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Citation for published version:

Hallatschek, O, Datta, SS, Drescher, K, Dunkel, J, Elgeti, J, Waclaw, B & Wingreen, NS 2023, 'Proliferating active matter', *Nature Reviews Physics*, vol. 2023. <https://doi.org/10.1038/s42254-023-00593-0>

Digital Object Identifier (DOI):

[10.1038/s42254-023-00593-0](https://doi.org/10.1038/s42254-023-00593-0)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

Nature Reviews Physics

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Proliferating active matter

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24 Abstract

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

44

45

46 [H1] Introduction

47 At least since Erwin Schrödinger’s influential book *What Is Life?*¹, physicists have been
48 captivated by the quest to reduce life to its most basic components. Schrödinger emphasized
49 the importance of continuous energy consumption, as living systems must be kept away from
50 thermodynamic equilibrium to establish order and develop complexity. This aspect of life is
51 idealized in what is now called active matter, namely systems composed of self-driven agents
52 that perform mechanical work on themselves and their environment^{2,3}. Classical examples are
53 active gels⁴, such as biopolymer networks actuated by molecular motors or tissues in which
54 cells pull and push on each other and the environment, and collections of self-propelled
55 particles⁵, such as swarming bacteria, flocking birds or inanimate Janus particles⁶. In all these
56 cases, mechanical energy is locally injected by the active agents through the conversion of
57 stored or ambient free energy into mechanical work.

58

59 Another aspect of living systems is that they are typically made up of ‘squishy’ components,
60 which can be deformed or restructured by weak forces, either because the involved materials
61 are soft, like cells and tissues⁷, or because they have soft modes, which arise near critical points
62 (such as jamming) or from a broken continuous symmetry (such as a Goldstone mode in active
63 nematics). The resulting feedback between movement, deformation and active forces generates
64 a wealth of fascinating collective phenomena, including so-called odd mechanical and

65 topological properties, large fluctuations, order–disorder transitions, pattern formation on
66 mesoscopic scales and active turbulence. Most of these emergent phenomena have been
67 successfully predicted or at least explained by theory, despite their non-equilibrium nature. The
68 surprising effectiveness of theory far from equilibrium has contributed to the rapid growth of the
69 field of soft active matter^{8,9}.

70

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

80

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

90

91 [H1] Making “more is different”

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

98

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

$$100 \quad \partial_t \varrho = -\nabla \cdot j + k\varrho, \quad (1)$$

101 where ϱ is the local mass, volume or number density, j is the associated current and k is the
102 local growth rate. In conventional active matter models, one sets $k = 0$ and asks what happens
103 if motility arises from an active process, such as swimming^{8,17}. In this Perspective, we are
104 primarily concerned with situations in which motion is purely passive and activity is introduced
105 via the growth term. We later address the effects of an extra active contribution to motility. Note

106 that exponential growth implied by a constant growth rate k can only last temporarily, because
107 such rapid population growth quickly outpaces any realistic resource supply (a “Malthusian
108 crisis”). The long-term dynamics, therefore, depends on non-linear feedbacks that keep the
109 population density at bay and often provide a mechanism for biologically significant pattern
110 formation.

111
112 The above continuum picture of the effects of proliferation is incomplete, however, as it misses
113 the discreteness of the proliferating entities. The associated fluctuations are usually thought to
114 be small in large systems, but they can cause macroscopic effects when they are amplified by
115 the expansion of the population or near a phase transition (such as jamming). For example, the
116 state of systems that have grown from just a few initial cells can reflect microscopic fluctuations
117 that occurred early in the expansion, similar to the cosmic microwave background being a noisy
118 trace of primordial fluctuations¹⁸.

119
120 A complementary way to view the impact of proliferation is in terms of space-time
121 representations of the dynamics. Conventional active particles can be described by space-time
122 trajectories. Proliferating entities, instead, give rise to space-time trees, such as Charles
123 Darwin’s first genealogical tree (Fig. 1). The tree structure correlates different lineages through
124 their shared genealogy. For example, closely related cells tend to be more closely located within
125 a bacterial colony, embryo or solid tumor, and tend to behave similarly, as measured by gene
126 expression patterns^{19,20}. These spatial, genetic and behavioral correlations can qualitatively
127 change the dynamics of the system, producing order in situations where increasing entropy
128 might otherwise be expected, eventually giving rise to Darwinian evolution.

129
130

131 [H1] Continuum theory of biomass injection

132 We begin by illustrating how growth-induced mechanical instabilities shape proliferating
133 materials; such instabilities in turn can feed back onto growth to produce functional self-
134 organized structures. These effects have been explored in several different types of dense
135 cellular structures, for example in plants and animals²¹. Here, we mostly focus on bacteria,
136 which are the simplest form of self-replicating unicellular life and employ a rich spectrum of
137 mechanically induced pattern formation.

138
139 In nature, bacteria are often found in biofilms: dense conglomerates of cells on surfaces, which
140 are embedded in an adhesive extracellular polymer matrix. With cell doubling times of less than
141 an hour, bacterial biofilms have become a popular model system for studies of proliferative
142 development, aided by techniques for detecting all individual cells in images of biofilms^{22,23}.

143
144 Physical interactions among cells, the surface and the matrix are key to shaping a biofilm²⁴. At a
145 macroscopic scale, proliferation of cells and continued production of the polymer matrix leads to
146 the cohesive expansion of the biofilm, often opposed by friction effects, such as those arising
147 from adhesion of cells to the surface that is colonized by the biofilm²⁵. In addition, the growth-

148 driven displacement of cells in the center of the biofilm can be restricted by the cells in the outer
149 region of the biofilm, as the cells are bound together by the matrix. The result of both effects is
150 that compressive stresses build up within the biofilm. A growing body of work now relates these
151 stresses and the resulting mechanical instabilities to the complex and beautiful patterns of
152 wrinkles characteristic of late-stage biofilms (Fig. 2). In a nutshell, the growth of a biofilm
153 adhered to a substrate is an example of differential expansion of layered materials²¹: above a
154 certain compressive stress in the biofilm, the system becomes unstable to undulations into the
155 third dimension, and the wavelength of these undulations is well predicted by mechanical
156 theory^{26–28}.

