior of Active Brownian particles moving in an external periodic field (*Miguel Ángel Sandoval Puentes, Ramón Castañeda Priego and Francisco Alarcón Oseguera*) 31
Self-oscillation, Bistability and Maxwell demons in nanosystems (*Jorge Tabanera Bravo*) 32

Inclusion of RNA strands in protein condensates can decelerate pathological structural transitions (*A.R. Tejedor , I. Sanchez-Burgos, M. Estevez-Espinosa, A. Garaizar , R. Collepardo-Guevara, J. Ramirez, J.R. Espinosa*) 33
(*Berta Tinao*) 35
Bio-inspiration of insects pheromonal communication by a microfluidic system (*Alexandra Tiryaeva*) 36
Gel reconfiguration using active doping (*Mengshi Wei, C. Patrick Royal, and Olivier Dauchot*) 37
Collective motion of model phoretic particles (*Qianhong Yang*) 38
Delay-induced phase transition in a simple model of flocking (*Fatemeh Pakpour and Tamas Vicsek*) 39

Author Index **41**

Poster's Sessions

Session on Monday

1. Vipin Agrawal
2. Zahra Akbari
3. Ojus Bagal
4. Bantysh Olga
5. Richard Campusano
6. Sebastian Cremaschini
7. Nestor Manuel De los Santos Lopez
8. Ramya Deshpande
9. Andreas Ehrmann
10. Oliver France
11. Galor Geva
12. Swareena Jain
13. Mónica Ledesma Motolinía
14. Pablo Llombart
15. Juan Luengo Márquez

Session on Tuesday

1. Paula Magrinya
2. Pablo Martínez Martínez
3. Jose Martín Roca
4. Alessio Meggiolaro
5. Juan Miranda López
6. Mikel Ocio Moliner
7. Samaneh Rahbar
8. Darcey Ridway Brown
9. Isabella Sandak-Lewin
10. Miguel Angel Sandoval Puntes
11. Jorge Tabanera Bravo
12. Berta Tinao
13. Alexandra Tiryaeva
14. Mengshi Wei
15. Fatemeh Pakpour

Abstracts

Active buckling of pressurized spherical shells : Monte Carlo Simulation

Vipin Agrawal, Vikash Pandey, Dhrubaditya Mitra
Nordic institute for theoretical physics

We study the buckling of pressurized spherical shells by Monte Carlo simulations in which the detailed balance is explicitly broken – thereby driving the shell active, out of thermal equilibrium. Such a shell typically has either higher (active) or lower (quiescent) fluctuations compared to one in thermal equilibrium depending on how the detailed balance is broken. We show that for the same set of elastic parameters, a shell that is not buckled in thermal equilibrium can be buckled if turned active. Similarly, a shell that is buckled in thermal equilibrium can unbuckle if turned quiescent. Based on this result, we suggest that it is possible to experimentally design microscopic elastic shells whose buckling can be optically controlled.

Preparation and characterization of stearic acid nanoparticles through rapid expansion of supercritical solution (RESS)

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Solid lipid nanoparticles (SLN) are the new generation of nanoparticle active substance vehicles and stearic acid is one of the most important lipids which has been used as colloidal drug carrier. Supercritical fluid technology is a relatively new technique for SLN production. Hence in this paper, formation of stearic acid nanoparticles was reported by rapid expansion of supercritical solutions (RESS). The unprocessed and processed stearic acid powder was characterized by means of scanning electron microscopy (SEM), X-ray diffraction (XRD), differential scanning calorimetry (DSC) and Fourier Transform Infrared Spectrophotometry (FTIR). FT-IR analysis and XRD pattern of processed stearic acid showed that the degree of crystallinity was reduced without any chemical structural change. DSC analysis showed a 2.7 ∘C decrease in the melting point from that of bulk stearic acid. Also, the RESS processing of stearic acid leads to spherical particles in the range from 100 micrometer diameter to 150 nm which are about 600 times smaller than the unprocessed powder.

Artificial transcription in lipid containers

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Liposomes are bilayer vesicle structures that can be artificially synthesized from lipids to allocate biologically active moduli able to recreate the essential features of living organisms, DNA transcription machineries, for instance. Metal ionophores are studied by its activity as transmembrane transporters of metal cations that catalyze transcriptional processes and their possible applications in artificial life realizations. Our aim in this work is to ensemble artificial magnesium ionophores into lipid bilayers to reproduce the transport of magnesium from the outer medium to its lumen, where the transcription enzyme RNA-polymerase will operate to translate DNA into RNA. For this purpose, we will use a lipid model of giant unilamellar vesicles (GUVs) synthesized by the electroswelling technique. For the optical studies, we inserted Texas-Red in the GUVs to observe its membrane, and in its aqueous phase, Mag-Fluo-4 for detecting magnesium ions and UTP--AmNS for displaying the consumption of UTP during the transcription process. After colloidal synthesis, we observed an entrance of magnesium to the liposomes with the presence of the magnesium I and VI ionophores. These transporters were evaluated in terms of membrane incorporation and Mg transport. A higher efficiency of magnesium VI ionophore was quantified. Finally, we used this magnesium transport system as a switch to activate liposome-encapsulated DNA transcription machinery including the RNA-polymerase from B. subtillis. We observed how, when the magnesium entered the vesicles, transcription inside the GUVs took place.

