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Perspective

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Proliferating active matter

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Abstract

The fascinating patterns of collective motion created by autonomously driven particles have fuelled active-matter research for over two decades. So far, theoretical active-matter research has often focused on systems with a fixed number of particles. This constraint imposes strict limitations on what behaviours can and cannot emerge. However, a hallmark of life is the breaking of local cell number conservation by replication and death. Birth and death processes must be taken into account, for example, to predict the growth and evolution of a microbial biofilm, the expansion of a tumour, or the development from a fertilized egg into an embryo and beyond. In this Perspective, we argue that unique features emerge in these systems because proliferation represents a distinct form of activity: not only do the proliferating entities consume and dissipate energy, they also inject biomass and degrees of freedom capable of further self-proliferation, leading to myriad dynamic scenarios. Despite this complexity, a growing number of studies document common collective phenomena in various proliferating soft-matter systems. This generality leads us to propose proliferation as another direction of active-matter physics, worthy of a dedicated search for new dynamical universality classes. Conceptual challenges abound, from identifying control parameters and understanding large fluctuations and nonlinear feedback mechanisms to exploring the dynamics and limits of information flow in self-replicating systems. We believe that, by extending the rich conceptual framework developed for conventional active matter to proliferating active matter, researchers can have a profound impact on quantitative biology and reveal fascinating emergent physics along the way.

Sections

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Introduction

At least since Erwin Schrödinger's influential book *What Is Life?*[1], physicists have been captivated by the quest to reduce life to its most basic components. Schrödinger emphasized the importance of continuous energy consumption, as living systems must be kept away from thermodynamic equilibrium to establish order and develop complexity. This aspect of life is idealized in what is now called active matter, namely systems composed of self-driven agents that perform mechanical work on themselves and their environment[2,3]. Classical examples are active gels[4], such as biopolymer networks actuated by molecular motors or tissues in which cells pull and push on each other and the environment, and collections of self-propelled particles[5], such as swarming bacteria, flocking birds or inanimate Janus particles[6]. In all these cases, mechanical energy is locally injected by the active agents through the conversion of stored or ambient free energy into mechanical work.

Another aspect of living systems is that they are typically made up of 'squishy' components, which can be deformed or restructured by weak forces, either because the involved materials are soft, like cells and tissues[7], or because they have soft modes, which arise near critical points (such as jamming) or from a broken continuous symmetry (such as a Goldstone mode in active nematics). The resulting feedback between movement, deformation and active forces generates a wealth of fascinating collective phenomena, including odd mechanical and topological properties, large fluctuations, order–disorder transitions, pattern formation on mesoscopic scales and active turbulence. Most of these emergent phenomena have been successfully predicted or at least explained by theory, despite their non-equilibrium nature. The surprising effectiveness of theory far from equilibrium has contributed to the rapid growth of the field of soft active matter[8,9].

Yet theoretical frameworks for soft active matter often do not include cell proliferation — a hallmark of life. There are well-reasoned limits where proliferation can be ignored. Over time spans shorter than the cell doubling time, the mechanics of tissues[10–12] or the swimming behaviour of starving bacteria, which heavily invest in motility[13–15], can be modelled without including proliferation. But proliferation must be accounted for to understand how bacterial cells form biofilms over days, how a fertilized egg turns into an embryo over months, or how tissues become tumours over years. Proliferation is a singular perturbation of active matter, poorly approximated by setting it to zero. If it is to serve as a viable theory of soft living systems, we argue that active matter needs to embrace cellular proliferation and death.

In this Perspective, we discuss how proliferating active matter not only takes in and dissipates free energy, but it also injects biomass, sources of proliferation, degrees of freedom and mutations. We describe how these features lead to unique ways of falling out of equilibrium and generate exciting avenues for active-matter research. We first consider how proliferating active matter is fundamentally different from conventional active matter. We review the continuum picture of proliferating active matter and the feedback loops present in such systems, before turning to the effects of the discrete nature of real living systems. We then discuss how to bring together conventional active-matter physics with proliferation, in the form of motile proliferating matter, before identifying promising future research directions.

Making more is different

New physics often arises when important symmetries or conservation laws are broken[16]. Proliferation breaks the conservation of mass, volume and number densities, and hence its introduction may be viewed as a standard move on the chessboard of physics. However, there is more to proliferation, because the newly copied discrete entities keep replicating themselves, occasionally with errors (mutations), which generates the potential for autocatalytic feedback and evolution.

The autocatalytic production of biomass can be represented by a continuity equation of the form

$$\partial_t \varrho = -\nabla \cdot j + k\varrho \tag{1}$$

where ϱ is the local mass, volume or number density, j is the associated current and k is the local growth rate. In conventional active-matter models, one sets $k = 0$ and asks what happens if motility arises from an active process, such as swimming[8,17]. In this Perspective, we are primarily concerned with situations in which motion is purely passive and activity is introduced via the growth term. We later address the effects of an extra active contribution to motility. Note that exponential growth implied by a constant growth rate k can only last temporarily, because such rapid population growth quickly outpaces any realistic resource supply (a 'Malthusian crisis'). The long-term dynamics, therefore, depends on nonlinear feedbacks that keep the population density at bay and often provide a mechanism for biologically significant pattern formation.

The above continuum picture of the effects of proliferation is incomplete, however, as it misses the discreteness of the proliferating entities. The associated fluctuations are usually considered to be small in large systems, but they can cause macroscopic effects when they are amplified by the expansion of the population or near a phase transition (such as jamming). For example, the state of systems that have grown from just a few initial cells can reflect microscopic fluctuations that occurred early in the expansion, similar to the cosmic microwave background being a noisy trace of primordial fluctuations[18].

A complementary way to view the impact of proliferation is in terms of space–time representations of the dynamics. Conventional active particles can be described by space–time trajectories. Proliferating entities, instead, give rise to space–time trees, such as Charles Darwin's first genealogical tree (Fig. 1). The tree structure correlates different lineages through their shared genealogy. For example, closely related cells tend to be more closely located within a bacterial colony, embryo or solid tumour and tend to behave similarly, as measured by gene expression patterns[19,20]. These spatial, genetic and behavioural correlations can qualitatively change the dynamics of the system, producing order in situations where increasing entropy might otherwise be expected, eventually giving rise to Darwinian evolution.

Continuum theory of biomass injection

We begin by illustrating how growth-induced mechanical instabilities shape proliferating materials; such instabilities in turn can feedback on growth to produce functional self-organized structures. These effects have been explored in several different types of dense cellular structures, for example in plants and animals[21]. Here, we mostly focus on bacteria, which are the simplest form of self-replicating unicellular life and show a rich spectrum of mechanically induced pattern formation.

