# MicroMotility: state of the art, recent accomplishments and perspectives on the mathematical modeling of bio-motility at microscopic scales

Daniele Agostinelli[a], Roberto Cerbino[b], Juan C. Del Alamo[c], Antonio DeSimone[a,d,*], Stephanie Höhn[e], Cristian Micheletti[a], Giovanni Noselli[a], Eran Sharon[f], Julia Yeomans[g]

[a] *SISSA–International School for Advanced Studies, 34136 Trieste, Italy*
[b] *Università degli Studi di Milano, 20090 Segrate (MI), Italy*
[c] *Mechanical and Aerospace Engineering Dept., University of California San Diego, 9500 Gilman Drive, La Jolla CA, USA*
[d] *The BioRobotics Institute, Scuola Superiore Sant'Anna, 56127 Pisa, Italy*
[e] *University of Cambridge, UK*
[f] *The Hebrew University of Jerusalem, Israel*
[g] *University of Oxford, UK*

**Abstract**

Mathematical modeling and quantitative study of biological motility (in particular, of motility at microscopic scales) is producing new biophysical insight and is offering opportunities for new discoveries at the level of both fundamental science and technology. These range from the explanation of how complex behavior at the level of a single organism emerges from body architecture, to the understanding of collective phenomena in groups of organisms and tissues, and of how these forms of swarm intelligence can be controlled and harnessed in engineering applications, to the elucidation of processes of fundamental biological relevance at the cellular and sub-cellular level. In this paper, some of the most exciting new developments in the fields of locomotion of unicellular organisms, of soft adhesive locomotion across scales, of the study of pore translocation properties of knotted DNA, of the development of synthetic active solid sheets, of the mechanics of the unjamming transition in dense cell collectives, of the mechanics of cell sheet folding in volvocalean algae, and of the self-propulsion of topological defects in active matter are discussed. For each of these topics, we provide a brief state of the art, an example of recent achievements, and some directions for future research.

*Keywords:* cell motility, unicellular swimmers, adhesive locomotion, active matter, knotted DNA, unjamming transition, cell sheet folding, topological defects

## 1. Introduction

The study of biological motility and, in particular, motility at microscopic scales (MicroMotility) has enjoyed considerable success in recent years. A vast new body of knowledge, growing at a very fast pace, is being collected in a rapidly growing literature. Quantitative mathematical modeling of biological processes is producing new biophysical insight. The opportunities for new discoveries, at the level both of fundamental science and of the development of innovative engineering applications are extraordinary.

A prototypical case, which is also one of the most widely studied ones, is locomotion of individual cells and biological organisms such as bacteria and unicellular algae, worms, slugs, cephalopods and up to higher organisms exhibiting extraordinary capabilities as very dexterous manipulators, like octopus. Of particular relevance is the elucidation of how complex organismal behavior emerges from specific body architectures, and how this is affected by environmental cues. Examples range from the way single adhesive cells respond

*Corresponding author.
*Email address:* desimone@sissa.it (Antonio DeSimone)

to chemical patterning of the substrate (contact guidance, see Shishvan et al. (2018); Buskermolen et al. (2019)), how phytoplankton clusters in columns and layers by exploiting the ability to swim along the direction of gravity (gravitaxis, see Guasto et al. (2012)), to how snakes and lizards can adapt their gaits to move successfully on and through granular media (Aydin et al. (2019); Aguilar et al. (2016); Hosoi and Goldman (2015)). The examples of swimming unicellular algae (see Section 2) and crawling amoeboid cells (see Section 3) are analyzed in more detail below.

Motility is also involved in important processes in the inner working of a cell, hence at the sub-cellular scale, often related to the interaction of biofilaments (actin, microtubules, but also DNA and RNA) with molecular motors (myosin, dynein, kinesin) and enzymes acting as molecular machines (ATP-synthase, RNA-synthase, etc.), see e.g., Keller and Bustamante (2000); Bustamante et al. (2001); Bustamante (2017); Zhang et al. (2019a). The mechanical interactions between microtubules and molecular motors is responsible for the beating of eukaryotic flagella and cilia. They are made of assemblies of microtubule bundles and motors according to a typical architecture (the '9+2' structure, which is conserved across all eukaryotes). Their beating drives many biological processes that are fundamental for life, from the motility of sperm cells, to the clearance of mucus from airways. While much is already known about the way that flagella beat, see e.g. Sartori et al. (2016b); Geyer et al. (2016); Sartori et al. (2016a), many questions are still open, including the fundamental one of how the beat is actually regulated. More generally, the way geometric and mechanical properties of biofilaments impact on their biological function is a far-reaching fundamental question. The way knotting affects translocation of DNA across membrane pores is examined in more detail in Section 4 below.

Motion in plants, a field of study initiated with some pioneering work by Darwin (1880), is attracting renewed and considerable attention. This includes both active motion triggered by specific response mechanisms and powered by biochemical reactions, and passive conformational changes triggered by changes in the environmental conditions.

The study of active movements of plants such as tropisms and nastic movements has attracted renewed interest in recent years and is already providing new discoveries and breakthroughs (see the recent paper by Agostinelli et al. (2019) and the references provided therein for a brief review). Gravitropism, the ability of plants to control their vertical posture and align with the direction of gravity, is an illustrative example. It requires a sensing apparatus (to detect the direction of the gravity vector) and a mechanism of response (for adjustment when misalignment occurs). Only very recently a coherent picture of gravitropism is starting to emerge, and it is the following one. Gravitropism is the result of differential cell elongation in growing tissues. The gravitational signal is perceived through the sedimentation of starch-filled plastids (statoliths) in specialized cells (statocytes). This is then converted into biochemical signals leading to an auxin gradient that is responsible for differential growth across a stem and, in turn, bending to restore alignment of a growing shoot with the direction of gravity, see Chauvet et al. (2019).

Shape changes in plants triggered by changes of the environmental conditions (e.g., humidity), leading to changes of their material properties, provide an example of passive motile response. Recent progress has also been made in the understanding of the mechanisms governing these passive shape changes, which are often encoded in clever micro-architectures. For examples, plants can synthesize materials that actuate with varying humidity and provide motility in the context of seed dispersal. These (non-living) shape-changing materials are composites based on cellulose nanofibrils in a polysaccharide-rich matrix that swells with water uptake. The combination of a swelling matrix and inextensible fibrils provides actuation depending on fiber architecture, see Fratzl and Barth (2009). The energy source for the movement is the interaction of water from the atmosphere with cellulose and other polysaccharides in the cell wall (Bertinetti et al., 2013). A special case are seed pods from Banksia trees, in which fire triggers the opening of the woody fruits, followed by humidity-mediated seed release after the passage of fire (Huss et al., 2018). Another interesting example is the mechanism of explosive seed dispersal in *Cardamine hirsuta*, see Hofhuis et al. (2016). These and other similar results have prompted the study of synthetic materials capable of emulating this response by controlled swelling in micro-patterned heterogeneous materials, or through the incorporation of stiff fibers in soft swelling polymeric matrices, see e.g. Agostiniani et al. (2018) and Section 5 below.