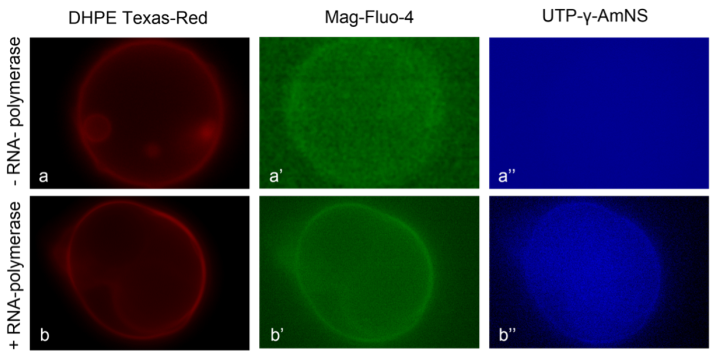

Figure shows the magnesium transported (green) and the transcription process (blue) inside liposomes (red)

Quasi-Laminar Active Nematic Flows Under Confinement

O. Bantysh[1], J. Ignés-Mullol[1,2] and F. Sagués Mestre1,2[1,2]

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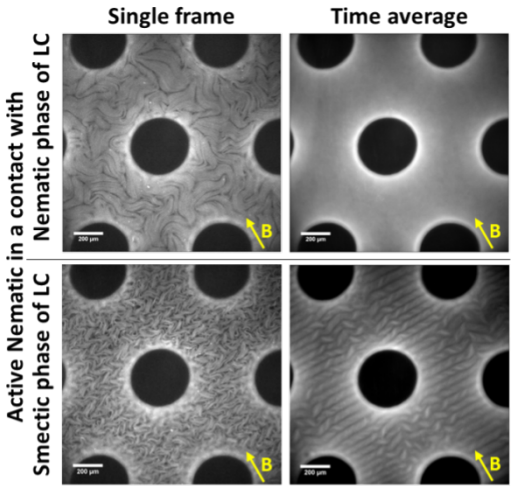
It is possible to assemble a biomimetic active material from microscopic components like cells' filaments and protein motors. This material consumes energy and generates continuous motion. Such active systems are capable of self-organization at different length and time scales, often exhibiting turbulent flows and the emergence of long-range orientational order, which is characteristic of active nematics (AN). Previously, it was demonstrated that, by bringing into contact a two-dimensional AN with an anisotropic oil that features smectic liquid-crystalline order, it is possible to transform the originally turbulent flow of the active fluid into well-aligned flows ordered by a magnetic field [1]. Alternatively, the flow of active nematic could be controlled by confining walls [2] or arrangements of obstacles [3].

In present work we combine both approaches: well-aligned flows of AN ordered by a magnetic field were confined between ensembles of PDMS pillars. The resulting quasi-laminar flows of AN are perturbed by closely located obstacles and at first sight AN adapt turbulent behavior. But the time averaging of sequential images demonstrate that AN reorganize the flow and form a new pattern, with a 'hot spots' where density of the defects (probability to find a 1/2 defects) is much lower than average. By this way, the described system can be used to generate a variety of liquid crystal defect configurations, in order to control the flows of AN.



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B. subtilis and *E. coli* swimming motility in structured media

Richard A. Campusano[1,2], Laura R. Arriaga[1,2,3], Juan L. Aragones[1,2,3], Pablo Llombart[1,2], Paula Magrinya[1,2] and Berta Tinao[1,2]

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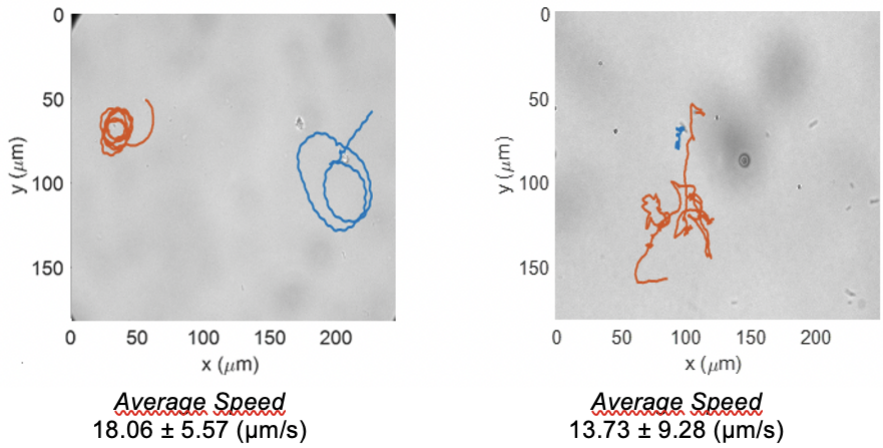
Bacteria have developed a swimming strategy to outrun diffusion, which is required to find food or colonize surfaces. Bacterial species such as *E. coli* or *B. subtilis* exploit a flagellum-mediated swimming motility, which is sensitive to the presence of a substrate. The dynamics of each bacterial species is significatively different. E. coli swimming strategy is based on the paradigmatic run and tumbling protocol in which the bacteria alternate periods of swimming in straight lines at constant speed with sudden tumblings that randomize its swimming direction [1], while B. subtilis swimming strategy exhibits a characteristic wiggling motion with a continuous change in the swimming direction [2]. Here, we analyze the dynamics of the swimming motility of *E. coli* and *B. subtilis* in both liquid broth and microstructured environments [3]. We consider the effect of the growth phase exponential and stationary phase of the bacterial growth and the presence of static (passive particles) and dynamic obstacles (magnetic particles) on the single o pairs of bacterium dynamics.



Representative trajectories of E. coli at the phase exponential in the presence of passive particles (left) and rotating magnetic particles at 2 Hz (right), both 5 microns in diameter.

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Optofluidic platform for the manipulation of water droplets on engineered $LiNbO_3$ surfaces

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The actuation and control of liquid droplets on a surface have important implications in many industrial applications and microfluidics. Reproducible motion of water droplets on a solid surface is very difficult to achieve because of the presence of surface defects. Bioinspired liquid-infused surfaces (LISs), made of textured materials imbibed with a low surface tension oil, exhibit various unique properties attributed to their liquid-like and molecularly smooth nature. In particular, they enable low friction droplet motion. In this work, droplet actuation is achieved by exploiting the photovoltaic effect of iron-doped lithium niobate (LiNbO3): when the crystal is illuminated, surface charges of opposite sign are generated on the two faces of the crystal. This effect allows to overcome the main drawbacks of techniques such as electrowetting by creating virtual reconfigurable electrodes, that can be exploited to achieve droplet manipulation. The face of LiNbO3 in contact with the droplets is coated with the LIS to create a low friction surface. We have realized LISs by impregnating a porous Teflon filter with a fluorinated oil using a dip-coater to ensure high reproducibility. This process allows one to obtain very slippery hydrophobic surfaces for prolonged use. Their performances are tested by analyzing the motion and speed of repeated sequences of water droplets with different volumes and deposited on a sample tilted at different angles; it is found that the LIS can be used safely for the motion of thousands of droplets (about a week of laboratory use). In this way sessile water droplets having volumes of microliters, corresponding to millimeters in size, can be easily actuated, guided, merged and split by projection on the crystal of suitable static or dynamic light patterns by exploiting a spatial-light modulator. The actuated droplets can cover distances of centimeters on a timescale of a few seconds.