157
158 Importantly, the physical principles of growth-induced pattern formation are general and thus
159 extend beyond the microbial world to macroscopic organisms, such as plants²⁹ or animals²¹.
160 Phyllotactic patterns (the arrangements of leaves on plant stems) may be understood in terms
161 of energy-minimizing buckling patterns^{30–32} that arise from compressive growth stresses.
162 Similarly, the deep folding patterns of animal brains are believed to be remnants of deformations
163 that arise from an elastic sheet (the grey matter cortex) growing over a much softer foundation
164 (the white matter core)^{33–37}. Brain-like folding patterns can be produced experimentally in
165 reconstituted two-layered brain prototypes made of polymeric gels with differential swelling
166 properties³⁸. Similar growth-induced mechanical instabilities are believed to govern the
167 formation of the vilification and looping of guts^{39–41} and the branching of lungs^{42,43}.

168 [H2] Feedback between growth and form

169 Whereas the most basic, linear, instabilities can be studied assuming a constant pattern of
170 biomass production, one often deals with non-linear feedback cycles. The most common type of
171 feedback arises due to biofilm shape transformations steering the growth behavior of the biofilm,
172 which in turn influences future biofilm shape. For example, differential growth rates that arise
173 from differential access to nutrients and metabolites^{44,45} lead to complex patterns of self-
174 organization, which can explain the wide range of biofilm morphologies. Examples include a
175 general 2D roughening^{46–50}, radial wrinkles, circumferential wrinkles and herringbone patterns,
176 among others, for colonies on agar surfaces⁵¹, as well as fingered^{47,52–55} and highly branched
177 broccoli-like shapes^{56,57} observed in 2D and 3D biofilms and colonies. Related instabilities occur
178 for pellicles (biofilms growing at the surface of a liquid)^{58,59}. Interestingly, the continued growth of
179 pellicles leads to a cascade of wrinkling transitions, with a well-defined fractal dimension^{58,60}.

180
181 Insofar as natural bacterial environments often include fluid flow — in the ocean, in rivers, in
182 soils, or in the “plumbing” of eukaryotic hosts, for example — the influence of flow on biofilm
183 proliferative development has also become a topic of growing interest. For sufficiently strong
184 flow, shear forces orient cells along the flow lines, and the combination of flow-alignment and
185 growth pressure produces teardrop shaped colonies^{61,62}. Growing microbes can also modify the
186 flow fields they are exposed to. For example, colonies of baker’s yeast growing on a soft
187 viscous substrate have been observed to metabolically generate a vortex ring underneath the
188 edge of the colony, leading extensile stresses that can tear apart the colony⁶³. A separate
189 observation is that proliferation within a complex 3D flow environment can lead to biofilm

190 'streamers' – extended biofilm filaments which grow both by proliferation and by the capture of
191 additional cells and/or matrix – and which can eventually choke off the fluid flow. In a biomedical
192 context, such behaviour can have profound implications⁶⁴.

193
194 Interestingly, microbes can form spatial structures on even the largest oceanic scales^{65,66}, as
195 evidenced by the intricate patterns resulting from phytoplankton blooms, which are sometimes
196 visible from the sky (Box 1). Phytoplankton, composed of algae and photosynthesizing bacteria,
197 are confined within well-lit surface layers, ranging in thickness from several centimeters to a few
198 meters⁶⁷. Models show that, provided the characteristic eddy turnover times are long compared
199 to the microbial doubling times, the combination of growth and an effectively compressible 2D
200 fluid flow can cluster blooms of surface-dwelling microbes into fractal-like convergence zones⁶⁸,
201 in which flow lines point downwards. This clustering effect is believed to strongly reduce the
202 carrying capacity of the well-lit surface layers^{69,70}.

203

204 [H2] Feedback between growth and force

205 Growth rates can vary in space and time not only due to modulation of chemicals, such as
206 nutrients or antibiotics, but also due to mechanical stresses. For example, growth must stop if a
207 confining contact pressure is sufficiently large, an effect essential to the regulation and
208 termination of tissue development in higher organisms^{71–73}. The pressures required to fully stall
209 growth differ widely across systems. Whereas mammalian cells can be confined by kPa
210 pressures⁷⁴, it requires MPa pressures to confine walled microbes⁷⁵ or plants⁷⁶ — think of the
211 humble dandelion breaking through concrete.

212
213 If the growth-modulating mechanical stresses are themselves growth-induced, one arrives at
214 direct feedback between growth and force. The most generic way to mathematize this feedback
215 is to allow the growth rate k to depend on the mechanical stress. In the simplest case, ignoring
216 non-isotropic effects, the growth rate can be expanded to lowest order as $k(P) \approx \kappa(P_H - P)$,
217 where P_H is a fix point pressure at which the growth rate vanishes, called the homeostatic
218 pressure⁷⁷. A simple thought experiment can help visualize the concept of a stress-dependent
219 growth rate: imagine a box that confines a growing material, with one of the walls being a
220 movable piston connected to a spring. As the material grows, it presses on the piston and
221 compresses the spring. Eventually the material can no longer expand and reaches a steady
222 state; the steady-state pressure exerted by the piston on the material is the homeostatic
223 pressure. Entering the growth rate $k(P)$ as a source into the continuity equation (1) provides a
224 simple analytic description of a continuous material with a stress-dependent growth rate.

225

226 In tissues, cells are usually embedded in a complex microenvironment, which often also plays
227 an important role in controlling growth⁷⁸. Consider, for example, a cell growing in an elastic gel.
228 To deform the gel and grow, the cell effectively inserts a strain-dipole into the material, which
229 costs elastic energy. This insertion energy is substantially lowered near a free surface, leading
230 to increased growth near surfaces (similar arguments can be made for liquid or viscoelastic

231 environments with sufficient viscosity). This purely mechanical surface growth effect can lead,
232 for instance, to steady-state growth and stabilization of a negative homeostatic pressure⁷⁹.