The biophysical and mathematical modeling of the way model organisms work is elucidating new aspects of the way biological functions are performed. In addition, quantitative study of the mechanics of biological

organisms allows for a two-way interaction between basic science and engineering applications. Indeed, the lessons learned from the study of biological organisms can inform the design of new bio-inspired engineered devices. Conversely, looking back at biology through the functionalist view of an engineer wishing to replicate its successes can help us understand how biological machines function, with a level of detail which is unprecedented. This two-directional interaction between biology and mechanics is promoting a new approach in robotic research, in particular in the new field of Soft Robotics: understanding biology by constructing bio-inspired machines, build new machines thanks to bio-inspiration (Kim et al., 2013; Laschi and Mazzolai, 2016).

Finally, an important topic of vibrant current research is the passage from individual to collective behavior, which has many aspects worth mentioning. One is the collective behavior of tissues, and the prospects that better understanding their properties may lead to improvements in drug delivery techniques (Michor et al., 2011). Recent progress in the mechanics of epithelial tissues is reported in Latorre et al. (2018), while further details on the motility of dense cell collectives thanks to an unjamming transition is discussed further in Section 6.

Another related topic is the collective behavior of groups of motile organisms. Bacterial colonies are particularly interesting and it has been recently shown how their collective motion can be controlled by light (Vizsnyiczai et al., 2017; Frangipane et al., 2018). More generally, the emergence of coordination as a form of collective intelligence has been studied in bird flocks and insect swarms (Cavagna et al., 2018), and in groups of plants and forests (Tovo et al., 2017). These topics are further expanded in Section 7 on the behavior of algal colonies, and in Section 8 on the role of self-propelled topological defects in bacterial colonies, epithelial tissues and, more generally, in active matter.

The examples briefly presented above provide a vivid illustration of the recent progress and of the spectacular opportunities provided by the quantitative study of biological motility at microscopic scales. Some of these are explored further below, where in each thematic section we provide a brief state of the art, an example of recent achievements, and some directions for future research.

## 2. Locomotion by shape control in unicellular organisms

### *2.1. State of the art*

Locomotion strategies employed by biological organism are a rich source of inspiration for studying mechanisms for shape control. In fact, in an overwhelming majority of cases, biological locomotion can be described as the result of the body pushing against the world, by using shape changes. Motion is then a result of Newton's third and second law: the world reacts with a force that can be exploited by the body as a propulsive force, and this force puts the body into motion following the laws of mechanics. Strategies employed by unicellular organisms are particularly interesting because they are invisible to the naked eye, and offer surprising new solutions to the question of how shape can be controlled.

Swimming motility of unicellular organisms (for example: bacteria, sperm cells, unicellular algae and planktonic micro-organisms) is a relevant and well-studied example (Lauga and Powers, 2009; Alouges et al., 2008). Here, inertia is negligible with respect to viscous forces and the surrounding fluid is modeled through the Stokes, rather than the Navier-Stokes equations, as it is customary in low Reynolds (Re) number hydrodynamics. Often inertia is negligible also in other forms of locomotion at small scales, such as crawling of cells and of small organisms. Here asymmetry of friction interactions, such as in the case of undulatory locomotion in snakes (Cicconofri and DeSimone, 2015), and control of friction by protrusion of fine-small features, such as the setae of earthworms (Agostinelli et al., 2018), can be used to produce net displacements and to rectify body shape changes that are symmetric under time-reversal.

Within the specific context of low Re swimming, two equivalent but complementary points of view have emerged, one focussing on the the equations of motion of the swimmer (propelled by the forces exerted by the surrounding fluid in reaction to the swimmer shape changes), the other one focussing on the equations of motion of the surrounding fluid (driven by the equal and opposite forces exerted by the swimmer on the

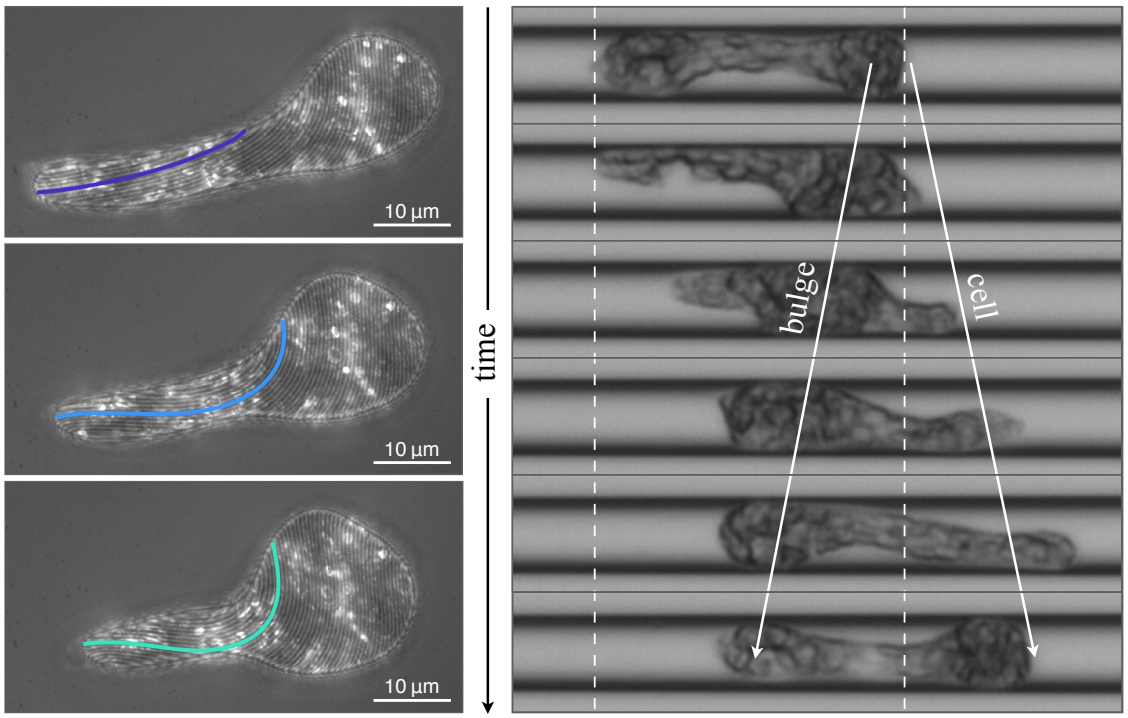


Figure 1: Left: a sample of *Euglena gracilis* imaged in bright-field, reflected light microscopy while exhibiting cell body shape changes (metaboly) concomitant with the reconfiguration of the striated cell envelope. Right: micrographs of *Euglena gracilis* effectively crawling in a capillary under significant spatial confinement by means of peristaltic shape changes. Notice the forward motion of the cell leading edge corresponding to the retrograde motion of a travelling bulge adhering on the capillary wall.