Uncovering Rules for Collective Multicellular Behavior in Developmental Biology

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Living cells display a remarkable ability to self organize into increasingly complex structures - from "symmetry breaking" of identical cells in the embryo to the formation of organoids in vitro. During development, cells can undergo a complex sequence of intercellular interactions and movements to create spatiotemporal organization. However, uncovering the developmental programs that orchestrate this multicellular behavior has proven to be a challenge. In this work, we leverage advances in machine learning technologies to optimize over physics and biology based simulations of individual cells, to learn which rules can drive collective behavior. We apply this framework to recover cell-based rules to drive (i) homogeneous tissue growth, (ii) homeostasis between cell types and (iiiI) elongation and sorting of a symmetric cluster of cells. Our work opens new avenues for designing cellular interactions to program complex multicellular behavior, as well as to learn mechanisms from experimental data of developmental trajectories.

Converting energy into work using coupled colloidal clusters

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Can biology-inspired complexity be obtained without biological or biochemical components? Can we replicate ubiquitous biological processes like ATP hydrolysis using only model physical building blocks like DNA-coated colloids that have simple but programmable interactions? The last decades have seen tremendous progress in understanding the self-assembly mechanisms that enable the formation of complex, sub-micron scale structures, but embedding these structures with bio-inspired functional behaviors remains a considerable challenge. Here, we demonstrate a scheme for transferring energy between two colloidal clusters, with one acting as a fuel source – in analogy to ATP – and the other as a receiver. By coupling the two clusters, we show how the receiver catalyzes a structural transition in the fuel source, releasing energy that drives the receiver into a higher energy structural state. The coupled system shows a significantly reduced mean-first passage time and we find a speed-efficiency trade-off. This work demonstrates that a fundamental and enabling biological process can be replicated without complex biochemical reactions. In contrast, theories of active matter often focus on the effect of energy consumption, not on the mechanism of energy consumption itself. However, the mechanism is intimately connected to the type of physical phenomena that can result. In a next step, we extend the scheme to convert energy into work by driving a net flux in the receiver, which is not possible in equilibrium and requires a fuel source. This work will pave the way for uncovering the physical principles that enable us to understand and control the emergence of kinetic and functional features: how non-equilibrium micro-machines assemble, move, and perform tasks.

Artificial organelles encapsulating autocatalytic enzyme reactions for application in controlled release and chemotactic transport

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Despite incredible advancements in modern medicine, many modern drug formulations are still unable to localise at their target sites, resulting in off target side effects and poor therapeutic effect. Nanoparticle-based drug delivery systems (nanomedicines) provide an extremely promising solution to many of the problems associated with conventional drug delivery. Most of the advantages of nanomedicines can be attributed to enhanced temporal and spatial control of the active pharmaceutical ingredient (API) within the body, allowing controlled and targeted drug delivery. A novel possibility for controlled release is to utilize nanoparticle encapsulated enzyme reactions as intrinsic stimuli to create more sophisticated temporal control. By utilising reactions such as the urea-urease reaction, which displays clock like behaviour, changes from low to high pH could be utilised as intrinsic stimuli to trigger drug release. In addition, recent findings regarding enhanced enzyme diffusion and enzyme chemotaxis, demonstrate promise for targeted nanomedicine that utilises encapsulated enzymes to direct nanomedicine to target sites. Several different nanoparticles have been investigated for application in nanomedicine and could potentially encapsulate such a reaction, however liposomes remain the most clinically established nano-carriers.

Programming the transport of colloidal particles in arrays of obstacles

Galor Geva[1], Alfredo Alexander-Katz[3], Laura R. Arriga[1,2] and Juan L. Aragones[1,2]

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We are working on the development of an active material with programmable transport properties. Our design consists of magnetic particles suspended in a fluid and confined in an array of obstacles. Under external action, the particles will rotate in place, and the hydrodynamic coupling with the obstacle network causes them to move through the netwotk. Depending on the angular velocity of the particles, we find that the particles translate along closed stationary trajectories, but if we temporarily modulate the angular velocity of the particles we can alternate between these closed states, thus achieving ballistic transport through the lattice. We will use this time modulation of the rotation speed of the particles to program their transport.

Modelling Motility in Confined Epithelia: From Single-Cell to Collective Behaviours

James Graham
University of Oxford, United Kingdom

Individual and collective migration is a key feature of many biological processes, from tumour invasion to wound healing and morphogenesis. Individual cells migrate according to their polarisation, biophysically encoded in lamellipodia or other protrusions. Cell polarisation also plays a role in collective migration. However, in confluent systems forces between cells can dominate and epithelial monolayers can behave as active nematics.

One specific in vitro behaviour is that of persistent collective rotation, which develops on scales ranging from pairs of cells to roughly ten and several tens. Accordingly, we have used a multi-phase field model to study collective cell motility. We first consider a system of two cells persistently rotating in confinement with polar activity. This system displays a dependence on the strength of cell-cell adhesions as well as on the activity and the rotational diffusion of the polarisation. In addition, we have investigated the flow in a channel of confluent cells subject only to inter-cellular forces. Flow is evident in both extensile and contractile nematic monolayers, given suitable boundary conditions. The origin of persistent collective rotation in larger circular systems and the influence of the effective extensile activity inherent to cell division remain open questions.