233 [H2] Feedback between growth and species composition

234 Additional dynamical richness arises when different cell types are brought together. Whereas
235 different non-growing tissues tend to undergo phase separation in a manner that depends on
236 self- non-self-interactions^{80–82}, when the different cell types grow and compete for the same
237 resources, such as nutrients or space, one generally observes the proverbial “survival of the
238 fittest”. The resulting exclusion process qualitatively depends on the effective number of
239 dimensions: the dynamics follow fast logistic growth of the fitter cell type in well-mixed
240 environments, but generically yield propagating fronts of constant speed in one or two
241 dimensions (Fig. 3), unless dispersal is long-ranged⁸³. Like the free interface of a growing
242 population of a single cell type^{46–49,56}, these interfaces between competing types can be
243 unstable to the formation of fingering patterns^{52,84–87}, or can exhibit self-similar fractal properties
244 characteristic of growing interfaces (as can be described by the KPZ equation⁸⁸).

245
246 The outcome of competition dynamics does not necessarily depend on growth rate alone. For
247 example, in 1D, a slower growing strain can win if it has a higher diffusivity, because the
248 (deterministic) front propagation speed⁸⁹ is proportional to the geometric mean of both growth
249 rate and diffusivity, $v \propto \sqrt{Dk}$. Migration has also been studied in cancer models, with
250 qualitatively similar conclusions^{90,91}. If growth rates depend on mechanical pressure, it is usually
251 the tissue with higher homeostatic pressure that prevails, rather than the more prolific one^{77,92}.
252 Interestingly, this force-dependent exclusion process follows fast exponential (logistic) growth,
253 as normally expected in the well-mixed mean-field limit, even though the tissue is spatially
254 structured. Mean-field theory is successful in this case because pressure, propagating
255 throughout the tissue, generates an effective all-against-all competition. The linear growth rate
256 $s = \kappa (P_{H1} - P_{H2})$ of the fitter type is proportional to the difference in homeostatic pressure^{77,92}.
257 Conversely, friction with the substrate results in a finite range for the pressure, and thus also
258 yields a front invading at constant speed^{86,93}.

259
260 The interactions between different species do not have to be competitive – they can instead be
261 mutualistic⁹⁴ and/or asymmetric. For example, different bacterial species often cooperate by
262 cross-feeding on each other’s metabolites⁴⁵, but they can also engage in microbial warfare, for
263 example by killing each other using specific chemical ‘daggers’⁹⁵. The interactions between
264 bacterial viruses (called phages) and their hosts are asymmetric: phages kill bacteria but
265 bacteria feed phages. Theoretical studies have identified universal dynamical patterns that arise
266 when interaction type and strength are drawn from random distributions^{96–100}. These results offer
267 potential resolutions to the question of why high levels of species diversity can be stably
268 maintained in large complex systems, despite long-standing concerns based on a random-
269 matrix argument¹⁰¹.

270

271 Yet, to date it is unclear whether the interaction patterns commonly assumed in abstract
272 ecological models naturally arise in soft matter systems of different interacting cell types.

273 Empirical studies have only begun to map out quantitatively the spatio-temporal interaction
274 networks emerging from the self-organization of bacterial multi-species communities. The
275 dynamic malleability of microbial communities combined with the finite range of metabolic
276 interactions have been found to assort species and their interactions⁴⁵. In dense cell packings in
277 which proliferation requires collective rearrangements, mechanics can induce long-range
278 cooperative interactions between different cell types. For example, a cell with lowered adhesion
279 forces promotes growth in the local environment, which benefits not just the cell itself. Thus,
280 cells of different types can benefit from the mutant cell, resulting in divergent evolution¹⁰².
281 Mechanical interactions can also screen fitness differences over short distances, leading to an
282 anomalously slow decay of slower growing types^{103,104}. Remarkably, long-range interactions can
283 also arise from ion channels conducting electrical signals through spatially propagating waves of
284 ions^{105,106}. These findings indicate that the maintenance of species diversity in dense soft matter
285 systems requires a deeper understanding of the spatio-temporal self-organization of dense
286 communities, which depends on the physical interactions between different cell types. A
287 promising build-to-understand method is to use synthetic biology to engineer physico-chemical
288 interactions between different microbes with the goal to bias self-organization towards certain
289 target patterns¹⁰⁷.

290 [H1] The effects of being discrete

291 Mechanical instabilities and their feedback on growth, which we have discussed above, can be
292 captured by a continuum theory of a growing visco-elastic medium^{21,84,85,87,108}. However, self-
293 replication generally occurs via discrete entities, and this discreteness introduces unique
294 fluctuations and correlations that can be amplified via subsequent autocatalytic growth.
295

296 [H2] Injection of degrees of freedom

297 Collections of repulsive particles can resist shear when their packing fraction exceeds a certain
298 threshold — the jamming threshold. The mechanics of jammed packings reflects a pronounced
299 excess of spatially extended soft modes. Powerful analogies between the elusive physics of
300 glasses and the seemingly simpler paradigm of jamming have been a continued inspiration for
301 new developments in soft matter physics¹⁰⁹. More recently, attention has been given to
302 confluent tissues and embryo morphogenesis, where dynamic changes in cell shape and active
303 stress fluctuations can drive the unjamming of tissues^{11,12,110–112}.

304
305 Non-motile bacteria growing in confined spaces can be viewed, to a first approximation, as
306 packings of repulsive particles that grow and divide. Growth naturally causes the packing
307 fraction to increase until jamming is reached. The packing becomes rigid when there are more
308 interparticle contacts than degrees of freedom. A single cell division or death event, however,
309 can be enough to produce a soft mode along which the packing can melt^{113–116}, which over long
310 times drives the liquefaction of the packing^{11,117}.