fluid through its shape changes). The first approach is based on viewing low Re swimming as a problem in control theory (how do swimmers produce flows able to steer them along desired trajectories?). It has been pioneered by physicists of the caliber of Purcell and Wilczeck (Lauga and Powers, 2009), and more recently used to formulate and solve optimal swimming problems as problems of optimal control in geometric control theory (Alouges et al., 2008). The second approach studies the flows induced by a swimmer moving in a fluid, often through the use of the superposition of special singular solutions recapitulating the signature (e.g., pusher vs puller in the case of a dipole of Stokeslets) that a swimmer leaves in the surrounding fluid (Lauga and Powers, 2009; Ishimoto et al., 2017). Both approaches are conducive to the discovery of guiding principles that help rationalize observations that have often been made empirically in zoology, and used on a trial-and-error basis in robotics, but never recognized as templates that help us understand biological locomotion by distilling key guiding principles, which can then be used for the rational design of artificial, bio-inspired artifacts. One example is the optimality of peristaltic waves in one-dimensional systems, which has been recently proved to emerge as the optimal actuation gait in crawling locomotion by propagation of extension/contraction waves (Agostinelli et al., 2018), and in swimming locomotion by propagation of waves of lateral undulation (Alouges et al., 2019). Interestingly, this last example shows that optimality of traveling bending waves in the regime of small lateral undulation is the result of the underlying geometric symmetry (invariance with respect to shifts along the axis of the body when lateral defamations are small), but it leaves the question open as to which gaits are optimal if the amplitude of the shape undulations is large (since the geometric symmetry of the straight body axis is no longer relevant when deformations are large).

### 2.2. Recent accomplishments

In recent years, we have studied locomotion and shape control in *Euglena gracilis* using a broad range of tools ranging from theoretical and computational mechanics, to experiment and observations at the microscope, to manufacturing of prototypes. This unicellular protist is particularly intriguing because it can adopt different motility strategies: swimming by flagellar propulsion, or crawling thanks to large amplitude shape changes of the whole body (a behavior known as metaboly), see Fig. 1. The first behavior can be studied through optical microscopy, and 3d helical trajectories, the accompanying body rotations, and the 3d flagellar shapes that propel swimming can be reconstructed using the so-called Helix Theorem (Rossi et al., 2017; Cicconofri and DeSimone, 2019). This is the statement that, in the absence of inertia and far away from walls, any microscopic swimmer propelled in a homogeneous and isotropic fluid by the periodic beating of cilia and flagella will trace a generalized circular helix. Body rotations accompany the helical motion and the simultaneous knowledge of the trajectories and body rotation allows for the reconstruction of 3d flagellar shapes form (partial) 2d views. The second behavior arises from the coordinated sliding of pellicle strips, a fact that can be confirmed in precise quantitative detail by a model that recognizes that peristaltic waves are the manifestation of Gauss' Theorema Egregium. Spatio-temporally modulated patterns of surface shears can produce the spatio-temporal coordination of Gaussian curvature leading to a bulge travelling along the body axis, i.e., a peristaltic wave (Noselli et al., 2019b). These can be reproduced in artificial 3d printed structures mimicking the biological template (Noselli et al., 2019a). We are able to show that the switch between the two types of behavior is triggered by confinement (Noselli et al., 2019b). The hypothesis is that the presence of obstacles, or simply crowded environment interfere with the spontaneous beating of the flagellum; the organisms responds to this change of environmental conditions by activating body peristaltic waves. Parts of this behavior are understood, while other parts need further clarification. But the part of the story that is already clear is quite remarkable: the organism uses body rotation to obtain periodic patterns of light and shade on its lateral photoreceptor, and these pattern are sensitive to the relative orientation of light rays and body axis. Thus, helical motion is used for phototaxis. In turn, this helical motion is produced by the asymmetric 3d beating of a flagellum whose characteristic 3d wave forms are the non-generic result of a specific body architecture.

### 2.3. Perspectives

As an indication of possible avenues for future research, many other organisms may offer themselves as model problems to study how an organismal function can be correlated to a biophysical mechanism and, in particular, to specific details of the body architecture, just as what we found in the case of *E. gracilis*. This correlation can be made quantitative, contributing to the emergence of new quantitative biophysical methods in the life sciences and leading to new advances in the physics, engineering, and mathematics of living systems. One such example is the issue of sensing (of environmental cues) and control (of the response) in unicellular, brainless systems. In particular, a basic and fundamental model for the flagellar beat in eukaryotic cilia and flagella is still lacking, in spite this being one of the most thoroughly studied topics in the last several decades. How is the beat generated? How is the frequency of the beat set? Is it affected by environmental cues and, if so, through which mechanisms? Advances in the resolution experimental techniques (higher spatio-temporal resolution of observed configurations of motors and microtubules, allowing for direct visualization of the beat pattern) and concerted focus of both theoretical and experimental studies targeting the key aspects identified through a thorough conceptual analysis of the available evidence are likely to produce a breakthrough in the coming years.

## 3. Soft adhesive locomotion from microscopic to millimetric length scales

### 3.1. State of the art

The locomotion of soft-bodied microscopic organisms, from amoeboid cells to multicellular organisms lacking rigid skeletal support, has applications in diverse fields such as ecology, medicine and bio-inspired engineering design. The amoeboid migration of cells such as leukocytes (size $L \sim 10\ \mu m$) has been studied thoroughly in the past and still remains a subject of significant attention due to its significance to human

health and disease. These cells can move at a fast pace by creating repetitive cycles of fast shape changes in coordination with the forces exerted on the substrate (Del Alamo et al., 2007). Remarkably, leukocytes can navigate three-dimensional fibrillar networks without establishing specific substrate adhesions proteolytically degrading the matrix (Wolf et al., 2003). Previous works emphasized the important roles of cytoplasmic streaming and intracellular pressure in generating protrusions, in addition to the classic view based on polymerization of actin filaments (Charras and Paluch, 2008). Recent mechanistic studies have been focused on understanding how amoeboid cells can find paths of least resistance in tight 3D fibrillar networks (Renkawitz et al., 2019), and squeeze through endothelial monolayers to exit the circulation to reach injury sites (Yeh et al., 2018).

In contrast, the amoeboid locomotion of larger ($L > 100\ \mu m$) unicellular organisms such as Physarum polycephalum has received less attention. Physarum plasmodia have a membrane-bound filament cortex that generates contractile forces and can sustain large pressure differences across the cell. These pressure differences drive fast shuttle streaming: a rhythmic flow of cytoplasm that reaches speeds over 10 times faster than net locomotion speed. The cytoplasmic flows are important for the transport of chemical signals (e.g. calcium ions) that regulate cortical contractility, given that diffusion is slow for the relatively large length scale of these plasmodia (Goldstein and van de Meent, 2015). Amoeboid motility mediated by cytoplasmic pressure-driven flows can provide biomimetic inspiration for hydraulic or pneumatically actuated engineering systems, as well as for millimetric robots made of active self-oscillating hydrogels (Ilievski et al., 2011). The convective transport of signals in large amoebae also offers a biological model for fluidic logic control, which if it proves to be controllable, could offer advantages with respect to electronic controls in harsh or wet environments.