In nature, bacteria are often found in biofilms: dense conglomerates of cells on surfaces, which are embedded in an adhesive extracellular polymer matrix. With cell doubling times of less than an hour, bacterial biofilms have become a popular model system for studies of proliferative development, aided by techniques for detecting all individual cells in images of biofilms[22,23].

Physical interactions among cells, the surface and the matrix are key to shaping a biofilm[24]. At a macroscopic scale, proliferation of cells

and continued production of the polymer matrix leads to the cohesive expansion of the biofilm, often opposed by friction effects, such as those arising from adhesion of cells to the surface that is colonized by the biofilm[25]. In addition, the growth-driven displacement of cells in the centre of the biofilm can be restricted by the cells in its outer region, as the cells are bound together by the matrix. The result of both effects is that compressive stresses build up within the biofilm. A growing body of work now relates these stresses and the resulting mechanical instabilities to the complex and beautiful patterns of wrinkles characteristic of late-stage biofilms (Fig. 2). In essence, the growth of a biofilm adhered to a substrate is an example of differential expansion of layered materials[21]: above a certain compressive stress in the biofilm, the system becomes unstable to undulations into the third dimension, and the wavelength of these undulations is well predicted by mechanical theory[26–28].

Importantly, the physical principles of growth-induced pattern formation are general and thus extend beyond the microbial world to macroscopic organisms such as plants[29] or animals[21]. Phyllotactic patterns (the arrangements of leaves on plant stems) may be understood in terms of energy-minimizing buckling patterns[30–32] that arise from compressive growth stresses. Similarly, the deep folding patterns of animal brains are believed to be remnants of deformations that arise from an elastic sheet (the grey matter cortex) growing over a much softer foundation (the white matter core)[33–37]. Brain-like folding patterns can be produced experimentally in reconstituted two-layered brain prototypes made of polymeric gels with differential swelling properties[38]. Similar growth-induced mechanical instabilities are believed to govern the formation of the villification and looping of guts[39–41] and the branching of lungs[42,43].

Feedback between growth and form

Whereas the most basic, linear, instabilities can be studied assuming a constant pattern of biomass production, one often deals with nonlinear feedback cycles. The most common type of feedback arises from biofilm shape transformations steering the growth behaviour of the biofilm, which in turn influences future biofilm shape. For example, differential growth rates that arise from differential access to nutrients and metabolites[44,45] lead to complex patterns of self-organization, which can explain a wide range of biofilm morphologies. Examples include a general 2D roughening[46–50], radial wrinkles, circumferential wrinkles and herringbone patterns, among others, for colonies on agar surfaces[51], as well as fingered[47,52–55] and highly branched broccoli-like shapes[56,57] observed in 2D and 3D biofilms and colonies. Related instabilities occur for pellicles (biofilms growing at the surface of a liquid)[26,58]. Interestingly, the continued growth of pellicles leads to a cascade of wrinkling transitions, with a well-defined fractal dimension[58,59].

Insofar as natural bacterial environments often include fluid flow — in the ocean, in rivers, in soils or in the 'plumbing' of eukaryotic hosts, for example — the influence of flow on biofilm proliferative development has also become a topic of growing interest. For sufficiently strong flow, shear forces orient cells along the flow lines, and the combination of flow-alignment and growth pressure produces teardrop-shaped colonies[60,61]. Growing microbes can also modify the flow fields they are exposed to. For example, colonies of baker's yeast growing on a soft viscous substrate have been observed to metabolically generate a vortex ring underneath the edge of the colony, leading extensile stresses that can tear apart the colony[62]. A separate observation is that proliferation within a complex 3D flow environment can lead to biofilm 'streamers' — extended biofilm filaments which grow both by proliferation and by the capture of additional cells and/or matrix, and which can eventually choke off the fluid flow. In a biomedical context, such behaviour can have profound implications[63].

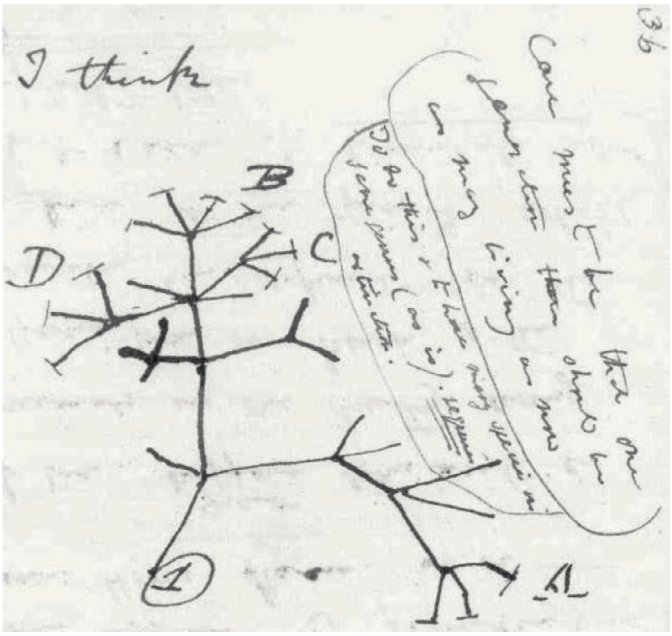


Fig. 1 | Proliferation generates tree structures. Charles Darwin's 1837 sketch, his first diagram of an evolutionary tree (1837). (Source: https://commons.wikimedia.org/wiki/File:Darwin_tree.png).

Interestingly, microbes can form spatial structures on even the largest oceanic scales[64,65], as evidenced by the intricate patterns resulting from phytoplankton blooms, which are sometimes visible from the sky (Box 1). Phytoplankton, composed of algae and photosynthesizing bacteria, are confined within well-lit surface layers, ranging in thickness from several centimetres to a few metres[66]. Models show that, provided the characteristic eddy turnover times are long compared with the microbial doubling times, the combination of growth and an effectively compressible 2D fluid flow can cluster blooms of surface-dwelling microbes into fractal-like convergence zones[67], in which flow lines point downwards. This clustering effect is believed to strongly reduce the carrying capacity of the well-lit surface layers[68,69].

Feedback between growth and force

Growth rates can vary in space and time not only owing to modulation of chemicals, such as nutrients or antibiotics, but also owing to mechanical stresses. For example, growth must stop if a confining contact pressure is sufficiently large, an effect essential to the regulation and termination of tissue development in higher organisms[70–72]. The pressures required to fully stall growth differ widely across systems. Whereas mammalian cells can be confined by kilopascal pressures[73], it requires megapascal pressures to confine walled microbes[74] or plants[75] — think of the humble dandelion breaking through concrete.