311

312 The ensuing back-and-forth of growth-induced jamming and unjamming can be readily
313 observed, for instance, when yeast cells grow in partially confined microfluidic incubators^{113,118}.
314 Similar dynamic arrangements, with additional contact dynamics due to dynamic cell shape
315 changes, have been modeled and observed in growing tissues and tumors over longer time
316 scales^{111,119,120}. These observations suggest that the large time and length scale limit of
317 proliferating active matter is akin to a visco-elastic material, in which stress relaxation, the
318 diffusion of cells and lineages is coupled to growth¹¹⁹. Near-critical systems, where these
319 dynamics are controlled by the birth and death of soft modes, are sensitive to even weak inter-
320 cellular interactions, which could give biological systems a tuning knob¹²¹ to control the
321 architecture and mechanical stiffness of cell collectives.

322

323 One might think that injecting degrees of freedom matters less when cells can move around,
324 which should attenuate crowding and, consequently, the short-range interactions between cells.
325 However, as we will see repeatedly, proliferation also plays an important role in less crowded
326 fluid systems. Dilution can arise from purely passive cell movement, driven by Brownian motion;
327 alternatively, cell movement can be active, for instance due to the growth and pushing of
328 neighboring cells, or due to active motility, which greatly enhances the cellular movement.
329 Motility is common among bacteria, where it can arise from the rotation of a flagellum or flagellar
330 bundle, due to the extension and retraction of a type IV pilus, or due to gliding. This allows
331 bacteria to randomly explore space with a strongly enhanced diffusivity (for instance, 100–1000
332 $\mu\text{m}^2/\text{s}$ for *E. coli*, which has a passive diffusivity of about 0.1 $\mu\text{m}^2/\text{s}$)^{122,123} resulting from the run-
333 and-tumble behaviour of individual cells. In the presence of environmental cues, this random
334 motion can be biased, enabling cells to purposefully search for food, in behaviours such as
335 chemotaxis, as detailed further below.

336

337 Motile bacteria can be idealized as self-propelled particles. Active matter theory shows that they
338 tend to exhibit phase separation at sufficiently high densities, provided that the active diffusivity
339 decreases with density. This motility-induced phase separation (MIPS)¹²⁴ arises from the non-
340 equilibrium nature of the motility-induced diffusivity. Purely passive diffusion can only increase
341 entropy and thus promotes homogenization. Local logistic growth leads to an arrested form of
342 MIPS, in which droplets or rings are separated by regions of lower density¹²⁵. This modification
343 of MIPS still requires active motility. However, proliferation can also induce phase separation
344 even when cells are only passively diffusing, provided they are near a reflecting boundary. For
345 example, a mixture of jammed and gas-like bacterial phases spontaneously form in pores
346 beyond a critical size¹²⁶ (Fig. 4). Theory and simulations suggest that this type of phase
347 separation is a generic consequence of proliferation-induced density gradients and should even
348 occur in idealized suspensions of (proliferating) hard spheres.

349

350 Whereas the macroscopic structure of proliferating active matter clearly reflects past growth
351 (Fig. 1), it is an interesting general question whether and how the statistical properties of dense
352 ensembles of self-replicating cells differ from the properties of disordered granular packings^{127–}
353 ¹²⁹. A topological study of 2D colonies of rod-shaped bacteria growing at a constant rate
354 observed that, although +1/2 and –1/2 defects were both produced at the same rate, +1/2
355 defects tended to move to the periphery¹³⁰, in contrast to the defect dynamics in non-growing

356 active nematics. Defects were also found to be involved in epithelial cell death and extrusion,
357 and feature prominently in fingerprints¹³¹ (Fig. 2c).

358 [H2] Proliferation-induced microstructure and its feedback on 359 macrostructures

360 Although the structure of a dense cell packing often looks random at first glance, it frequently
361 contains a statistical trace of the growth process that produced it. Large-scale topological
362 analysis of disordered structures^{132,133} revealed that the statistical properties of local
363 neighborhood networks^{134,135} in random colloidal packings differ significantly from those of
364 various grown multicellular systems, suggesting that cell division and hierarchical growth
365 processes can lead to special kinds of disorder. Growth-induced packings can also differ in their
366 response to forces, for instance when proliferation is stress-dependent, which can lead to
367 increased stiffness due to excess contacts¹¹⁴.

368
369 Rod-shaped bacterial species, which grow by cell elongation and division, tend to align when
370 they grow in dense populations, owing to steric nearest neighbor interactions, interactions with
371 confinement boundaries, or shear-induced alignment. Such cellular alignment are frequently
372 observed, for example, in microfluidic channels¹³⁶, where cells orient themselves parallel to the
373 channel walls, or when biofilms are embedded in hydrogels where order can spontaneously
374 form¹³⁷. On larger scales, in biofilms, growth induces mechanical stresses that perturb local cell
375 order and dynamics in ways that eventually influence the biofilm's macroscopic features. For
376 example, live imaging at single-cell resolution shows that rod-shaped cells of *Vibrio cholerae*
377 proliferating on a flat surface reorient from in-plane to vertical, starting at the colony center^{138,139}.
378 Because the cells grow by elongation, this verticalization transition led to out-of-plane as
379 opposed to outward in-plane growth of the bacterial colony. Subsequent modeling revealed
380 verticalization in this system to be driven by compressive stresses that arise from growth
381 against substrate friction¹⁴⁰. Similar 2D-to-3D transitions have been observed in colonies grown
382 from other rod-like bacterial species (*E. coli*, *Pseudomonas aeruginosa*, *Myxococcus xanthus*),
383 suggesting that 2D-to-3D transitions are a general feature of colony growth of rod-like bacteria
384 and that they can be influenced by buckling¹⁴¹, glassy dynamics¹⁴² and topological defects¹⁴³.