Despite the promising features of large unicellular organisms as model systems for biomimetic design, the non-linear mechano-chemical feedback between intracellular flow, molecular transport and cell contractility leads to complex dynamics that are not currently understood. Furthermore, we do not know how these dynamics may be affected by noisy environmental cues. Investigating these open questions in large amoeboid organisms has proven difficult. Most previous experimental works provide time-resolved data about cell shape, but lack detailed information about the spatio-temporal dynamics of chemical signals, cytoplasmic flow or cortical contractility. Mathematical models have assimilated the available experimental data into quantitative frameworks with subcellular resolution, including variables that are hard to access experimentally. Such models have successfully reproduced key features observed in experiments, such as the emergence of traveling, standing and rotating waves in cytoplasmic droplets (Radszuweit et al., 2013). However, they have been so far unable to recapitulate plasmodial locomotion as observed experimentally unless coordinated waves of adhesiveness and contractility are prescribed. Thus, the flow-driven self-organization of mechano-chemical in large amoeboid organisms, and how this organization can mediate robust directional locomotion are still outstanding problems.

### *3.2. Recent accomplishments*

Over the past few years, the emergence of spontaneous coordination between flow, contractility and adhesion in the amoeboid locomotion of large unicellular plasmodia of Physarum polycephalum has been examined (Lewis et al., 2015; Zhang et al., 2017). An interesting feature of Physarum is that one can prepare motile plasmodia of sizes ranging between 10 $\mu m$ to 1 $mm$, which allows for studying scaling phenomena in one same organism. An experimental methodology to simultaneously measure the spatio-temporal distributions of cytoplasmic and cortical flows, traction stresses and the concentration of free cytoplasmic calcium has been developed. In parallel, a collaboration with Dr. Guy's group at UC Davis has been established to develop computational models of motile plasmodia solved for the spatiotemporal dynamics of a viscous cytosol, a poro-elastic, contractile cytoskeleton and substrate adhesion.

Experiments showed that initially round plasmodia undergo rhythmic oscillations and eventually undergo a symmetry breaking instability, which is strongly affected by fragment size, substrate friction and cortical strength. After breaking symmetry, plasmodia tend to settle into two types of persistent directional

locomotion mediated by robust mechano-chemical wave patterns. Slow-moving plasmodia display standing wave patterns of contractility and calcium concentration, and reciprocal waves of cytoplasmic flow. Albeit slowly, these plasmodia are able to migrate directionally over long periods of time, even if their cytoplasm is observed to experience zero net flow. Fast moving fragments exhibit unidirectional traveling waves in both contractility (i.e. peristaltic contractions) and cytoplasmic flow. This gait is conserved in larger organisms possessing a brain and a nervous system like annelids or gastropods, and is reminiscent of leg density waves in myriapod locomotion (Zhang et al., 2019b). But remarkably, our results suggest that peristalsis can be regulated by cytoplasmic streaming, which is biologically much simpler than neuro-muscular coordination.

Our computational models demonstrate that the coordination between contraction and adhesion controls the direction and speed of locomotion. Using the models, we identify forms of this coordination that generate model predictions consistent with our experiments, where we observe waves of stick-slip transitions propagating from the back to the front of the plasmodium. The models indicate that this coordination produces near optimal migration speed, but more importantly, that it makes this speed insensitive to spatial fluctuations in substrate adhesiveness. These results illustrate how coordination of adhesive and contractile forces facilitate robust amoeboid crawling in heterogeneous environmental conditions.

### *3.3. Perspectives*

A key property of flow-driven amoeboid locomotion is that it is mediated by relatively robust oscillatory behaviors. However, spontaneous shifts between wave patterns or leading to chaotic states are not uncommon, and these significantly affect locomotion speed and directional persistence. Here, the analogy with the self-oscillating polymer gels is also patent. So far, most experimental and modeling efforts have been devoted to understanding the emergence of self-organized motile states in flow-driven amoeboid locomotion, and their dependence on environmental factors such as substrate adhesiveness or geometrical factors such as cell size. However, while it is reasonable to assume that these biological systems may have evolved to allow for some kind of behavior control (e.g. migrate towards or away from other organisms, light or food sources, etc.), we currently do not know to which level of precision they are externally controllable. This is an open question where and mathematical modeling, quantitative experimentation and biochemistry will necessarily go hand in hand. The expected outcome will likely produce key knowledge and proof of principle of controllable microscale soft robots with custom-tailored fluidic logic.

## 4. Knotted DNA: conformational, dynamical and pore-translocation properties

### *4.1. State of the art*

Perhaps not unexpectedly, biological processes that define the central dogma of biology all involve the translocation of nucleic acids filaments through ATP-fueled molecular machines. In transcription, a DNA filament is run through an RNA polymerase, while an RNA filament is translocated through a ribosomal complex during translation (Alberts, 2014).

In both cases, translocation can be jammed by various forms of entanglement that are inherent to the structural architecture of nucleic acids. Transcription can proceeds thanks to the continuous removal of the supercoiling induced by torsional stress that builds up in front of the transcribing complex (Alberts, 2014), while particular RNA secondary structures are believed to cause programmed slippages during translation (Giedroc and Cornish, 2009).

Knots can occur in DNA too and their fatal consequences on the transcription and replication (Olavarrieta et al., 2002) are avoided thanks to the incessant action of topoisomerase enzymes that remove them.

With all this taken into account, the properties of small DNA viruses such as the P4 bacteriophage, are a double surprise. Not only the micron-long DNA filaments tightly packed inside the viral capsids are typically tied in complex knot, but the presence of these knots does not prevent the DNA filament to be

delivered to the infected host by being ejected through a channel too narrow to allow the passage of knots (Arsuaga et al., 2005). This effect clashes with our daily experience that a knot, by tightening at the pore entrance, would act as a stopper and inevitably stall the DNA translocation through the exit channel.

Analogous issues arise in the context of nanopore sequencing of DNA filaments. This modern technique relies on the driven translocation of DNA through biological or solid state nanopores that are sufficiently narrow and thin that the ionic current going through the pore is modulated by the nucleotides engaging the pore (Steinbock and Radenovic, 2015). With such design, the sequence of the translocating DNA can be inferred by continuous time measurements of the ionic current. As technological advancements allow for sequencing longer and longer stretches of DNA, the chances that the filament driven through the pore is knotted increase too. For this system, as for the ejection of knotted DNA through the capsid exit pore, it is important to understand how exactly knots affect the capability of DNA and other biopolymers to translocate through pores that are too narrow to accommodate knot.