If the growth-modulating mechanical stresses are themselves growth-induced, one arrives at direct feedback between growth and force. The most generic way to mathematize this feedback is to allow the growth rate k to depend on the mechanical stress. In the simplest case, ignoring non-isotropic effects, the growth rate can be expanded

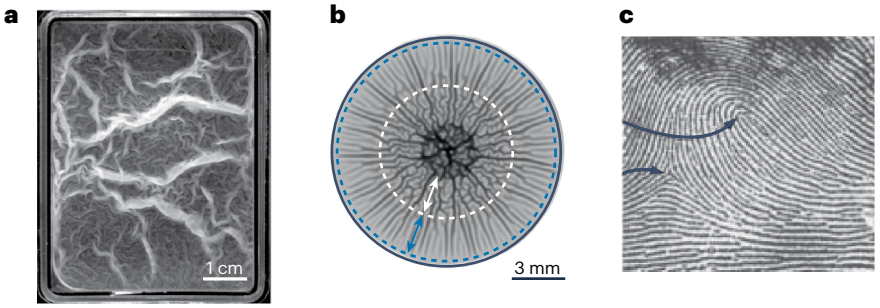


Fig. 2 | Self-organization driven by the feedback between growth and form. Stresses induced by differential growth in layered materials induce buckling instabilities, as shown here for different systems. **a**, *Bacillus subtilis* pellicles floating on liquid culture media. **b**, *Vibrio cholerae* biofilms. **c**, ±1/2 defects of dense nematics as seen in human fingerprints have been hypothesized to play key roles in directing layer formation. Part **a** adapted with permission from ref. 26, National Academy of Sciences. Part **b** adapted with permission from ref. 51, National Academy of Sciences. Part **c** adapted with permission from ref. 197, IOP.

to lowest order as $k(P) \approx \kappa(P_H - P)$, where P_H is a 'fixed point' pressure at which the growth rate vanishes, called the homeostatic pressure[76]. A simple thought experiment can help visualize the concept of a stress-dependent growth rate: imagine a box that confines a growing material, with one of the walls being a movable piston connected to a spring. As the material grows, it presses on the piston and compresses the spring. Eventually the material can no longer expand and reaches a steady state; the steady-state pressure exerted by the piston on the material is the homeostatic pressure. Entering the growth rate $k(P)$ as a source into the continuity equation (1) provides a simple analytic description of a continuous material with a stress-dependent growth rate.

In tissues, cells are usually embedded in a complex microenvironment, which often also plays an important role in controlling growth[77]. Consider, for example, a cell growing in an elastic gel. To deform the gel and grow, the cell effectively inserts a strain dipole into the material, which costs elastic energy. This insertion energy is substantially lowered near a free surface, leading to increased growth near surfaces (similar arguments can be made for liquid or viscoelastic environments with sufficient viscosity). This purely mechanical surface growth effect can lead, for instance, to steady-state growth and stabilization of a negative homeostatic pressure[78].

Feedback between growth and species composition

Additional dynamical richness arises when different cell types are brought together. Whereas different non-growing tissues tend to undergo phase separation in a manner that depends on self/non-self-interactions[79–81], when the different cell types grow and compete for the same resources, such as nutrients or space, one generally observes the proverbial 'survival of the fittest'. The resulting exclusion process qualitatively depends on the effective number of dimensions: the dynamics follow fast logistic growth of the fitter cell type in well-mixed environments, but generically yield propagating fronts of constant speed in one or two dimensions (Fig. 3), unless dispersal is long-ranged[82]. Like the free interface of a growing population of a single cell type[46–49,56], these interfaces between competing types can be unstable to the formation of fingering patterns[52,83–86], or can exhibit self-similar fractal properties characteristic of growing interfaces (as can be described by the KPZ equation[87]).

The outcome of competition dynamics does not necessarily depend on growth rate alone. For example, in 1D, a slower-growing strain can win if it has a higher diffusivity, because the (deterministic) front propagation speed[88] is proportional to the geometric mean of both growth rate and diffusivity, $v \propto \sqrt{Dk}$. Migration has also been studied in cancer models, with qualitatively similar conclusions[89,90]. If growth rates depend on mechanical pressure, it is usually the tissue with higher homeostatic pressure that prevails, rather than the more prolific one[76,91]. Interestingly, this force-dependent exclusion process follows fast exponential (logistic) growth, as normally expected in the well-mixed mean-field limit, even though the tissue is spatially structured. Mean-field theory is successful in this case because pressure, propagating throughout the tissue, generates an effective all-against-all competition. The linear growth rate $s = \kappa(P_{H1} - P_{H2})$ of the fitter type is proportional to the difference in homeostatic pressure[76,91]. Conversely, friction with the substrate results in a finite range for the pressure, and thus also yields a front invading at constant speed[85,92].

The interactions between different species do not have to be competitive – they can instead be mutualistic[93] and/or asymmetric. For example, different bacterial species often cooperate by cross-feeding on each other's metabolites[45], but they can also engage in microbial warfare, for example by killing each other using specific chemical 'daggers'[94]. The interactions between bacterial viruses (called phages) and their hosts are asymmetric: phages kill bacteria but bacteria feed phages. Theoretical studies have identified universal dynamical patterns that arise when interaction type and strength are drawn from random distributions[95–99]. These results offer potential resolutions to the question of why high levels of species diversity can be stably maintained in large complex systems, despite long-standing concerns based on a random-matrix argument[100].

Yet it is unclear at present whether the interaction patterns commonly assumed in abstract ecological models naturally arise in soft-matter systems of different interacting cell types. Empirical studies have only begun to map out quantitatively the spatiotemporal interaction networks emerging from the self-organization of bacterial multispecies communities. The dynamic malleability of microbial communities combined with the finite range of metabolic interactions has been found to assort species and their interactions[45]. In dense cell packings in which proliferation requires collective rearrangements, mechanics can induce long-range cooperative interactions between different cell types. For example, a cell with lowered adhesion forces promotes growth in the local environment, which benefits not just the cell itself. Thus, cells of different types can benefit from the mutant cell, resulting in divergent evolution[101]. Mechanical interactions can also

screen fitness differences over short distances, leading to an anomalously slow decay of slower-growing types[102,103]. Remarkably, long-range interactions can also arise from ion channels conducting electrical signals through spatially propagating waves of ions[104,105]. These findings indicate that the maintenance of species diversity in dense soft-matter systems requires a deeper understanding of the spatiotemporal