Mechano-signaling waves in epithelial tissues

Léna Guitou and Javier Buceta

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Shape remodeling is key to understand organ regeneration and embryo development. In addition, from a mathematical and physical viewpoint, shape remodeling implies understanding self-organization, patterning, and mechanics. In this context, it has been shown that the ERK/MAPK pathway is instrumental during cell migration and tissue regeneration through the interplay between mechanical and signaling cues. However, open questions remain. In particular, the robustness of the pathway activity due to cellular activities (e.g. cellular growth and division) is unclear. Here, by using simulations and analytical work, we revealed the effects of the cellular growth dynamics to either sustain or kill the oscillatory/excitatory activity of ERK at the tissue level. Moreover, our model provides a plausible argument to understand the origin of the aforementioned mechano-signaling feedback. Altogether, our study paves the way to understand the interplay between cellular mechanics and chemical/signaling cues during morphogenesis.

Design rules for highly selective multivalent DNA-nanostars

Jain Swareena
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Multivalent interactions are responsible for sharp transitions and switch-like behavior in biological systems. These are utilized by proteins and virus capsids, and could inspire the design of multivalent nanoparticles that can distinguish between cell membranes differing only slightly in receptor density or composition, a property known as super selectivity. The microscopic dynamics underlying super selectivity is challenging to probe experimentally, as it is difficult to distinguish between the different bound states of a multivalent particle. We propose a theoretical model to study the effect of the individual reaction rates in a system of nanostars, a DNA-origami synthesized molecule that has single-stranded DNA as free ends, which can bind with complementary strands embedded in a supported lipid bilayer. Our objective is to maximize the selectivity of the nanostars, which we quantify as the slope of the binding transition. Complementary simulations utilize the Gillespie Algorithm, a stochastic algorithm that incorporates the rates of the reactions as input parameters. To incorporate the effect of diffusion, the substrate is discretized into multiple reaction cells, such that we can monitor the evolution of concentration gradients over the substrate. The binding probability of weakly interacting multivalent nanostars appears to increase nonlinearly with the receptor density and we aim to optimize the nonlinear relation by tuning the microscopic reaction rates. By comparing the simulations to FRAP experiments we can extract the microscopic reaction rates of synthesized DNA-nanostars. We also interrogated the influence of cooperative and competitive interactions between the arms of the nanostars on the selectivity, and extracted several design rules for nanoparticles with high selectivity. The method is also used for other reaction networks, to study patch formation by proteins involved in yeast budding.

Self-buckling of filamentous cyanobacteria reveals gliding forces

Maximilian Kurjahn

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

Filamentous cyanobacteria are one of the oldest and today still most abundant lifeforms on earth, with manifold implications in ecology and economics. These photo-trophic organisms form long and flexible filaments that do not actively swim in bulk liquid but exhibit gliding motility in contact with solid surfaces. The underlying force generating mechanism of their gliding apparatus is not yet understood. We measure their bending modulus with micropipette force sensors, and investigate how filaments buckle after gliding onto an obstacle. Comparing Kirchhoff theory to the experiments, we derive the active forces and the friction coefficients associated with gliding from the observed critical filament length for buckling. Remarkably, we find that these two quantities are strongly coupled, while dependencies on other observables are largely absent. The critical length also aligns with the peak of their natural length distribution, indicating the importance of buckling for their collective.

Run-and-tumble motion in a nonvibrating 1D-granular-magnetic-system

Mónica Ledesma-Motolinía, José Luis Carrillo-Estrada, Ángeles Escobar, Fernando Donado, Pavel Castro-Villarreal

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If we study nature closely, we can observe that it is out of equilibrium, and in some cases, the collectives of organisms that make it up to move by extracting energy from their surroundings. These collectives are known as active matter. In the present work, a nonvibrating 1D-granular-system is used to understand the dynamics of a particle in a circular channel as a function of the effective temperature and channel radius. We identify that the dynamical behavior is well represented by a run-and-tumble model. Even, we can modulate the particle motion by changing the magnetization of the particle.

Chlorophyll aggregates for light-harvesting antennas

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The Chlorosome is a fantastic, yet poorly understood natural nanostructure. It is an array of chlorophyll molecules that self-assemble into a nanoantenna that is probably nature's best single-photon detector. The simulation of this system has been challenging from two aspects that ultimately need to be combined into a large-scale computer simulation. We will combine multi-scale simulations of the selfassembly of these large-scale structures of hundreds of thousands of atoms with the energy transfer mechanism that enables them to be such great light absorbers. Both areas, self-assembly and energy transfer, are presumably tied through evolution since the Chlorosomes (Chls) must be able to collect all the photons that arrive at its surface [1,2].

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Force-dependent mechanical properties of nucleic acids

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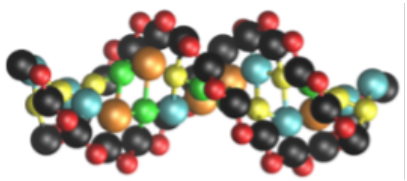
Double-stranded nucleic acids (dsDNA and dsRNA) are complex macromolecules with important biological functions inside the cell. The packaging conditions in which they are found in vivo, such as dsDNA bent around histones, suggest that the regulation of the genetic code is largely determined by the mechanical properties of nucleic acids [1].

Remarkably, some biological processes involve the deformation of the double helix with a force exerted at the base step level, e. g. the interaction of dsDNA with enzymes, but the existing method [2] to compute the elastic parameters of the Elastic Rod Model from the fluctuations of the double helix is not suitable for the study of perturbed chains. In this work, we overcome this limitation by presenting a generalization of the precedent method, and whose applicability range extends to stretched, twisted or bent chains under the action of some mechanical stress.