Translocation through wide pores is equally interesting too, theoretically and practically. Dekker and coworkers (Plesa et al., 2016) have recently pioneered a method for the detection of DNA knots that is precisely based on the detection of small variations in the ionic current accompanying the passage of a DNA knot through a wide pore. The study represented a technological breakthrough in that it allowed to detect knots in DNA chains of more than 100,000bp, a tenfold length increase compared to the maximum DNA lengths that can be topologically-profiled with gel electrophoresis. At the same time, the study posed a number of open problems regarding unexpected observed properties, namely a bias towards the late passage of knots, as well as very brief duration of current depletion event accompanying the knot passage, suggestive of unusually tight knots.

### *4.2. Recent accomplishments*

We first addressed these questions by modelling single-stranded DNA filaments as flexible chains of beads (Rosa et al., 2012). We considered chains of 15,000 beads, which were sufficiently long that a non-negligible fraction of their equilibrium population were knotted. We then translocated these spontaneously-knotted chains through a rigid pore, by applying a driving force exclusively to the beads inside the pore. We observed an unexpected behaviour. The presence of knots was not per se sufficient to halt translocation, as we were intuitively expecting.

Inspection of the results showed that knotted chains could still translocate through narrow pores thanks to thermal fluctuations that cause the tightened knot at the pore entrance to occasionally "breath" and open up favouring the sliding of the chain along its knotted contour.
Once clarified, this mechanism also suggested that by applying translocation (i.e. knot tightening) forces much larger than those exerted by thermal fluctuations, the breathing of the knot could be suppressed, and translocation stalled indefinitely. This is precisely what we observed (Rosa et al., 2012). A more in depth analysis (Suma et al., 2015) of the process revealed that the so-called topological friction that hinders in a force-dependent manner the sliding of the chain along the knotted contour is itself dependent on the knot type, see Fig 2. The two main topological families found among simple prime knots, namely torus and twist knots, behave quite differently in this respect, with twist knots offering the highest sliding resistance. Equally interesting is the case of composite knots, those resulting from the concatenation of simpler ones, which shows that frictional effects depend on the order of appearance of the knots (Suma et al., 2015), see Fig 2.

These results offer a simple and physically appealing solution to the conundrum of how knots in viral DNA can be compatible with the ejection of the genome from the narrow exit pore. In fact, the passive ejection forces that build up inside the capsid are smaller than those needed to jam the process (Rosa et al., 2012). In addition to this, DNA knots formed inside capsids are mostly delocalised, and not tight, and this allows knots to spontaneously simplify already inside the capsid as genome ejection progresses (Marenduzzo

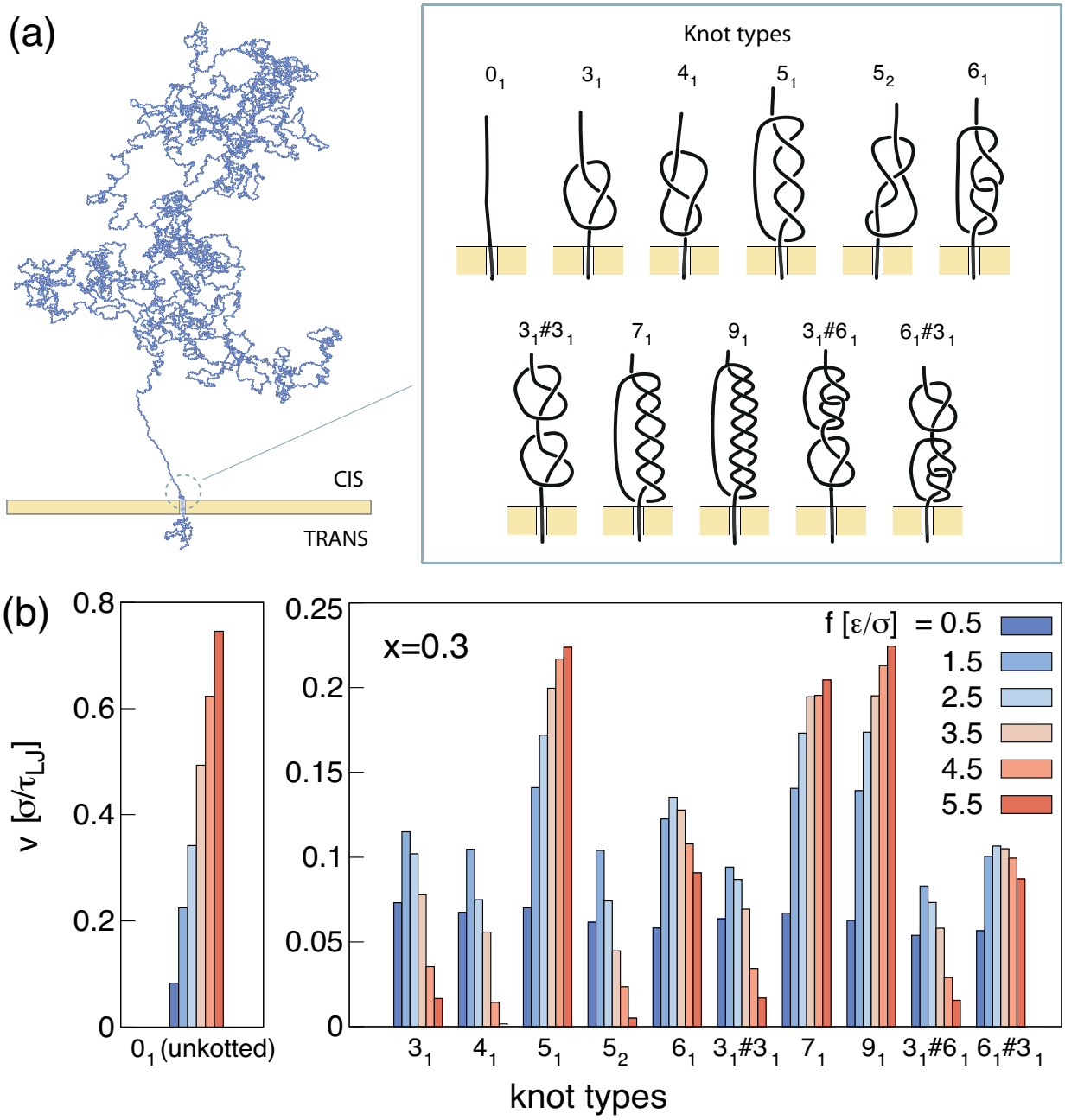


Figure 2: (a) Polymer chains can be driven through narrow pores even when they are knotted. During translocation, the knot tightens at the pore entrance, as schematically shown in the inset, but the chain is still capable of sliding along its knotted contour if the driving force is not too large. The friction introduced by the tangle depends on the knot type and affects how the translocation velocity depends on the driving force, see panel (b). Reproduced with permission from Suma et al. (2015), Copyright (2015) American Chemical Society.

et al., 2013).

We have also used a finer-grained models knotted DNA rings to address the intriguing translocation properties observed by Dekker and coworkers using wide pores. In this case, the models allowed us to point at more modes of knot translocation than previously envisioned, to explain the late passage events as due to the sliding of knots before being reaching the pore and finally to clarify that the ionic current depletion event captures the passage of the essential crossings, usually a smaller portion of the knot (Suma and Micheletti, 2017).