Box 1

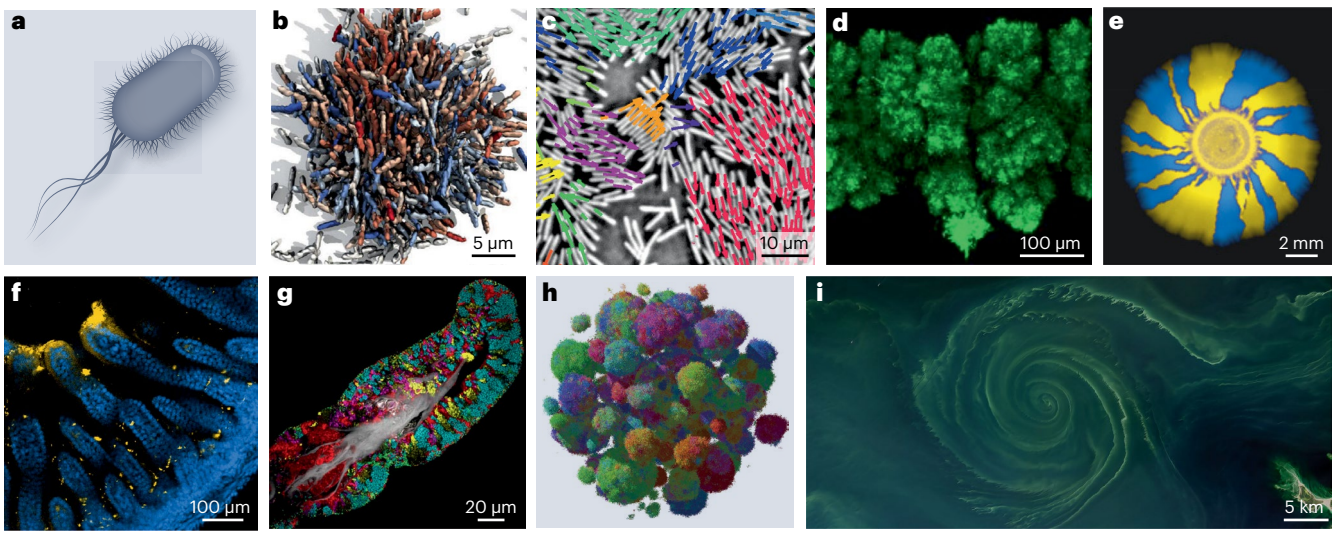
Examples of proliferating active matter

Growing cells, shapes and populations have been studied in mathematical biology for more than a century, often at a mean-field level, to capture phenomena observed in microbiology, development, ecology, epidemiology, population dynamics and evolution. In recent years, with increasingly quantitative and single-cell-level data, it has become clear that the established mean-field pictures are often qualitatively modified by the fluctuations, susceptibility and correlations that govern assemblages of proliferating cells. Several generic model systems of proliferating active matter have thus emerged.

One prototypical example combining soft matter and growth is provided by microbial biofilms[199], which can grow on solid, semisolid or liquid substrates into resilient communities[200]. These biofilms are highly abundant on Earth and can be composed either of clonal cells or of diverse species. Complex physical properties of biofilms contribute to their development, their evolutionary success and their important role in human disease[199,201]. Another example is the human gut microbiome[202] — a dense multispecies consortium of bacteria, which helps us to digest food and which avoids being flushed away by dividing roughly once a day. Finally, the highly structured tissues of an animal develop from a single fertilized egg in a process called embryogenesis that involves a rich interplay between biochemistry and mechanics[203]. Cells in tissues can die and are replaced by new cells regularly; sometimes they also mutate into a state of uncontrolled growth and develop into tumours. Although these examples of complex cellular systems are biologically very different, their macroscopic behaviours share similarities that can often be understood as a combination of just a few processes such as spatial competition, movement, growth, cell division, and death.

The figure depicts single bacteria such as *Escherichia coli* (part **a**); microscale bacterial biofilm colonies (part **b** shows *Vibrio cholerae* surrounded by surface-attached individual cells in grey); patches of swarming bacteria (part **c** shows *Bacillus subtilis* with overlaid velocity vectors coloured according to cluster identity); mesoscale biofilm colonies of bacteria such as *E. coli* (part **d**); enhanced genetic drift at the frontier of an expanding colony of bacteria (such as *E. coli*) generating sectors with fractal boundaries (part **e**); infectious bacterial biofilm (yellow in part **f**) inside the mouse intestine (blue); multispecies biofilm on a human tongue (part **g**); simulations of an expanding tumour with migration (part **h**), with colours reflecting the degree of genetic similarity; and green phytoplankton bloom in the Baltic Sea (part **i**).

Part **b** adapted with permission from ref. 60, Springer Nature Ltd. Part **c** adapted with permission from ref. 14, National Academy of Sciences. Part **d** adapted with permission from ref. 56, National Academy of Sciences. Part **e** adapted with permission from ref. 198, Wiley. Part **f** adapted with permission from ref. 22 under a Creative Commons licence CC BY 4.0. Part **g** adapted with permission from ref. 204, Cell Press. Part **h** adapted with permission from ref. 90, Springer Nature Ltd. Part **i** acquired by the Operational Land Imager (OLI) on Landsat 8 on 18 July 2018 (https://landsat.visibleearth.nasa.gov/view.php?id=92462).



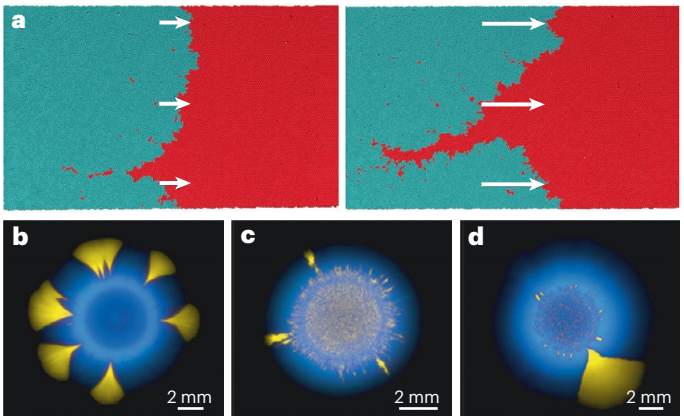


Fig. 3 | Natural selection. Combining two different types of proliferating systems generally leads to competition for space and resources. **a**, In confined space, competition often leads to moving interfaces, here simulated for two tissue types (red and blue-green): the blue-green tissue, having a higher homeostatic pressure, invades the red tissue, which also has a lower apoptosis rate with a constant velocity. As the difference in homeostatic pressure increases, the blue-green tissue invades the red ever faster (arrows), and the interface becomes unstable. **b**–**d**, With open boundaries, species compete to invade unoccupied territory, as shown here for colonies grown from a mixture of two differently labelled strains of budding yeast (*S. cerevisiae*) (**b**) and *E. coli* (strain Dh5α) grown at two different temperatures 21 °C (**c**) and 37 °C (**d**). The strains that expand faster (yellow) tend to increase in fractional abundance. The initial mixture of each colony was 0.5% yellow and 99.5% blue. The yellow strains grow faster by 15%, yet take over only in discrete sectoring events, the number of which is controlled by fluctuations early in the expansion process (jackpot events). Part **a** adapted with permission from ref. 52 under a Creative Commons licence CC BY 4.0. Parts **b**–**d** adapted with permission from ref. 198, Wiley.

self-organization of dense communities, which depends on the physical interactions between different cell types. A promising build-to-understand method is to use synthetic biology to engineer physico-chemical interactions between different microbes with the goal of biasing self-organization towards certain target patterns[106].