We exploit this novel approach by analyzing data of configurations of nucleic acid chains from atomistic MD simulations and computing the evolution of the elastic parameters with a stretching force. This inspection reveals another fundamental distinction between dsDNA and dsRNA: the former stiffens with the stretching force exerted, while the latter becomes softer. We find that this different behavior emerges from an opposite variation of the slide - a crucial micromechanical feature of double-stranded nucleic acids, whose importance has already been emphasized by previous studies [3].



Schematic representation of dsDNA

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Towards understanding out-of-equilibrium thermodynamics in biological systems

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Living systems dissipate energy constantly as they perform essential functions. Because of their ordered and self-organized dynamics, these processes frequently result in complex behaviors that can be classified as non-thermal processes however, it can often be challenging to tell whether a process' dynamics are significantly different from those of a thermally driven process. This work uses two systems as a reference to describe these out-of-equilibrium behaviors. One of them consists of an active-poroelastic theoretical framework to represent chromatin as an active-elastic solid coupled to a permeating fluid. Based on experimental data suggesting large-scale correlated mobility of chromatin inside the nuclei of live differentiated cells, we include the active stress into a two-fluid model that accounts for the spatiotemporal dynamics of the nucleus. This system is affected by both passive thermal fluctuations and active scalar events, such as condensation and decondensation, which we name spikes. The coupled set of equations showing the presence of emergent processes is simulated in this instance. Whereas in the other system, we study the bacteria as an active Brownian particle. The stochastic forces of the bacteria are accessed by trapping them with optical tweezers The overdamped dynamics of this simple system can be described by the Langevin equation in order to study the dynamics and energetics such as heat or dissipated energy.

Membrane mechanics as a regulator of motion in externally-driven spinning vesicles

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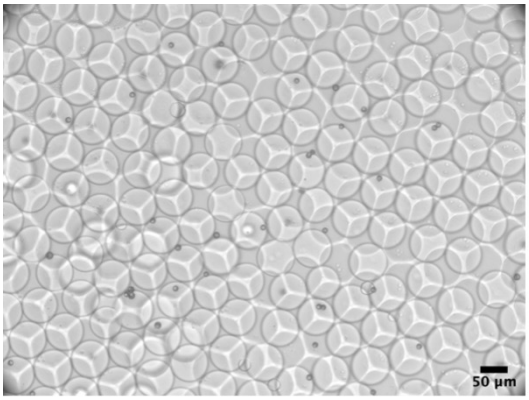
The active processes occurring within the cell cytoplasm are often confined in space by the presence of membranes and other cytoplasmatic self-assembled structures. The presence of such limiting surfaces likely affects the self-generated fluid flows emerging within cells from such active processes, which may influence cell motion. To understand how self-generated fluid flows are influenced by the mechanical properties of such limiting surface, we design a synthetic system that consists of vesicles with different membrane composition and thus different mechanical properties encapsulating a single ferromagnetic microparticle within their cores. This model system is produced with exquisite control using microfluidics approaches1 as illustrated in Figure 1. Our results show that the translational velocity of the encapsulated particle decreases as the vesicle becomes bigger and the self-generated flows are less confined. Furthermore, a significant decrease in particle's velocity can be seen when the membrane state changes from a fluid to a gel. These results open the creation of motile vesicles that exploit self-confined rotational flows to translate on substrates.



Example of a microfluidic production of PEG-b-PLA vesicles with encapsulated ferromagnetic microparticles.

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Quantitative Dynamics of the Zebrafish Retinogenesis. The role of Shh and Wnt in cell diferentiation

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Communication between cells is one of the most complex broad processes in the realm of biophysics. Cells have developed a number of pathways through which they can establish these channels of communication and thus react to environmental changes. We focus primarily on how stem cells differentiate to neurons, trying to unveil what each of these signaling pathways is responsible of in the process of tissue formation. Our model tissue is the zebrafish retina, an outstandingly compact system whose dynamics had failed to be quantified precisely. Through a simple time-dependent Markovian branching model, considering that only stem cells may proliferate (as differentiated neurons become quiescent), we can extract two fundamental parameters that govern the differentiation at the tissue level: the rate of proliferation, whose sign determines whether the number of stem cells is growing or being reduced; and the mean cell cycle. These parameters may be obtained by counting the number of stem and differentiated cells at each stage of development found in the retina. We have been able to automatize this process by an ellipse connectivity tool (OSCAR) developed in our laboratory that defines the extension of each cell based on their 2D projections as a stack of confocal microscopy images. Most importantly, our methodology is completely general and enables us to study the time-dependent dynamics of a stem cell pool under controlled environmental changes. In this instance, we have studied the relevance of two signaling pathways, Shh and Wnt, pushing the qualitative knowledge of the field to a new level by establishing the reasons behind the observed changes through the fluctuations of these two parameters. What is more, our findings may allow to manipulate the fate of a stem cells in contexts other than tissue formation, since these pathways are ubiquitous across the lifetime of the organism.

Rheology of Pseudomonas fluorescens biofilms: from experiments to DPD mesoscopic modelling

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The presence of bacterial biofilms in clinical and industrial settings is a major issue worldwide. A biofilm is a viscoelastic matrix, composed of bacteria producing a network of Extracellular Polymeric Substances (EPS) to which bacteria crosslink. Modelling of complex biofilms is relevant to provide accurate descriptions and predictions that include parameters as hydrodynamics, dynamics of the bacterial population and solute mass transport. However, up-to-date numerical modelling, even at a coarse-grained level, is not satisfactorily. In this work, we present a numerical coarse-grain model of a bacterial biofilm, consisting of bacteria immersed in an aqueous matrix of a polymer network, that allows to study rheological properties of a biofilm. We study its viscoelastic modulus, varying topology and composition (such as the number of crosslinks between EPS polymers, the number of bacteria and the amount of solvent), and compare the numerical results with experimental rheological data of Pseudomonas fluorescens biofilms grown under static and shaking conditions, as previously described by Jara et al, Frontiers in Microbiology (2021).