### *4.3. Perspectives*

A still largely unexplored aspect regards the extent to which the aforementioned topological friction depends on the finer structural details of the biopolymers, i.e. on the corrugations at atomic scale. Studying these effects with models of increasing detail ought to provide a more precise understanding of the translocation of entangled biopolymers through solid-state and biological pores. Over a longer-term scale such realistic models could be combined with multiscale models of biomolecular complexes to advance our understanding of the how structural and topological features of DNA and RNA affect their *in vivo* processing in transcription and translation.

## 5. Synthetic and active autonomous solid sheets

Autonomous actuation of soft tissues is common in a wide variety of natural systems, both on cellular and macroscopic scales. The success in mimicking such systems in manmade structures is limited. We start with a review on experimental (Sharon et al., 2002; Klein et al., 2007; Kim et al., 2012a; Klein et al., 2011; Armon et al., 2011; Gladman et al., 2016) and theoretical (Efrati et al., 2009b,a; Kim et al., 2012b; Moshe et al., 2013) works in the field of incompatible elastic sheets, and then present two extreme cases of such autonomous sheets.

The first is a completely synthetic autonomous shape-transforming sheet. Here the challenge is how to generate a synthetic sheet with periodic deformation cycles and how to predict its evolving three-dimensional (3D) configuration.

To address these challenges we construct thin sheets made of NIPA- Ruthenium copolymer gel. The sheets are placed in a solution of the Belousov-Zhabotinsky (BZ) reactants, leading to the spontaneous periodic propagation of chemical fronts within the gel. These front lead to local contraction and expansion of the gel, driving its periodic buckling into 3D evolving shapes. Using the theory of incompatible elastic sheets (Klein et al., 2007), we describe the system as an evolving non-Euclidean plate. The reference metric of the plate varies in time and space according to the BZ field evolution. We obtain a connection between the BZ field and the 3D configurations and confirm it experimentally.

The second example is that of a growing leaf. Here the challenges are to reveal the mechanisms that control the growth and maintain a "proper" growth distribution despite the absence of central control. This requires unique "tissue-intelligence", which is nothing but a rheology of an active solid. In order to reveal this rheology we take three different approaches: We apply hormonal and genetic manipulations on a growing leaf, altering its large scale growth. We show that these changes lead to alteration of the 3D leaf shape (Armon et al., 2014), a change which is dominated by the mechanics of non-Euclidean plates. In an another type of experiments, we measure the growth field of the leaf surface with high spatio-temporal resolution. We find that the field is not smooth. It consists of sharp variation in growth rate and directionality, which include extensive shrinkage events as part of normal growth. We identify dominant time and length scales as well as qualitative differences between growth during day and night. Finally, we measure the effect of mechanical stress on leaf deformation and growth. The measured effective rheology is viscoelastic with time varying parameters. We provide evidences for the effect of stress on growth at different time scales. The

effects include passive viscoelastic deformation at short ($\sim$ 20 min) times, growth correlated with stress during intermediated ($1-5$ hours) times and indications for tissue remodeling in response to extended ($< 5$ hours) application of mechanical stress (Sahaf and Sharon, 2016).

The better understanding of the behavior of natural living tissue, and the enhanced control over synthetic tissue, and its 'activation', decrease the gap between synthetic and natural system and improve our understanding of both.

## 6. The unjamming transition in dense cell collectives

### *6.1. State of the art*

Cells in a tissue are densely packed, normally with little or no possibility of mutual rearrangements between neighbors. Nevertheless, notable biological processes involve cellular rearrangements and collective migration, typical examples being wound healing, morphogenesis, and cancer invasion (Hakim and Silberzan, 2017). One of the emerging frameworks to account for this increased collective motility of cells is the so-called unjamming transition, according to which a solid-like tissue can locally "liquefy", with cells being able to move in small groups across the tissue without losing adhesion with their neighbors (Park et al., 2015). The unjamming transition as a gateway to epithelial collective motility acquires particular significance in light of recent experiment in cancer cell biology that show how an epithelial to mesenchymal transition (EMT), in which cells mainly lose contact with their neighbors, may not be always involved in cancer metastasis and dissemination (Cheung et al., 2013; Khalil et al., 2017). In principle, unjamming may thus play a role in cancer dissemination and metastasis, as it provides a simple gateway to collective motility in epithelial collectives. However, much remains to be done to fully understand the biomolecular drive, the biophysical consequences, and the physiological/clinical relevance of unjamming.

### *6.2. Recent accomplishments*

We recently discovered that over-expression of the GTPase RAB5A, a master regulator of endocytosis that is normally associated to mesenchymal invasion, has a dramatic effect also on the collective motility of multicellular, normal and tumorigenic, two-dimensional cell assemblies (Malinverno et al., 2017): in particular, otherwise kinetically arrested epithelial monolayers, acquire a flocking mode of locomotion which is similar to what is observed in other classes of organisms such as birds or fish (Marchetti et al., 2013). Combining experiments and simulations we find that RAB5A does so by increasing cell stiffness, cell adhesion and junctional tension, while concurrently accelerating the turnover of junctional E-cadherin. These changes lead to an increased capability of each individual cell to align its velocity to the one of the surrounding cells and, in turn, to cellular flocking (Malinverno et al., 2017; Giavazzi et al., 2017, 2018). More recently, we investigated cases with stronger connection to physiological/clinical settings, by performing experiments with a variety of three-dimensional (3D) cell collectives, including cysts, spheroids and ex-vivo slices of breast ductal carcinoma in situ (Palamidessi et al., 2019). Our experiments show that the over-expression of RAB5A has spectacular consequences also in 3D. In particular, unjamming by flocking is accompanied by impressive coherent rotations of the collectives that eventually lead to invasion into the extra-cellular matrix. Our observations highlight the sophisticated interplay of a novel biological pathway and of a mechano-physical action, which makes the invasion mechanism functional. Biologically, we rationalize RAB5A-induced unjamming as a consequence of increased internalization of epidermal growth factor receptors into endosomal vesicles, which become proficient signaling platforms for the prolonged and elevated activation of the extracellular signal-regulated protein kinase ERK1/2. The ERK 1/2 pathway plays a key role for cell growth, differentiation and senescence, and also in several forms of cancer. Here, we find that its activation induces hyper-phosphorylation of the WAVE2 protein, a member of the Wiskott-Aldrich syndrome protein (WASP)-family, which enhances cell migration persistence and polarity (Danson et al., 2007). In our experiments this leads to the extension of oriented cryptic lamellipodia which, by exerting increased traction forces and enhancing cell orientation, leads to flocking states and rotation in 3D. Physically, the collective cellular motion causes an augmented mechanical stress on the extracellular matrix, with its

consequent remodeling, and the concurrent "fluidification" of cells in the close proximity of the remodeled matrix. This unique combination of biomolecular and biomechanical effects causes the detachment of some of the cells from the cell collectives, highlighting a very powerful and general mechanism that advances our understanding of normal morphogenesis and cancer invasion and metastasis.