The effects of being discrete

Mechanical instabilities and their feedback on growth, which we have discussed above, can be captured by a continuum theory of a growing viscoelastic medium[21,83,84,86,107]. However, self-replication generally occurs via discrete entities, and this discreteness introduces unique fluctuations and correlations that can be amplified by subsequent autocatalytic growth.

Injection of degrees of freedom

Collections of repulsive particles can resist shear when their packing fraction exceeds a certain threshold — the jamming threshold. The mechanics of jammed packings reflects a pronounced excess of spatially extended soft modes. Powerful analogies between the elusive physics of glasses and the seemingly simpler paradigm of jamming have been a continued inspiration for new developments in soft-matter physics[108]. More recently, attention has been given to confluent tissues and embryo morphogenesis, where dynamic changes in cell shape and active stress fluctuations can drive the unjamming of tissues[11,12,109–111].

Non-motile bacteria growing in confined spaces can be viewed, to a first approximation, as packings of repulsive particles that grow and divide. Growth naturally causes the packing fraction to increase until jamming is reached. The packing becomes rigid when there are more interparticle contacts than degrees of freedom. A single cell division or death event, however, can be enough to produce a soft mode along which the packing can melt[74,112–114], which over long times drives the liquefaction of the packing[11,115].

The ensuing back-and-forth of growth-induced jamming and unjamming can be readily observed, for instance, when yeast cells grow in partially confined microfluidic incubators[74,116]. Similar dynamic arrangements, with additional contact dynamics due to dynamic changes in cell shape, have been modelled and observed in growing tissues and tumours over longer timescales[110,117,118]. These observations suggest that the large time and length scale limit of proliferating active matter is akin to a viscoelastic material, in which stress relaxation, the diffusion of cells and lineages are coupled to growth[117]. Near-critical systems, where these dynamics are controlled by the birth and death of soft modes, are sensitive to even weak intercellular interactions, which could give biological systems a tuning knob[119] to control the architecture and mechanical stiffness of cell collectives.

One might think that injecting degrees of freedom matters less when cells can move around, which should attenuate crowding and, consequently, the short-range interactions between cells. However, proliferation also plays an important role in the statistical physics of less crowded fluid systems. Dilution can arise from purely passive cell movement, driven by Brownian motion; alternatively, cell movement can be active, due for instance to the growth and pushing of neighbouring cells, or to active motility, which greatly enhances the cellular movement. Motility is common among bacteria, where it can arise from the rotation of a flagellum or flagellar bundle, due to the extension and retraction of a type IV pilus, or due to gliding. This allows bacteria to randomly explore space with a strongly enhanced diffusivity (for instance, 100–1000 $\mu m^2\ s^{-1}$ for *E. coli*, which has a passive diffusivity of about 0.1 $\mu m^2\ s^{-1}$)[120,121] resulting from the run-and-tumble behaviour of individual cells. In the presence of environmental cues, this random motion can be biased, enabling cells to purposefully search for food, in behaviours such as chemotaxis, as detailed further below.

Motile bacteria can be idealized as self-propelled particles. Active-matter theory shows that they tend to exhibit phase separation at sufficiently high densities, provided that the active diffusivity decreases with density. This motility-induced phase separation (MIPS)[122] arises from the non-equilibrium nature of the motility-induced diffusivity. Purely passive diffusion can only increase entropy and thus promotes homogenization. Local logistic growth leads to an arrested form of MIPS, in which droplets or rings are separated by regions of lower density[123]. This modification of MIPS still requires active motility. However, proliferation can also induce phase separation even when cells are only passively diffusing, provided they are near a reflecting boundary. For example, a mixture of jammed and gas-like bacterial phases spontaneously form in pores beyond a critical size[124] (Fig. 4). Theory and simulations suggest that this type of phase separation is a generic consequence of proliferation-induced density gradients and should even occur in idealized suspensions of (proliferating) hard spheres.

Whereas the macroscopic structure of proliferating active matter clearly reflects past growth (Fig. 1), it is an interesting general question whether and how the statistical properties of dense ensembles of self-replicating cells differ from the properties of disordered granular packings[116,125,126]. A topological study of 2D colonies of rod-shaped bacteria growing at a constant rate observed that, although +1/2 and −1/2 defects were both produced at the same rate, +1/2 defects tended to move to

the periphery[127], in contrast to the defect dynamics in non-growing active nematics. Defects were also found to be involved in epithelial cell death and extrusion, and feature prominently in fingerprints[128] (Fig. 2c).

Proliferation-induced microstructure and its feedback on macrostructures

Although the structure of a dense cell packing often looks random at first glance, it frequently contains a statistical trace of the growth process that produced it. Large-scale topological analysis of disordered structures[129,130] revealed that the statistical properties of local neighbourhood networks[131,132] in random colloidal packings differ significantly from those of various grown multicellular systems, suggesting that cell division and hierarchical growth processes can lead to special kinds of disorder. Growth-induced packings can also differ in their response to forces, for instance when proliferation is stress-dependent, which can lead to increased stiffness due to excess contacts[112].

Rod-shaped bacterial species, which grow by cell elongation and division, tend to align when they grow in dense populations, owing to steric nearest-neighbour interactions, interactions with confinement boundaries or shear-induced alignment. Such cellular alignment is frequently observed, for example, in microfluidic channels[133], where cells orient themselves parallel to the channel walls, or when biofilms are embedded in hydrogels where order can spontaneously form[134]. On larger scales, in biofilms, growth induces mechanical stresses that perturb local cell order and dynamics in ways that eventually influence the biofilm's macroscopic features. For example, live imaging at single-cell resolution shows that rod-shaped cells of *Vibrio cholerae* proliferating on a flat surface reorient from in-plane to vertical, starting at the colony centre[28,135]. Because the cells grow by elongation, this verticalization transition leads to out-of-plane as opposed to outward in-plane growth of the bacterial colony. Subsequent modelling revealed verticalization in this system to be driven by compressive stresses that arise from growth against substrate friction[136]. Similar 2D-to-3D transitions have been observed in colonies grown from other rod-like bacterial species (*E. coli, Pseudomonas aeruginosa, Myxococcus xanthus*), suggesting that 2D-to-3D transitions are a general feature of colony growth of rod-like bacteria and that they can be influenced by buckling[137], glassy dynamics[138] and topological defects[139].