Droplet microfluidic device based on magnetic microbeads handling for extracellular vesicle purification

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One of the most interesting open questions in biomedicine is the search for new techniques to diagnose tumors at early stage, preventing expensive tests and invasive biopsy. A promising alternative consists in the so-called "liquid biopsy" that screens body fluids, such as urine or blood, seeking for traces suggesting the presence of cancerous cells. In this context, during the last decade an increased attention has been given to extracellular vesicles (EVs) that, having size between 30-200 nm, are secreted by cells and contains genetic material. They were found to play crucial role in intercellular exchange of molecular constituents and tumor growth. However, the study of their properties requires an efficient isolation and this task is not yet satisfied by the available techniques, such as ultracentrifugation or filtration, that suffer from low recovery rate and reproducibility. To solve this issue, we propose a droplet microfluidic device based on the affinity capture of the EVs to solid magnetic beads, functionalized with specific antibodies. Droplet microfluidics is the technology that permits the generation and handling inside microchannels of tiny and independent droplets. The spontaneous recirculation within those droplets allows the high mixing between EVs and beads required for their capture, improving recovery rate and throughput, and reducing protein background. The customized chip was developed to co-encapsulate in droplets both EVs from cell culture media and magnetic beads. After incubation, droplets were driven towards a magnetic region within the device which acts as a trap for the magnetic beads decorated with vesicles. The droplet microfluidic protocol was compared to a more conventional method such as ultracentrifugation and affinity capture in batch and purified vesicles were characterized by flow cytometry, protein analysis and particle tracking, showing a good extraction rate and purification. Currently, isolations from more complex samples are under investigation.

Collective behavior of energy depot repulsive particles

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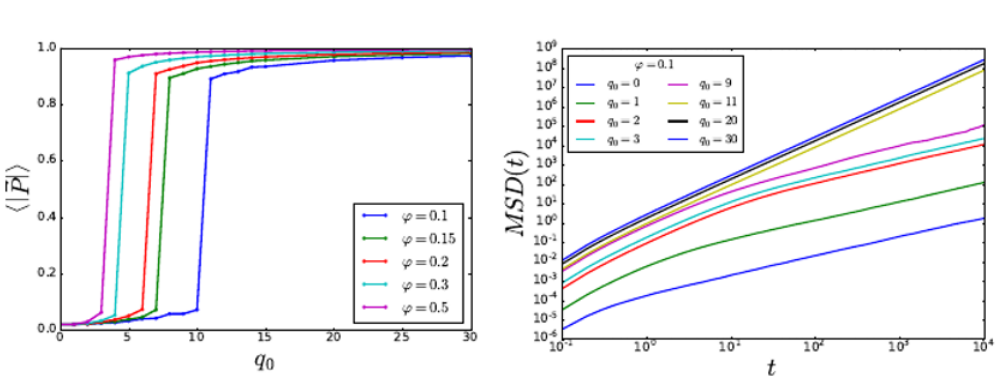
In this work we consider an active particle model [1] that reproduces the motion of microscopic biological objects, such as cells or bacteria, that is described with Langevin dynamics. The particles are able to take energy from their environment, store it into an internal energy depot and convert it into kinetic energy in the direction of motion. This model uses a velocity dependent friction function. We study the different diffusion regimes varying the parameters of the model. We implement a repulsive interaction with a WCA potential, and study how it affects the dynamical properties of the model.

We have studied a two dimensional suspension of repulsive particles, where the interaction between the particles is implemented with a WCA potential. We have studied both dynamical and structural features of the system. The main studied structural feature is a phase transition between an ordered and a disordered state for different volume fractions ϕ and values of the activity.



Left: Mean polar order parameter as a function of the activity q parameter for the studied volume fractions ϕ. Right: Mean squared displacement over time for different systems of $\phi = 0.1$ and different values of the activity q.

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Characterization of the TGF-β signalling cascade using FLIM-FRET

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The transforming growth factor beta (TGF-β) pathway is one of the most conserved and prolific signaling cascades. It is involved in the regulation of many processes, including growth, proliferation, differentiation, and survival. Extracellular ligands activate membrane receptors, which recruit and phosphorylate the downstream effectors R-Smad proteins, which form complexes that enter the nuclei and recruit co-factors to ultimately regulate target gene expression. TGF-β-induced Smad signal transduction is a dynamic network that couples Smad phosphorylation and dephosphorylation through continuous nucleocytoplasmic shuttling of Smads.

We have developed a biosensor constituted by a pair of fusion proteins R-Smad-ECFP and R-Smad-EYFP to detect the activation of the pathway in in vivo cells using FLIM-FRET. FLIM maps the spatial distribution of probe lifetimes inside living cells and can accurately measure the shorter donor lifetimes that result from FRET. We have generated different clonal cell lines expressing stably the fusion proteins. To verify the functionality of our tool, we have developed a simple mathematical model that describes the dimerization and translocation process of the R-Smad complexes between the cytoplasm and the nuclei, so we can characterize the translocation dynamics of the fusion and the endogenous proteins and compare them. We are also able to fit the model to experimental data for different activation states of the pathway.

We observe a differential translocation phenomenon predicted by the mathematical model: the cells with higher protein expression levels show a higher nuclear intensity, indicating a stronger activation of the pathway, even in the absence of ligand. We obtain FRET efficiencies up to 12% in fixed cells, providing a spatial mapping of the R-Smad dimerization, and, therefore, of the pathway activation. This tool can be used to test the effect of the different ligands of the TGF-β superfamily, as well as their specificity and the role of each R-Smad.