### *6.3. Perspectives*

Among the many questions that remain unanswered, there are three that particularly stimulate our interest. One is whether there is a minimum number of RAB5A-over-expressing cells that can trigger unjamming-via-flocking when embedded in control cells. Addressing this issue may give important information for cancer invasion and metastasis. Similarly, whether the jamming and unjamming transitions occur in the same way for different cell types is also unclear. For instance, to explain unjamming some investigators invoke excluded volume effects, whereas some others contact inhibition of locomotion or the maturation of cell-cell junctions. Do these different mechanism lead to the same type of unjamming or we need to consider different ways to unjamming? Finally, it would be of paramount importance to understand whether unjamming and EMT are two distinct mechanisms or there is some degree of overlap between them.

## 7. Mechanics of cell sheet folding in volvocalean algae

### *7.1. State of the art*

Living tissues are intelligent materials that can change their mechanical properties while they develop. In spite of extensive studies in multiple model organisms we are only just beginning to understand these dynamic properties and their role in tissue development. Although many tissues are known to exhibit visco-elastic properties, it is unclear which properties dominate three-dimensional shape changes of cellular monolayers, such as epithelia. The shape of many tissues and organs is achieved by folding and stretching of epithelia. Understanding how epithelial morphogenesis works mechanically is essential to address associated birth defects and to improve the precise shaping of lab grown organoids. Events of cell sheet folding (e.g. gastrulation, neurulation) involve cell shape changes (e.g. cell wedging) generating forces that are transmitted via cell-cell connections and drive global deformations. In conventional model organisms the effect of such cell shape changes is usually overlaid by that of cell migration, cell intercalation, and cell division. Owing to this complexity, and in spite of significant progress in identifying the molecular components involved, the correspondence between local cellular changes and global deformations of cell sheets remains poorly understood. The embryonic inversion process in the micro-algal family Volvocales is uniquely suited for comparative studies on epithelial morphogenesis (Matt and Umen, 2016). Inversion involves morphological processes, such as invagination and involution, that are usually associated with animals. Volvocalean embryos consist of cup-shaped (Höhn and Hallmann, 2016) or spherical (Höhn and Hallmann, 2011) cellular monolayers which invert their curvature in order to expose their flagella. In spite of a lack of cell intercalation and migration the embryonic cell sheet undergoes dramatic topological changes caused by local cell shape changes. These inversion processes involve a range of species-dependant complexity in terms of both the local cell shape changes and the resulting deformations of the cell sheet (Höhn and Hallmann, 2016). The question is how the cells of volvocalean embryos manage to generate the forces that deform the cell sheets globally.

### *7.2. Recent accomplishments*

We have been studying the mechanics of inversion as a simple model for epithelial morphogenesis combining time lapse fluorescence imaging, electron microscopy, micromanipulation and quantitative analyses based on a newly developed mathematical framework. *Volvox globator* exhibits one of the most striking processes of cell sheet folding: Through inwards folding along the equator the initially spherical cell sheet adopts a mushroom shape, the posterior moves into the anterior hemisphere, an anterior opening – the phialopore - widens and the anterior hemisphere moves over the subjacent cell sheet until the embryo has turned itself entirely inside-out. Our combined experimental and theoretical analyses revealed that the equatorial bending has to be complemented by active contraction in the posterior and expansion in the anterior hemisphere

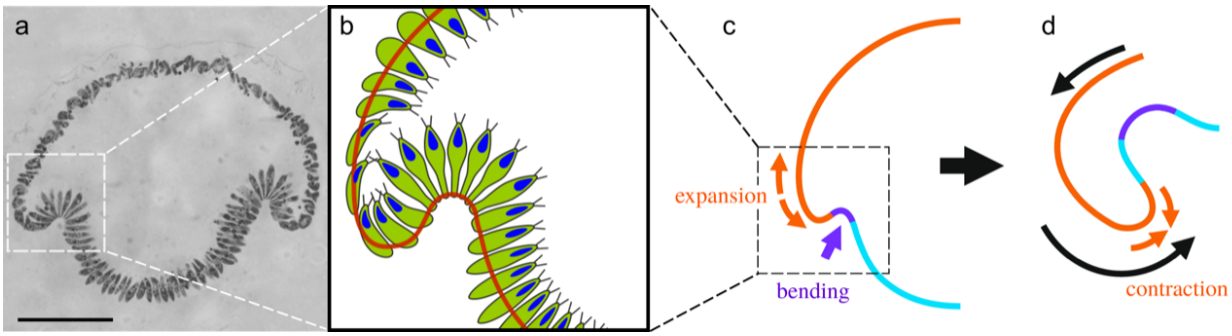


Figure 3: Cell sheet folding in *Volvox globator*. (a) Mechanical section of a *V. globator* embryo at an early stage of inversion. Scale bar: 30 µm. (b) Associated cell shapes. Red line: cytoplasmic bridges (cell-cell connections), blue: nuclei. (c) Areas of expansion and bending of the cell sheet. Orange: anterior hemisphere; blue: posterior hemisphere; purple: area of cell-wedging. (d) The following involution is driven by contraction. Colors as in (c). [Modified from Höhn and Hallmann (2011); Haas et al. (2018)]

(Höhn et al., 2015; Haas et al., 2018) in order to explain the occurring sequence of global shape changes. Bending and invagination are achieved by a wave of cell-wedging (cells becoming thinner at one pole), similar to events of cell sheet folding in animals. However, while extension of a cell sheet requires intercalation (i. e. convergent extension) in *Xenopus* (Keller et al., 2003) and *Drosophila* (Tada and Heisenberg, 2012), a different mechanism was revealed in *V. globator* (Fig. 3a-c): the cells flatten, rotate and re-locate their connections towards the long axis of the cells. This movement simultaneously flattens the cell sheet and extends it along the anterior-posterior axis. Involution of cells (Fig. 3d) is achieved by contraction of the region on the inner side of an inflection point rather than by migrating cells, as it is the case in *Xenopus* gastrulation (Keller et al., 2003). Laser ablation experiments have shown that the posterior hemisphere is under stress throughout the entire inversion process and reacts elastically when cut mechanically. Further ablation experiments might reveal differences in the elastic properties across the cell sheet [in preparation].

### *7.3. Perspectives*

The ability to perform sophisticated topological changes without the need of cell intercalation, migration, division or apoptosis is of particular interest in the context of tissue engineering. To date the 3D shape of lab grown tissues is mostly generated by cultivating cells on scaffolds or using different substrate properties to control cell behaviour. However, the ultimate goal of tissue engineering is self-assembly. Programming cell-shape changes alone (e.g. using optogenetics) to achieve self-folding of tissues seems more feasible than trying to control a whole range of cellular behaviours. To test this idea on volvocalean cell sheets we first need to elucidate the signals that trigger and propagate waves of different cell behaviours in these organisms. It is for example unclear how the equatorial location of the initial cell wedging is determined. This question is the focus of ongoing experimental and theoretical analyses. Is it unknown to date whether volvocalean morphogenesis involves morphogen-like chemical or mechanical signals, and combined molecular biological and theoretical studies might in fact reveal entirely new mechanisms of coordinating cell behaviour.