By modifying the average cell length and thus the tendency to verticalize cell orientations, biofilms can be converted from tall and narrow to flat and broad, reflecting a biologically relevant tradeoff between growth into 3D for greater access to nutrients provided by the bulk fluid versus expansion in 2D to stake out more territory. Interestingly, the same verticalization transition leads to radial orientation of the remaining horizontal cells because their continued in-plane growth generates a strong gradient of in-plane velocity that reorients the rod-shaped cells[140]. By genetically modifying the cell density and cell aspect ratio, it is possible for biofilms of one species to mirror the biofilm morphology and cell arrangements observed in biofilms of other species, indicating that the molecular details of the extracellular polymer matrix can be accurately coarse-grained into effective mechanical interactions[141].

Giant fluctuations and jackpot events

All living systems, even those with sophisticated proof-reading mechanisms, occasionally make errors when they attempt to replicate themselves. Mutations are replication errors that, provided they are not lethal, are inherited by the progeny and are the source for new behaviours, new cell types and new information — with fascinating consequences for the population at large.

Watching a friend playing the slot machine at a faculty dance, Salvador Luria realized that mutations can be lucky and hit a genetic jackpot[142,143]. His intuition was that if mutations arise early in an expansion process, they will likely have many descendants in the future. Mathematizing this insight, Max Delbrück showed that mutant abundances are therefore broadly distributed, leading to giant sample-to-sample variations in experiments[142].

By confirming their predictions, Luria and Delbrück provided strong evidence for the existence of spontaneous mutations (although whether external stress can increase the probability of adaptive over deleterious mutations has been a topic of long-standing debate[144]). But the importance of jackpot events goes far beyond the Darwin–Lamarckian debate, because they are rare and extreme events that can hold sway over the fate of entire populations and induce giant fluctuations on the scale of the population size. These 'black swan' events can propel mutants to high abundance within a population, not because they

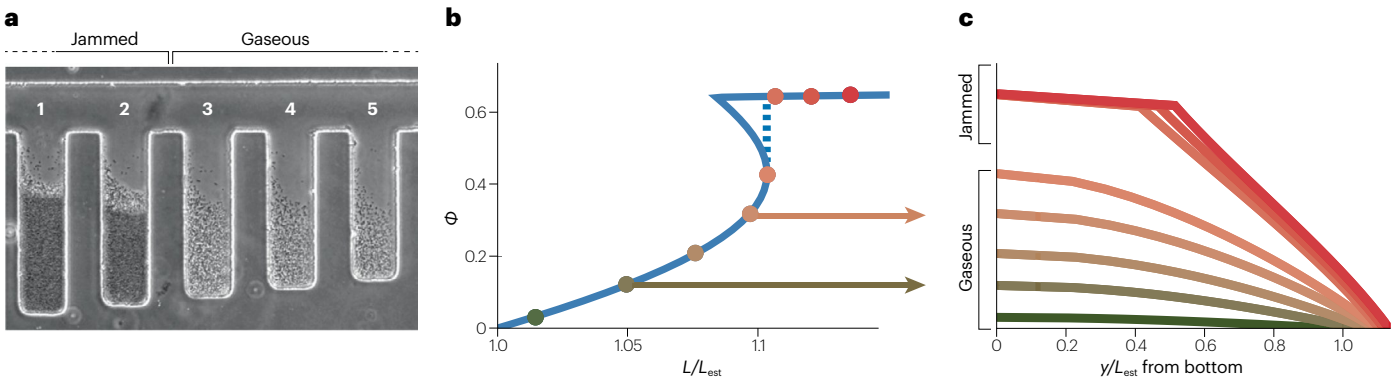


Fig. 4 | Proliferating particles phase separate due to crowding-induced slowdown of passive diffusion. a, Bacteria (*Acetobacter indonesiensis*) colonizing cavities (numbered 1…5) of different length. The lower parts of the longer cavities 1 and 2 exhibit a dark phase where bacteria are densely packed ('jammed' phases); the population in cavities 3, 4 and 5 are far more dilute ('gaseous phase'). **b**, **c**, A model of proliferating hard spheres reproduces the length-dependent transition from gaseous to jammed. The maximum fraction $\Phi(0)$ at the floor of the cavities is shown in **b** as a function of vertical length L of the colonized region. Colonization is only possible if L is larger than a critical length L_{est}, the 'establishment' length. The computed density profiles $\Phi(y)$ are shown in **c** for a few select points in **b**. Figure adapted with permission from ref. 124, National Academy of Sciences.

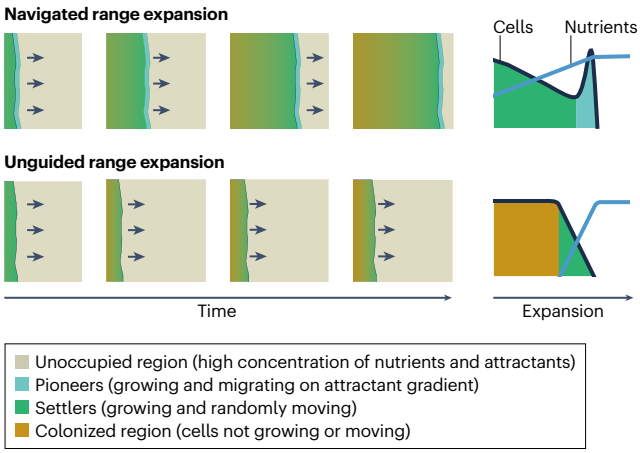


Fig. 5 | Proliferating motile matter. Chemotactic range expansions are guided by self-produced attractant gradients (top). The resulting propagating fronts are faster than unguided range expansions, which are described by Fisher–Kolmogorov wave equations. Figure adapted with permission from ref. 167, Springer Nature Ltd.

increase Darwinian fitness but simply because they have been lucky to arise at the onset of an expansion process. In the context of epidemics, for example, jackpot events can lead to superspreading events[145], which have been well documented in the SARS-CoV-2 pandemic. It has been shown that, depending on the jackpot statistics, the resulting dynamics differ greatly from standard models of population genetics, which assume that the distribution of demographic fluctuations is short-tailed[146–148].