Mechanical interaction of bacterial colonies inside a matrix

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Artificial cells with biochemical clocks: oscillatory enzyme reactions in confinement

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Non-equilibrium reactions lead to the emergence of complex behaviour such as oscillations. Oscillatory reactions are ubiquitous in nature, created through the existence of feedback mechanisms in single-celled and multicellular organisms. Creating periodic fluctuations in signalling pathways, oscillations are often employed in regulatory networks to synchronize cellular function; performing as biological clocks for physiological behaviours such as heart beats, cell division and the circadian sleep-wake cycle. The complexity of these intricate and interconnected reaction systems makes oscillatory processes challenging to study in vivo, motivating many to replicate processes in biomimetic systems, such as artificial cells. These simplified experimental models allow the systematic study of biological processes in isolation. Allowing us to explore the design principles required for the emergence of complex dynamic behaviour, developing a comprehensive understanding of chemical self-organisation utilized in cells. Additionally, a biocompatible oscillatory system might be the key to developing artificial systems with autonomous and periodic behaviour for nanomedical applications such as pulsatile drug release.

It was proposed that a biological clock could be generated through exploiting the pH dependency of enzymatic reactions that produce or consume H+, displaying autocatalytic behaviour, such as the urea-urease system. Due to the base-catalysed feedback, when initiated at a low pH, the reaction rate increases as the reaction progresses. Urease rate was modelled using Michaelis-Menten with the additional considerations of product/substrate inhibition, pH dependence and the diffusion coefficients of H+ and urea in a reaction cell. This model found when H+ exchange rate was faster than urea exchange rate with the environment, the steady state of the system could be destabilized, producing the parameters for oscillatory behaviour. Herein, the aim of this project is to construct the first artificial pH oscillator controlled by membrane transport rates in lipid vesicles, utilizing the base-catalysed feedback mechanism of the urea-urease system.

Topology controls the emergent dynamics in nonlinear flow networks: towards an excitable fluidic system

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Flow networks are essential for both living organisms and engineered systems. These networks often present complex dynamics controlled, at least in part, by their topology. Here we present a model for complex flow networks with non-linear conductance that allows for internal accumulation/depletion of volume, without any inherent oscillatory or excitable behavior at the nodes. In the absence of any time dependence in the input and output we observe emerging stationary pattern formation and complex dynamics in the form of self-sustained waves, which travel through the system. The frequency of these waves depends strongly on the network architecture and it can be explained with a topological metric. Our results can be tested using fluidic flow networks whose elements present negative differential resistance. We will describe how to build such systems in the fluidic realm using COMSOL simulations and preliminary experimental results.

Perovskite@metal-organic framework for bioimaging applications

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Owing to their outstanding photophysical properties, metal halide perovskites (PVKs) offer promising potential as fluorophores in bioimaging applications, enabling better resolution and quicker imaging while opening pathways to novel methodologies such as hyperspectral bioimaging. Recently, a novel method to encapsulate PVKs within monolithic metal-organic-frameworks (MOFs) has resulted in a nanocomposite material (PVK@MOF) that is stable in moisture and retains the excellent emission of PVK. The latter, is achieved following state-of-the-art monolithic MOF synthesis by Tian et al. resulting in a transparent structure capable of maintaining the encapsulated PVKs emission.

Besides strong emission and stability, for PVK@MOFs to be used as novel fluorophores for bioimaging, it is important to determine their cytotoxicity. While most PVKs, like MAPbBr3, contain lead, it is hypothesised that cytotoxicity could be reduced by encapsulation within a biocompatible MOF, like zinc imidazolate framework 8 (ZIF-8). Determining this, is key to enabling opportunities in bioimaging.

Therefore this report aims to determine the cytotoxicity of MAPbBr3@ZIF-8 (monolithic) compared to MAPbBr3 through an optimized MTS cytotoxicity assay on both cell lines representing both normal and diseased (HEK293 and HeLa) states. Through synthesising the materials in question (MAPbBr3, ZIF-8 and MAPbBr3@ZIF-8), culturing cells and designing/performing an MTS cytotoxicity assay, a suitable MAPbBr3@ZIF-8 dosing concentration (100 g/ml) was identified to ensure enough cell viability when performing bioimaging. As such, confocal microscopy of HeLa cells using MAPbBr3@ZIF-8 as fluorophores was successfully confirmed. Building on this research, various avenues can be explored to optimise PVK@MOFs as novel fluorophores: from MOF functionalisation methods for highly-specific subcellular targeting to encapsulation with lead-free PVK alternatives.

Transport properties and phase behavior of Active Brownian particles moving in an external periodic field

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The structural and dynamical properties and the phase behavior of colloidal active particles have attracted the interest of the scientific community in recent years. Interesting collective phenomena have been reported in experiments, theoretical approximations and computer simulations. Moreover, the motion of active particles in complex environments has gained the attention of recent physics researches because the novel phenomena that emerge, such as as trapping, sorting, clogging and also ratchet effects, mainly due to the disorder of the environment. In this work, by means of extensive Brownian dynamics computer simulations, a systematic analysis of the transport properties of single and interacting active Brownian particles moving in an external periodic field has been performed . Our results point out on the existence of dynamical regimes that emerge due to the competition between the self-propulsion force and the strength of the external potential. Also, oscillatory behavior in the self-intermediate scattering function has been observed, as it is expected for pure active Brownian particles or another systems out of equilibrium, as in driven colloidal systems. The well-known phase diagram of interacting active Brownian particles was modified by the presence of the external field. The analysis of the effect of the external periodic potential on the phase diagram and the dynamical properties are explicitly discussed.

Self-oscillation, Bistability and Maxwell demons in nanosystems

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At the nanoscale, thermal and electronic fluctuations become very relevant, forcing us to review our basic knowledge of thermodynamics. Stochastic thermodynamics describes energy exchange in the presence of fluctuations, but still faces numerous theoretical and experimental challenges. Electromechanical systems are bipartite systems in which electric currents are coupled with moving parts with very low friction, making them ideal devices for the analysis of stochastic thermodynamics, allowing us to implement various protocols as well as to measure energy and information flows in a very accessible way.

Within the FQXi-NanoQit project, we analyse the interaction of fluctuations in electromechanical systems with nonlinear physics phenomena (Self-oscillation), as well as the possible implementation and interpretation of Maxwell's Demon in the framework of Information Thermodynamics. In recent studies, we have been able to observe and characterise the presence of Self-oscillations in the Coulomb blockade regime, revealing new phenomenology. We have proposed a model capable of explaining these results, opening the door to new experiments.