385
386 By modifying the average cell length and thus the tendency to verticalize cell orientations,
387 biofilms can be converted from tall and narrow to flat and broad, reflecting a biologically relevant
388 tradeoff between growth into 3D for greater access to nutrients provided by the bulk fluid versus
389 expansion in 2D to stake out more territory. Interestingly, the same verticalization transition
390 leads to radial orientation of the remaining horizontal cells because their continued in-plane
391 growth generates a strong gradient of in-plane velocity which reorients the rod-shaped cells¹⁴⁴.
392 By genetically modifying the cell density and cell aspect ratio, it is possible for biofilms of one
393 species to mirror the biofilm morphology and cell arrangements observed in biofilms of other
394 species, indicating that the molecular details of the extracellular polymer matrix can be
395 accurately coarse-grained into effective mechanical interactions¹⁴⁵.

396 [H2] Giant fluctuations and jackpot events

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

401
402 Watching a friend playing the slot machine at a faculty dance, Salvador Luria realized that
403 mutations can be lucky and hit a genetic jackpot^{146,147}. His intuition was that if mutations arise
404 early in an expansion process, they will likely have many descendants in the future.
405 Mathematizing this insight, Max Delbrück showed that mutant abundances are therefore broadly
406 distributed, leading to giant sample-to-sample variations in experiments¹⁴⁶.

407
408 By confirming their predictions, Luria and Delbrück provided strong evidence for the existence of
409 spontaneous mutations (although whether external stress can increase the probability of
410 adaptive over deleterious mutations has been a topic of long-standing debate¹⁴⁸). But the
411 significance of jackpot events goes far beyond the Darwin–Lamarckian debate, because they
412 are rare and extreme events that can hold sway over the fate of entire populations and induce
413 giant fluctuations on the scale of the population size. These ‘black swan’ events can propel
414 mutants to high abundance within a population, not because they increase Darwinian fitness but
415 simply because they have been lucky to arise at the onset of an expansion process. In the
416 context of epidemics, for example, jackpot events can lead to superspreading events¹⁴⁹, which
417 have been well documented in the SARS-CoV-2 pandemic. It has been shown that, depending
418 on the jackpot statistics, the resulting dynamics differ dramatically from standard models of
419 population genetics, which assume that the distribution of demographic fluctuations is short-
420 tailed^{150–152}.

421
422 Recent years have revealed that large fluctuations are more ubiquitous than previously thought,
423 because mutations can produce many descendants by chance even if they do not arise early in
424 an exponential growth process. One such mechanism is ‘gene surfing’, which refers to
425 mutations growing to high abundance when they arise at the edge of a spatially expanding
426 population, where organisms and their offspring benefit from elevated growth rates^{129,153–156}. A
427 similar phenomenon occurs when beneficial mutations arise in exceptionally fit individuals, with
428 which they hitchhike to high frequency¹⁵⁷. When stationary bacterial populations are suddenly
429 supplied with fresh media, jackpot events can arise from cells that leave dormancy anomalously
430 early¹⁵⁸. It is also noteworthy that these mechanisms do not even require the strict heritability of
431 genetic mutations. Jackpot events also arise when phenotypic changes are transient, provided
432 they persist for longer than a cell division. Remarkably, this has been demonstrated in growing
433 melanoma tissues, where a transient non-genetic memory of the cellular state gives rise to
434 Luria–Delbrück-like jackpot events in gene expression¹⁵⁹.

435
436 Much analytical progress has been made in simple systems by using analogies to stochastic
437 Fisher–Kolmogorov waves, where jackpot events are induced by cell number fluctuations in the
438 tip of the waves^{160–163}. But new active matter theory is needed to capture the universal features

439 of fluctuations in dense, higher-dimensional, or multi-component systems. Empirically, it is found
440 that mutant abundance distributions generally differ from Delbrück's mean-field results but they
441 too have broad power-law tails that reflect correlations arising during population growth. These
442 correlations can be induced, for instance, by surface roughness (described by the KPZ
443 equation⁸⁸) in the case of interface growth^{164,165} or by effective self-avoidance interactions of
444 branching bacterial colonies⁵⁵, which resemble patterns known from diffusion-limited
445 aggregation¹⁶⁶, and epithelial structures^{167,168}.

446 [H1] Motile proliferating matter

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

456
457 For bacteria, the speed at which populations spread through their environment—thereby
458 escaping from harmful environments or colonizing new terrain—is determined by both growth
459 and motility, albeit in fundamentally different ways. Growth engenders spreading through the
460 injection of new cells, either by simply expanding the boundaries of the population or, as
461 described above, by generating mechanical stresses in dense populations that cause cells to be
462 pushed outward. Motility instead promotes spreading in two ways: through random undirected
463 motion, which can be thought of as a diffusive process, or through directed motion in response
464 to external cues (such as chemotaxis in response to a chemical gradient). When bacteria
465 continually consume a surrounding chemical attractant, they collectively generate a local
466 gradient that they, in turn, bias their motion along. This effect can lead to the formation of a
467 coherent front of cells that continually propagates¹⁶⁹. However, at very high cell densities the
468 frequent collisions between cells cause frequent changes in movement directions which
469 ultimately suppress chemotactic movement¹⁷⁰.

470
471 In biology, chemotaxis has traditionally been viewed as a response to stress or starvation.
472 However, recent work has demonstrated that even under nutrient-replete conditions, low levels
473 of chemo-attractants act as cues to direct front-like spreading of cells at the boundary of the
474 population; the remaining nutrients allow subsequent population growth behind this front¹⁷¹ (Fig.
475 5). Importantly, this process of 'navigated' range expansion gives rise to faster population
476 spreading compared to unguided expansion that follows the canonical Fisher–Kolmogorov
477 dynamics in which the population spreads solely through the growth and random motion of cells
478 at the front¹⁷². By generating a steep chemoattractant gradient at the front of the expanding
479 population, cell proliferation helps direct the chemotactic propulsion towards virgin territory, thus
480 greatly accelerating the bacterial colonization (Fig. 5).