Recent years have revealed that large fluctuations are more ubiquitous than previously thought, because mutations can produce many descendants by chance even if they do not arise early in an exponential growth process. One such mechanism is 'gene surfing', which refers to mutations growing to high abundance when they arise at the edge of a spatially expanding population, where organisms and their offspring benefit from elevated growth rates[116,149–152]. A similar phenomenon occurs when beneficial mutations arise in exceptionally fit individuals, with which they hitchhike to high frequency[153]. When stationary bacterial populations are suddenly supplied with fresh media, jackpot events can arise from cells that leave dormancy anomalously early[154]. It is also noteworthy that these mechanisms do not even require the strict heritability of genetic mutations. Jackpot events also arise when phenotypic changes are transient, provided they persist for longer than a cell division. Remarkably, this has been demonstrated in growing melanoma tissues, where a transient non-genetic memory of the cellular state gives rise to Luria–Delbrück-like jackpot events in gene expression[155].

Much analytical progress has been made in simple systems by using analogies to stochastic Fisher–Kolmogorov waves, where jackpot events are induced by cell number fluctuations in the tip of the waves[156–159]. But new active-matter theory is needed to capture the universal features of fluctuations in dense, higher-dimensional or multicomponent systems. Empirically, it is found that mutant abundance distributions generally differ from Delbrück's mean-field results, but they too have broad power-law tails that reflect correlations arising during population growth. These correlations can be induced, for instance, by surface roughness (described by the KPZ equation[87]) in the case of interface growth[160,161] or by effective self-avoidance interactions of branching bacterial colonies[55], which resemble patterns known from diffusion-limited aggregation[162], and epithelial structures[163,164].

Motile proliferating matter

As demonstrated above, cell growth, division and death are special activities that can have peculiar consequences for soft-matter systems. However, growing matter should also be considered in the context of other forms of activity inside biological materials. When active stresses from growth and motility are combined, the phenomenology can become even richer. Growth and motility are coupled in many biological systems, from simple bacterial communities to developing embryos. The shared phenomena seen in growing and motile systems of bacteria and eukaryotes are striking because bacterial genome sizes are substantially smaller than those of eukaryotes, and it is therefore likely that eukaryotic cells are capable of much more complex biological interactions. The similarities hint at the underlying shared physics of these systems.

For bacteria, the speed at which populations spread through their environment – thereby escaping from harmful environments or colonizing new terrain – is determined by both growth and motility, albeit in fundamentally different ways. Growth engenders spreading through the injection of new cells, either by simply expanding the boundaries of the population or, as described above, by generating mechanical stresses in dense populations that cause cells to be pushed outward. Motility instead promotes spreading in two ways: through random undirected motion, which can be thought of as a diffusive process, or through directed motion in response to external cues (such as chemotaxis in response to a chemical gradient). When bacteria continually consume a surrounding chemical attractant, they collectively generate a local gradient along which they, in turn, bias their motion. This effect can lead to the formation of a coherent front of cells that continually propagates[165]. However, at very high cell densities, the frequent collisions between cells cause frequent changes in movement directions, which ultimately suppress chemotactic movement[166].

In biology, chemotaxis has traditionally been viewed as a response to stress or starvation. However, recent work has demonstrated that even under nutrient-replete conditions, low levels of chemoattractants act as cues to direct front-like spreading of cells at the boundary of the population; the remaining nutrients allow subsequent population growth behind this front[167] (Fig. 5). Importantly, this process of 'navigated' range expansion gives rise to faster population spreading compared with unguided expansion that follows the canonical Fisher–Kolmogorov dynamics in which the population spreads solely through the growth and random motion of cells at the front[168]. By generating a steep chemoattractant gradient at the front of the expanding population, cell proliferation helps to direct the chemotactic propulsion towards virgin territory, thus greatly accelerating the bacterial colonization (Fig. 5).

This interplay between growth-driven and chemotaxis-driven spreading can then be characterized, for example, by comparing the cell doubling time γ^{-1} to the time required to chemotax over the chemoattractant diffusion length $\sqrt{Dt_c}$, where D is the attractant diffusivity and $t_c \equiv c_\infty/(b\kappa)$ is a characteristic timescale of consumption of attractant with far-field concentration c_∞ by a population of cell density b and a maximal consumption rate per cell κ (ref. 169). Because proliferation, motility and attractant consumption all depend sensitively on intrinsic cellular properties as well as the properties of their environment, either growth or motility can dominate spreading under different

conditions – leading to marked differences in the dynamics and morphology of the spreading population that remain challenging to describe theoretically[168,169]. This interplay between growth and motility can also have important consequences for the onset and extent of biofilm formation[170]. A different form of self-guided chemotactic spreading arises when bacteria are stressed and excrete their own chemoattractant, which can lead to the formation of ordered arrays of spot-like cellular aggregates[171] and travelling bands[172]. Although growth is not necessary to form these patterns, theoretical analysis suggests that the conditions at which they occur and their characteristics can be strongly modulated by growth[173,174].

At even higher packing densities and on flat surfaces, and during bacterial biofilm formation of some species, growth and motility are coupled in a process termed bacterial swarming. Whereas the term 'swarming' is used in physics to generally describe collective motion of any group of objects, the term 'bacterial swarming' in the microbiology literature refers specifically to the movement of cells across a semisolid surface (typically agar)[175–178]. This movement across surfaces is a 2D process, and colliding cells interact strongly, often resulting in collective movement and the formation of groups of cells co-moving temporarily before breaking apart and regrouping[179]. While the cells are forming such a highly active fluid-like phase, the cell population grows and expands across the agar surface. However, there is a well-defined separation between the cell population ('swarm') and the uncolonized surface, and the expansion speed of the swarm front is highly correlated with the bacterial growth rate[179]. For some species, like *Bacillus subtilis*, the swarm front of wild-type cells in rich agar is nearly circular, yet for several *B. subtilis* mutants and other species (notably *Pseudomonas aeruginosa*, *Proteus mirabilis* and *Myxococcus xanthus*), the swarm front can display a range of beautiful finger-like structures that are reminiscent of viscous fingering phenomena in passive fluids[180,181]. Interestingly, these swarm-front patterns often display chirality on the macroscopic scale[182], which probably arises from the directionality of the microscopic flagellar rotation[183]. As a swarm expands across a surface, different phases of cellular behaviour emerge in different spatiotemporal locations in the swarm, a phenomenon that has been characterized in detail for *B. subtilis*[179]: while the expanding frontier displays active collective motion, the locations towards the centre of the swarm display clusters of cells for which motility ceases (these ultimately become confluent and develop into 3D biofilms that are driven by proliferation without motility). For *B. subtilis*, the transition from motile cells in the swarm into a biofilm phase may be the result of MIPS[184], although this interpretation is contested[185]. Whereas for *B. subtilis* swarming relies on flagella-based motility, for *P. aeruginosa* and *M. xanthus* swarming relies on twitching motility and gliding motility respectively, which are much slower than flagella-driven motility[186,187]. Twitching motility can also couple with bacterial proliferation during biofilm formation of *P. aeruginosa*[188].