Inclusion of RNA strands in protein condensates can decelerate pathological structural transitions

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Cell function heavily relies on the formation of membraneless compartments which, sustained by the physical chemistry of liquid-liquid phase separation (LLPS), selectively organize in space and time the cell material[1]. These coexisting liquid compartments can age over time becoming gel-like pathological systems[2]. Malfunction of LLPS represents a key pathological step in the onset of several neurodegenerative disorders such as Alzhemier, ALS or even cancer[3]. One of the proposed mechanisms to explain the liquid-to-solid mesoscale transformation of biomolecular condensates during ageing is the gradual accumulation of inter-protein structural transitions over time[4].

Here, we develop a multiscale computational approach, integrating atomistic simulations and residue-resolution coarse-grained models to shed light on the thermodynamic and kinetic factors that explain ageing of biomolecular condensates via gradual accumulation of -sheet content. Our dynamical algorithm integrates atomistic simulations with sequence-dependent coarse-grained modelling of condensates that age over time due to accumulation of inter-protein -sheets. We report a notably increment of condensate viscosity after ageing while keeping the same phase diagrams. Strikingly, the network of molecular connections within condensates is drastically altered during ageing and culminates in gelation when the network of strong inter-protein -sheets fully percolates. Furthermore, the precise effect of poly-Uridine RNA is investigated on the regulation of ageing by varying both the concentration[3,5]. When high concentrations of RNA are recruited by phase-separated droplets, a significant reduction in the disorder-to-order transition rate can be found. Our study uncovers molecular and kinetic factors explaining condensate ageing and suggests a potential mechanism to slow ageing down.

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Berta Tinao

1

Bio-inspiration of insects pheromonal communication by a microfluidic system

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The marvelous long-distance communication in moths using chemical pheromones is still unsolved. How can they find each other with such minute amounts produced and over kilometers? While several aspects of this communication system have been thoroughly studied, a system approach is missing. The question of how low the level of molecule release can be for at least some to reach the sensory system is thus still unsolved. We address this question by producing a bio-inspired microfluidic chip combining pheromone release, transport, and capture enabling control with unmatched precision. Our project, while inspired by the silk moth Bombyx mori, will be a proof-of-concept study, with pheromone-laden microdroplets immobilized on surface-energy anchors for release, channels of varying geometries for transport, and electrophysiological recording of Xenopus eggs incorporating receptors for bombykol for capture. This project is a new approach study of the interface field between microfluidics and insect science on a system level.

Gel reconfiguration using active doping

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One of the distinctive properties of living systems is to be self-driven. They thereby access emergent properties. Molecular motors, which stiffen and contract cytoskeletal networks, make a good example in nature. We study a quasi-2D colloidal gel doped with Janus particles, the activity of which is switched on using light once the gel is formed. The activity level is controlled by the power of the light. We monitor both the structure and dynamics, before, during, and after the active period. The mobility of the passive particles increases and exhibits a characteristic scale-dependent response to the activation. Simultaneously, the gel reorganizes, with smaller strands coalescing with larger ones and leaving larger holes in the structure. Interestingly, once activation is switched off, the gel keeps the memory of the activation period. The gel after activation adopts the structure inherited from the active phase. However, the dynamics of the so newly formed gel is frozen with the mean square displacement plateaus, but with an absolute value that is larger than that before activation. The system has turned into a genuine different gel, the structure of which looks like that of an older gel, but the dynamics of which is actually that of a softer gel.

Collective motion of model phoretic particles

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Delay-induced phase transition in a simple model of flocking

Fatemeh Pakpour and Tamas Vicsek
Arak University of technology

The coherent motion of animal collectives has been extensively studied by modelling systems made of many self-propelled units. Such systems exhibit a broad range of fascinating collective motion patterns, the examples ranging from macromolecular level to groups of organisms. The transition from a disordered to ordered flocks has mostly been investigated by considering random, shot noise-type fluctuations acting on the particles. On the other hand, the very realistic assumption regarding the potential role of delays (in other words, reaction times are present in every natural or technological system) in destroying coherence has not been explored yet. Although a few recent studies have demonstrated that introducing time delays does not lead to diminishing ordered motion in the basic models of flocking, here we show that including repulsion between the particles in a simple model of self-propelled particles results in a not yet described kind of phase transition in which the gradual increase of the delay times results in a sharp decrease of the global order in the pattern of collective motion. Our result has relevance to interpreting some of the anomalous behaviours observed during relatively fast, coherent directional changes of animal groups and robotic flocks.

Author Index

Agrawal
Vipin, 3
Akbari
Zahra, 4
Arroyo
Ane, 5

Bantysh
Olga, 6

Campusano
Richard, 7
Cremaschini
Sebastian, 8

Deshpande
Ramya, 9

Ehrmann
Andreas, 10

France
Oliver, 11

Geva
Galor, 12
Graham
James, 13
Guitou
Léna, 14

Kurjahn
Maximilian, 16

Ledesma-Motolinía
Monica, 17
Llombart
Pablo, 18
Luengo
Juan, 19
Luque-Rioja
Clara, 20

Magrinya
Paula, 21
Martín-Roca
José, 23
Martínez
Pablo, 22
Meggiolaro
Alessio, 24
Miranda
Juan Pablo, 25

Ocio
Mikel, 26

Pakpour
Fatimeh, 39

Rahbar
Samaneh, 27
Ridway Brown
Darcey, 28
Ruiz-Garcia
Miguel, 29

Sandak-Lewin
Isabella, 30
Sandoval Puentes
Miguel Ángel, 31
Swareena
Jain, 15

Tabanera Bravo
Jorge, 32
Tejedor
Andres, 33
Tinao

Berta, 35
Tiryaeva
Alexandra, 36
Wei
Mengshi, 37
Yang
Qianhong, 38