481
482 This interplay between growth-driven and chemotaxis-driven spreading can then be
483 characterized, for example, by comparing the cell doubling time γ^{-1} to the time required to
484 chemotax over the chemoattractant diffusion length $\sqrt{Dt_c}$, where D is the attractant diffusivity
485 and $t_c \equiv c_\infty/(b\kappa)$ is a characteristic time scale of consumption of attractant with far-field
486 concentration c_∞ by a population of cell density b and a maximal consumption rate per cell κ
487 (Ref.¹⁷³). Because proliferation, motility and attractant consumption all depend sensitively on
488 intrinsic cellular properties as well as the properties of their environment, either growth or
489 motility can dominate spreading under different conditions—leading to marked differences in the
490 dynamics and morphology of the spreading population that remain challenging to theoretically
491 describe^{172,173}. This interplay between growth and motility can also have important
492 consequences for the onset and extent of biofilm formation¹⁷⁴. A different form of self-guided
493 chemotactic spreading arises when bacteria are stressed and excrete their own
494 chemoattractant, which can lead to the formation of ordered arrays of spot-like cellular
495 aggregates¹⁷⁵ and traveling bands¹⁷⁶. Although growth is not necessary to form these patterns,
496 theoretical analysis suggests that the conditions at which they occur and their characteristics
497 can be strongly modulated by growth^{177,178}.

498
499 At even higher packing densities and on flat surfaces, and during bacterial biofilm formation of
500 some species, growth and motility are coupled in a process termed bacterial swarming.
501 Whereas the term “swarming” is used in physics to generally describe collective motion of any
502 group of objects, the term “bacterial swarming” in the microbiology literature refers specifically to
503 the movement of cells across a semi-solid surface (typically agar)^{179–182}. This movement across
504 surfaces is a 2D process and colliding cells interact strongly, often resulting in collective
505 movement and the formation of groups of cells co-moving temporarily before breaking apart and
506 regrouping¹⁸³. While the cells are forming such a highly active fluid-like phase, the cell
507 population grows and expands across the agar surface. However, there is a well-defined
508 separation between the cell population (termed “swarm”) and the uncolonized surface, and the
509 expansion speed of the swarm front is highly correlated with the bacterial growth rate¹⁸³. For
510 some species, like *Bacillus subtilis*, the swarm front of wild type cells in rich agar is nearly
511 circular, yet for several *B. subtilis* mutants and other species (notably *Pseudomonas*
512 *aeruginosa*, *Proteus mirabilis*, and *Myxococcus xanthus*), the swarm front can display a range of
513 beautiful finger-like structures that are reminiscent of viscous fingering phenomena in passive
514 fluids^{184,185}. Interestingly, these swarm front patterns often display chirality on the macroscopic
515 scale¹⁸⁶, which likely arises from the directionality of the microscopic flagellar rotation¹⁸⁷. As a
516 swarm expands across a surface, different phases of cellular behavior emerge in different
517 spatiotemporal locations in the swarm, a phenomenon that has been characterized in detail for
518 *B. subtilis*¹⁸³: While the expanding frontier displays active collective motion, the locations
519 towards the center of the swarm display clusters of cells for which motility ceases (these
520 ultimately become confluent and develop into 3D biofilms that are driven by proliferation without
521 motility). For *B. subtilis*, the transition from motile cells in the swarm into a biofilm phase may be
522 the result of MIPS¹⁸⁸, although this interpretation is contested¹⁸⁹. Whereas for *B. subtilis*
523 swarming relies on flagella-based motility, for *P. aeruginosa* and *M. xanthus* swarming relies on
524 twitching motility and gliding motility respectively, which are much slower than flagella-driven

525 motility^{190,191}. Twitching motility can also couple with bacterial proliferation during biofilm
526 formation of *P. aeruginosa*¹⁹².

527
528 Qualitatively analogous phenomena are also present in eukaryotic systems with potentially
529 much higher biological complexity. One such example is observed in epithelial monolayers,
530 often studied in Madin–Darby canine kidney (MDCK) cell monolayers. When a small colony of
531 these cells expands, cells undergo strong collective motion and form vortices and eddies.
532 Interestingly, no cells escape the mother colony¹⁹³, and thus a “liquid and vacuum” coexistence
533 forms between the liquid-like colony and the cell-free region around the colony¹⁹⁴. With time, the
534 colony grows, but interestingly the growth is not caused by the pressure of the growing cells, but
535 rather the boundary is pulled outwards by cells many layers away from the edge of the
536 colony¹⁹⁵. The resulting tensile stress feeds back on cellular growth and can favor division.
537 Corroborating this interpretation are observations of the alignment of cellular divisions with the
538 cell movement velocity field. When cells fill the experimental growth dish, they are still very
539 motile, but over time, their motion ceases and cells undergo a glass-like arrest. Whether this
540 arrest in motion is due to growth and the related density increase, or due to cellular shape,
541 adhesion, substrate friction, or other factors is a matter of ongoing debate. It may well be that
542 different biological systems undergo arrest due to different mechanisms or combinations
543 thereof.

544 [H1] Discussion

545 A wide variety of unique phenomena can arise in proliferating active matter. This diversity arises
546 from the different ways in which proliferation breaks the particle number constraint of
547 conventional active matter. Complex patterns of self-organization are driven by the injection of
548 biomass, because the associated mechanical stresses lead to deformations and potentially
549 feedback to growth rates. Additional unintuitive mechanical effects arise because the systems
550 consist of entities (cells, organisms) that are discrete. As a result, their proliferation tends to
551 locally inject degrees of freedom, leading, for instance, to unique packing structures, local
552 melting of a jammed material, or to the build-up of diffusion gradients, which can result in flows.
553 Moreover, those locally injected degrees of freedom act themselves as sources of proliferation,
554 which drive autocatalytic processes that amplify mass, correlations and information. Finally, self-
555 replication is never perfect. If the associated errors (which are mutations in living systems) are
556 heritable, they introduce new bits of information that, filtered by their effect on fitness, can be
557 autocatalytically amplified to take over the population – this is the basis of Darwinian evolution.