## 8. Self-propelled topological defects in active matter

### *8.1. State of the art*

Active materials, such as bacteria, molecular motors and self-propelled colloids, are Nature's engines. They continuously transform chemical energy from their environment to mechanical work. Dense active matter, such as films of swimming bacteria or confluent cell layers, shows mesoscale turbulence, the emergence of chaotic flow structures characterised by high vorticity and strong flow jets (Thampi and Yeomans, 2016). A theory that gives a good description of active turbulence in systems with explicit hydrodynamics, is based on the continuum equations which describe nematic liquid crystals. Activity is introduced by an

additional term in the stress tensor which is proportional to the strength of the activity $\zeta$ and the nematic tensor order parameter $Q$. Any fluctuation in the nematic order leads to additional active stresses and flows which destabilise the nematic ordering and result in active turbulence (Doostmohammadi et al., 2018).

Topological defects are familiar features of passive liquid crystals. In 2D nematics the prevalent defects have topological charge $\pm 1/2$ and the director configurations shown in Fig. 4. Unless there is pinning, due to e.g. disorder or surfaces, elastic forces cause oppositely charged defects to move towards each other and annihilate, restoring perfect nematic order. Similar defects are found in active nematics but now the distorted director field around the defect results in local stresses. For the $+1/2$ defects these are unbalanced and, as a result, these defects are self-propelled (Giomi et al., 2014). As the active forcing produces enough energy to form defect pairs the $+1/2$ defects move away from the $-1/2$ defects before they can re-annihilate. This means that, in the active turbulent steady state, there is a gas of topological defects that are continually being created and destroyed in $\pm 1/2$ pairs (Giomi et al., 2013; Thampi et al., 2013).

One of the easiest places to observe active topological defects is in suspensions of microtubule bundles driven by two-headed motor proteins absorbed at an oil-water interface (Sanchez et al., 2012). The kinesin motors, which walk towards the plus end of the polar biopolymers, bridge pairs of microtubules. For a pair of microtubules with the same polarity the motors' motion has no effect. However microtubule pairs of different polarities are driven to slide relative to each other. Hence the motors lead to polarity sorting within microtubule bundles and in time the bundles extend, bend and disintegrate, and then re-form giving a dynamical steady state that is well described as an active nematic. Bundle bending can be interpreted in terms of a pair of topological defects forming and then moving apart.

### *8.2. Recent accomplishments*

A recent development is the identification of active topological defects in biological systems. For example, topological defects have been tracked in confluent epithelial cell layers (Saw et al., 2017). This is surprising as the cells are, on average, isotropic. However forces between cells can induce correlated anisotropy in cell shapes corresponding to local nematic ordering and allow the identification of motile topological defects (Mueller et al., 2019). The defect positions are correlated with sites where cells die and are expelled from the epithelial layer, a biological process termed apoptosis which is necessary for homeostasis, the maintenance of an appropriate cell density. The proposed mechanism behind the connection is that the additional stress at the defects drives the protein YAP from the nucleus to the cytoplasm, an established signal for cell death. This is the first suggestion of a mechanical, as opposed to a chemical, route to apoptosis.

Topological defects have also been observed in other cellular systems. Kawaguchi et al. worked with neural progenitor cells showing that, at high densities and under confinement, they are capable of aligning along large length scales, forming migratory streams (Kawaguchi et al., 2017). The cells showed a clear tendency to deplete the neighbourhood of $-1/2$ defects and instead to accumulate at $+1/2$ defects, forming 3D mounds. Friction between the cells and the substrate was suggested as a potential mechanism for this behaviour; however the reason for the formation of the mounds is not yet fully explained. Other systems that demonstrates that motile particles are attracted to $+1/2$ defects are living liquid crystals. These are bacteria dispersed in aqueous-based liquid crystals, which allows the swimming characteristics of the bacteria and the orientational order of the medium to be controlled independently. If the passive liquid crystal is patterned with fixed topological defects bacteria deplete regions around the $-1/2$ defects and are attracted to the $+1/2$ ones (Peng et al., 2016).

### *8.3. Perspectives*

In the future it will be interesting to look for topological defects in other cellular systems both plant and animal cells and, given that they are often more obviously nematic in shape, bacteria, and to assess whether they are relevant to biological function. Moreover, in three dimensions point defects are replaced by defect lines and loops, and whether these can be identified, and how they behave, in three-dimensional active matter such as tissues and tumors remains a completely open question.

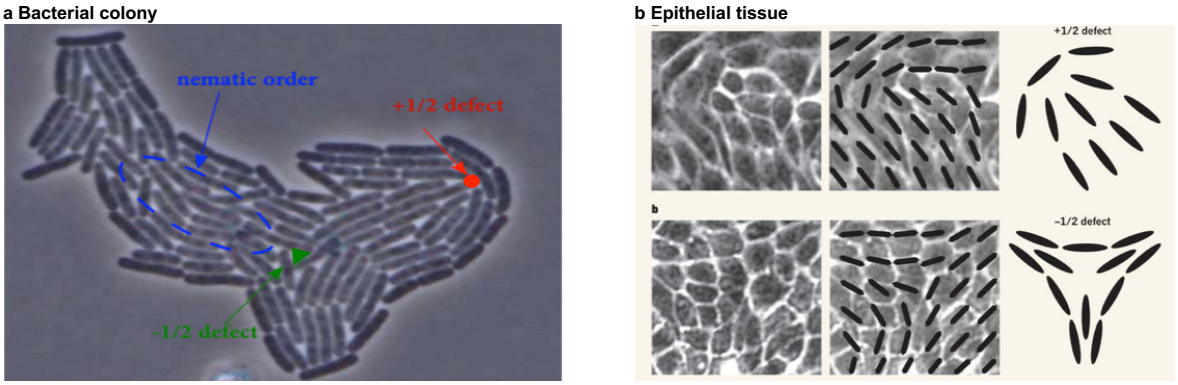


Figure 4: Topological defects in (a) a bacterial colony; (b) epithelial tissue. [Adapted from Doostmohammadi et al. (2018)]

## 9. Conclusions and outlook

The body of knowledge on biological and bio-inspired motility at microscopic scales is vast and growing at a very fast pace. The field offers extraordinary opportunities for quantitative modeling, mathematical analysis, new biophysical insight, and novel engineering applications. All these were surveyed at the recent international workshop MicroMotility 2019[1]. The goal of this paper is to disseminate the information gathered during the workshop, together with the outcome of scientific discussions and exchanges among the participants in the months that have followed.

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