Qualitatively analogous phenomena are also present in eukaryotic systems with potentially much higher biological complexity. One such example is observed in epithelial monolayers, often studied in Madin–Darby canine kidney (MDCK) cell monolayers. When a small colony of these cells expands, cells undergo strong collective motion and form vortices and eddies. Interestingly, no cells escape the mother colony[189], and thus a 'liquid and vacuum' coexistence forms between the liquid-like colony and the cell-free region around the colony[190]. With time, the colony grows, but interestingly the growth is not caused by the pressure of the growing cells deep inside the colony; rather, the cells at the edge try to migrate outwards. This migratory force is generated even by cells many layers behind the edge, pulling the colony bulk apart[191]. The resulting tensile stress feeds back on cellular growth and can favour division. Corroborating this interpretation are observations of the alignment of cellular divisions with the cell movement velocity field. When cells fill the experimental growth dish, they are still very motile, but over time, their motion ceases, and cells undergo a glass-like arrest. Whether this arrest in motion is due to growth and the related density increase, or due to cellular shape, adhesion, substrate friction or other factors is a matter of ongoing debate. It may well be that different biological systems undergo arrest due to different mechanisms or combinations thereof.

Discussion

A wide variety of unique phenomena can arise in proliferating active matter. This diversity arises from the different ways in which proliferation breaks the particle number constraint of conventional active matter. Complex patterns of self-organization are driven by the injection of biomass, because the associated mechanical stresses lead to deformations and potentially feed back to growth rates. Additional unintuitive mechanical effects arise because the systems consist of entities (cells, organisms) that are discrete. As a result, their proliferation tends to locally inject degrees of freedom, leading, for instance, to unique packing structures, to local melting of a jammed material, or to the build-up of diffusion gradients, which can result in flows. Moreover, those locally injected degrees of freedom themselves act as sources of proliferation, which drive autocatalytic processes that amplify mass, correlations and information. Finally, self-replication

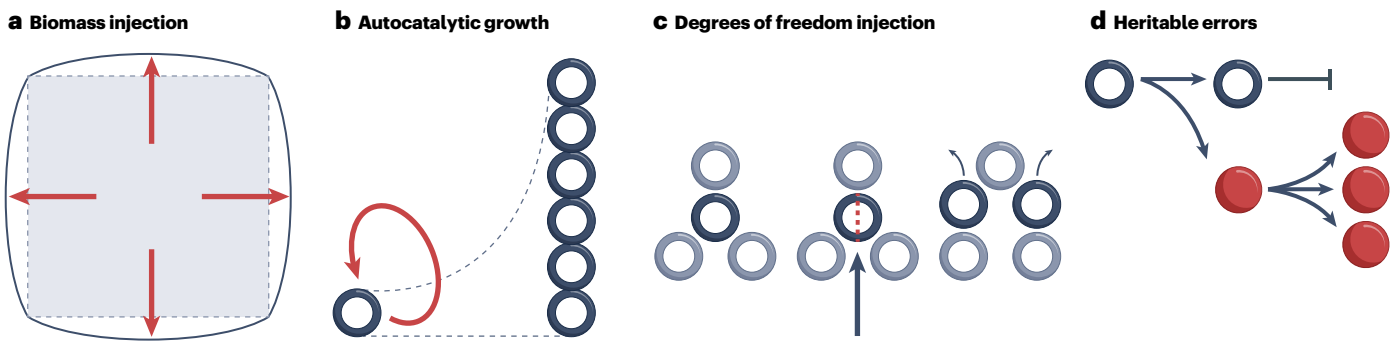


Fig. 6 | Four aspects of proliferation. a–**d**, Proliferation injects: biomass (part **a**); sources of proliferation (part **b**); degrees of freedom (part **c**); and, by making heritable errors, it also injects information (part **d**).

is never perfect. If the associated errors (which are mutations in living systems) are heritable, they introduce new bits of information that, filtered by their effect on fitness, can be autocatalytically amplified to take over the population. This is the basis of Darwinian evolution.

These different aspects of proliferation (Fig. 6) have served as an ordering principle for this Perspective and may be useful to guide further research to combine soft active-matter physics with proliferation. Embracing proliferation will enable active-matter researchers to make connections to developmental biology, microbiology, population genetics and ecology — fields that have for a long time explored the consequences of growth and division, but rarely considered proliferation in the context of the soft-matter physics of living systems. We believe that reaching across the aisle from both sides will create opportunities to explore both new physics and biology in concrete combinations of theory and experiments.

Outlook

Because biological systems are to some extent frozen accidents of the history of evolution, it would be fruitful to have purely synthetic realizations of proliferating active matter. Doing so would allow one to apply Occam's razor not only to theory but also to experiments, as it would be possible to study growth-induced self-organization and evolutionary dynamics in a minimal system with full control over many essential ingredients. However, although self-replication is biology's 'bread and butter', it is extremely difficult to realize in a synthetic system. Aspects of proliferation can already be readily generated, such as a volume expansion induced by osmotic stresses or the generation of more degrees of freedom by breaking up interparticle bonds. There are also proposals and even some technological realizations of growth and division of a fixed 'platonic' template, for example based on active droplets[192,193]. But so far, researchers seem to be reliant on biology for true self-replication capable of storing and transmitting random copying errors. Nevertheless, there are promising synthetic systems composed of biological parts, such as DNA origami cross-tile motifs[194,195] or bioengineered programmable bacterial systems, as an approach to replicating multicellular systems. Still, developing physical objects capable of replicating themselves, with all their errors, remains one of the biggest technological challenges. Meanwhile, computer models of growing and replicating entities remain the best virtual realization of growing active matter, offering full control overall parameters.

Proliferation also brings formidable challenges to active-matter theory, which has been developed for fixed particle numbers whose trajectories neither branch nor end. Liberating active-matter systems from the fixed number constraint leads to inherently dynamical systems, with complex information cascades running from single cells to clusters of descendants that are correlated by their genealogical tree. Although some generic principles have emerged and much progress has been made in the continuum description of growth-active matter[21,107,196], the field largely lacks a unified framework that accounts for mutations, inheritance, physico-chemical feedbacks, fluctuations and their effects on emergent material properties and order parameters. One challenge is to consistently formulate the dual picture of birth–death dynamics forward in time and the backward-time picture of a non-dividing set of coalescing active particles. Both pictures are needed in eco-evolutionary scenarios in which the genealogical correlations feedback onto the population dynamics.

Considering the ever-churning rare-event dynamics of actual evolution, it might never be possible to fully predict long-term dynamics of proliferating active systems. But through the lens of coarse-grained physics, one can hope to gain a unified view of different kinds of proliferating active matter and separate generic collective phenomena from microscopic details.

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