558
559 These different aspects of proliferation (Fig. 6) have served as an ordering principle for this
560 Perspective and may be useful to guide further research to combine soft active matter physics
561 with proliferation. Embracing proliferation will enable active matter researchers to make
562 connections to developmental biology, microbiology, population genetics and ecology — fields
563 that have for a long time explored the consequences of growth and division, but rarely
564 considered proliferation in the context of the soft matter physics of living systems. We believe
565 that reaching across the aisle from both sides will create opportunities to explore both new
566 physics and biology in concrete combinations of theory and experiments.

567
568

569 [H1] Outlook

570 Because biological systems are to some extent frozen accidents of the history of evolution, it
571 would be fruitful to have purely synthetic realizations of proliferating active matter. Doing so
572 would allow one to apply Occam's razor not only to theory but also to experiments, as it would
573 be possible to study growth-induced self-organization and evolutionary dynamics in a minimal
574 system with full control over many essential ingredients. However, although self-replication is
575 biology's bread and butter, it is extremely difficult to realize in a synthetic system. Aspects of
576 proliferation can already be readily generated, such as a volume expansion induced by osmotic
577 stresses or the generation of more degrees of freedom by breaking up inter-particle bonds.
578 There are also proposals and even some technological realizations of growth and division of a
579 fixed 'platonic' template, for example based on active droplets^{196,197}. But to date, researchers
580 seem to be reliant on biology for true self-replication capable of storing and transmitting random
581 copying errors. Nevertheless, there are promising synthetic systems composed of biological
582 parts, such as DNA origami cross-tile motifs^{198,199} or bioengineered programmable bacterial
583 systems, as an approach to replicating multicellular systems. Still, developing physical objects
584 capable of replicating themselves, with all their errors, remains one of the biggest technological
585 challenges. Meanwhile, computer models of growing and replicating entities remain the best
586 virtual realization of growing active matter, offering full control over all parameters.

587
588 Proliferation also brings formidable challenges to active matter theory, which has been
589 developed for fixed particle numbers whose trajectories neither branch nor end. Liberating
590 active matter systems from the fixed number constraint leads to inherently dynamical systems,
591 with complex information cascades running from single cells to clusters of descendants that are
592 correlated by their genealogical tree. Although some generic principles have emerged and much
593 progress has been made in the continuum description of growth-active matter^{21,108,200}, the field
594 largely lack a unified framework that accounts for mutations, inheritance, physico-chemical
595 feedbacks, fluctuations and their effects on emergent material properties and order parameters.
596 One challenge is to consistently formulate the dual picture of a birth–death dynamics forward in
597 time and the backward-time picture of a non-dividing set of coalescing active particles. Both
598 pictures are needed in eco-evolutionary scenarios in which the genealogical correlations
599 feedback onto the population dynamics.

600
601 Considering the ever-churning rare-event dynamics of actual evolution, it might never be
602 possible to fully predict long-term dynamics of proliferating active systems. But through the
603 coarse-grained physics lens, one can hope to gain a unified view of different kinds of
604 proliferating active matter and separate generic collective phenomena from microscopic details.

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1060 Acknowledgements

1061 O.H. acknowledges support by a Humboldt Professorship of the Alexander von Humboldt
1062 Foundation and by the National Institute of General Medical Sciences of the NIH under award
1063 R01GM115851. S.S.D. acknowledges funding from the Camille Dreyfus Teacher-Scholar Award

1064 of the Camille and Henry Dreyfus Foundation, Pew Biomedical Scholars Program, and NSF
1065 Grant DMR-2011750. K.D. was supported by the Swiss National Science Foundation
1066 Consolidator Grant TMCG-3_213801. J.D. acknowledges support by the National Science
1067 Foundation Award DMR-2214021 and the Sloan Foundation grant G-2021-16758. J.E. was
1068 supported by the Helmholtz ERC Recognition Award grant number ERC-RA-0044 and the
1069 Jülich Innovation Fund. B.W. acknowledges funding under Dioscuri, a programme initiated by
1070 the Max Planck Society, jointly managed with the National Science Centre in Poland, and
1071 mutually funded by Polish Ministry of Science and Higher Education and German Federal
1072 Ministry of Education and Research (UMO-2019/02/H/NZ6/00003). N.S.W.
1073 acknowledges support by the National Science Foundation, through the Center for the Physics
1074 of Biological Function (PHY-1734030); National Institutes of Health (www.nih.gov) Grant R01
1075 GM082938.

1076 Author contributions

1077 All authors contributed to all aspects of the article.

1078 Competing interests

1079 The authors declare no competing interests.
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1081 Peer review information

1082 *Nature Reviews Physics* thanks Yilin Wu, Henry Mattingly and the other, anonymous, referee(s)
1083 for their contribution to the peer review of this work.

1084 Figures

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1087 *Figure 1 | Proliferation generates tree structures.* Charles Darwin's 1837 sketch, his first
1088 diagram of an evolutionary tree (1837). (Source:
1089 https://commons.wikimedia.org/wiki/File:Darwin_tree.png)
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1093 *Figure 2 | Self-organization driven by the feedback between growth and form.* Stresses
1094 induced by differential growth in layered materials induce buckling instabilities, as shown here
1095 for different systems. **a**, *Bacillus subtilis* pellicles floating on liquid culture media. **b**, *Vibrio*
1096 *cholerae* biofilms. **c**, $\pm 1/2$ defects of dense nematics as seen in human fingerprints have been
1097 hypothesized to play key roles in directing layer formation. Part **a** adapted with permission from

1098 Ref. ²⁰¹. Part **b** adapted with permission from Ref. ⁵¹. Part **c** adapted with permission from Ref.
1099 ²⁰².

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1102 *Figure 3 | Natural selection.* Combining two different types of proliferating systems generally
1103 leads to competition for space and resources. **a**, In confined space, competition often leads to
1104 moving interfaces, here simulated for two tissue types (red and blue): a blue tissue having a
1105 higher homeostatic pressure invades the red tissue with a lower apoptosis rate with a constant
1106 velocity. As the difference increases the blue tissue invades the red ever faster (arrows) and the
1107 interface becomes unstable. **b–d**, With open boundaries, species compete to invade
1108 unoccupied territory, as shown here for colonies grown from a mixture of two different yeast
1109 strains. The strains that expand faster (yellow) tend to increase in fractional abundance. The
1110 initial mixture of each colony was 0.5% yellow and 99.5% blue. The yellow strain grows faster
1111 by 15%, yet take over only in discrete sectoring events, the number of which is controlled by
1112 fluctuations early in the expansion process (jackpot events). Part **a** adapted with permission
1113 from Ref.⁵² Parts **b–d** adapted with permission from Ref.²⁰³

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1116 *Figure 4 | Proliferating particles phase separate due to crowding-induced slowdown of*
1117 **passive diffusion.** **a** Bacteria (*A. indonesiensis*) colonizing cavities (numbered 4...8) of
1118 different length. The lower parts of the longer cavities 7 and 8 exhibit a dark phase where
1119 bacteria are densely packed (“Jammed” phases); the population in cavities 4, 5, 6 are far more
1120 dilute (“gaseous phase”). **b, c** A model of proliferating hard spheres reproduces the length-
1121 dependent transition from gaseous to jammed. **b** shows the maximum fraction $\Phi(0)$ at the floor
1122 of the cavities as a function of vertical length L of the colonized region. Colonization is only
1123 possible if L is larger than a critical length L_{est} , the “establishment” length. **c** shows the
1124 computed density profiles $\Phi(y)$ for a few select points in **b**. Figure adapted with permission from
1125 Ref.¹²⁶.

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1128 *Figure 5 | Proliferating motile matter.* Chemotactic range expansions are guided by self-
1129 produced attractant gradients (top). The resulting propagating fronts are faster than unguided
1130 range expansions, which are described by Fisher-Kolmogorov wave equations. Figure adapted
1131 with permission from Ref.²⁰⁴

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1134 *Figure 6 | Four aspects of proliferation.* Proliferation injects: biomass (part **a**), sources of
1135 proliferation (part **b**), degrees of freedom (part **c**) and, by making heritable errors, it injects
1136 information (part **d**).

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1139 Box 1: Examples of Proliferating Active Matter

1140 Growing cells, shapes and populations have been studied in mathematical biology for more than
1141 a century, often at a mean-field level, to capture phenomena observed in microbiology,
1142 development, ecology, epidemiology, population dynamics and evolution. In recent years, with
1143 increasingly quantitative and single-cell level data, it has become clear that the established
1144 mean-field pictures are often qualitatively modified by the fluctuations, susceptibility and
1145 correlations that govern assemblages of proliferating cells. Several generic model systems of
1146 proliferating active matter have thus emerged.

1147
1148 One prototypical example combining soft matter and growth is provided by microbial biofilms²⁰⁵,
1149 which can grow on solid, semi-solid or liquid substrates into resilient communities²⁰⁶. These
1150 biofilms are highly abundant on Earth, and can either be composed of clonal cells, or of diverse
1151 species. Complex physical properties of biofilms contribute to their development, evolutionary
1152 success, and their important role in human disease^{205,207}. Another example is the human gut
1153 microbiome²⁰⁸ - a dense multi-species consortium of bacteria, which helps us digest food while
1154 avoiding being flushed away by dividing roughly once a day. Finally, the highly structured
1155 tissues of an animal develop from a single fertilized egg in a process called embryogenesis
1156 which involves a rich interplay between biochemistry and mechanics²⁰⁹. Cells in tissues can die
1157 and are replaced by new cells regularly; sometimes they also mutate into a state of uncontrolled
1158 growth and develop into tumors. While these examples of complex cellular systems are
1159 biologically very different, their macroscopic behaviors share similarities that can often be
1160 understood as a combination of just a few processes such as spatial competition, movement,
1161 growth, cell division, and death.

1162
1163 The figure depicts single bacteria such as *E. coli* (part a); micro-scale bacterial biofilm colonies
1164 (part b shows *V. cholerae* surrounded by surface-attached individual cells in gray); patches of
1165 swarming bacteria (part c shows *B. subtilis* with overlaid velocity vectors colored according to
1166 cluster identity); meso-scale biofilm colonies of bacteria such as *E. coli* (part d); enhanced
1167 genetic drift at the frontier of an expanding colony of bacteria (such as *E. coli*) generating
1168 sectors with fractal boundaries (part e); infectious bacterial biofilm (yellow in part f) inside the
1169 mouse intestine (blue); multi-species biofilm on a human tongue (part g); simulations of an
1170 expanding tumor with migration (part h), with colors reflecting the degree of genetic similarity;
1171 green phytoplankton bloom in the Baltic Sea (part i).

1172
1173 *Part b* adapted with permission from Ref.²¹⁰. *Part c* adapted with permission from Ref.¹⁴. *Part d* adapted with
1174 permission from Ref.⁵⁶. *Part e* adapted with permission from Ref.²⁰³. *Part f* adapted with permission from Ref.²¹¹. *Part*
1175 *g* adapted with permission from Ref.²¹². *Part h* adapted with permission from Ref.⁹¹. *Part i* acquired by
1176 the Operational Land Imager (OLI) on Landsat 8 On July 18, 2018.
1177 (<https://landsat.visibleearth.nasa.gov/view.php?id=92462>).

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1185 Active matter locally dissipates energy to produce systematic motion. This Perspective
1186 highlights proliferation as a special type of activity that breaks particle number conservation and
1187 thereby gives rise to a unique set of collective phenomena characteristic of life.
1188