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Roadmap for Animate Matter

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Roadmap for Animate Matter

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Abstract
Humanity has long sought inspiration from nature to innovate materials and devices. As science advances, nature-inspired materials are becoming part of our lives. Animate materials, characterized by their activity, adaptability, and autonomy, emulate properties of living systems. While only biological materials fully embody these principles, artificial versions are advancing rapidly, promising transformative impacts in the circular economy, health and climate resilience within a generation. This roadmap presents authoritative perspectives on animate materials across different disciplines and scales, highlighting their interdisciplinary nature and potential applications in diverse fields including nanotechnology, robotics and the built environment. It underscores the need for concerted efforts to address shared challenges such as complexity management, scalability, evolvability, interdisciplinary collaboration, and ethical and environmental considerations. The framework defined by classifying materials based on their level of animacy can guide this emerging field to encourage cooperation and responsible development. By unravelling the mysteries of living matter and leveraging its principles, we can design materials and systems that will transform our world in a more sustainable manner.

Introduction

Humankind has always looked at nature for inspiration to design new devices and materials. As science and technology progress, nature-inspired artificial materials that previously could only exist in the realms of myths and fantasy [1] are now part of everyday life, including self-healing materials [2, 3], energy and water harvesting systems [4, 5], and autonomous devices mimicking cognition [6, 7].

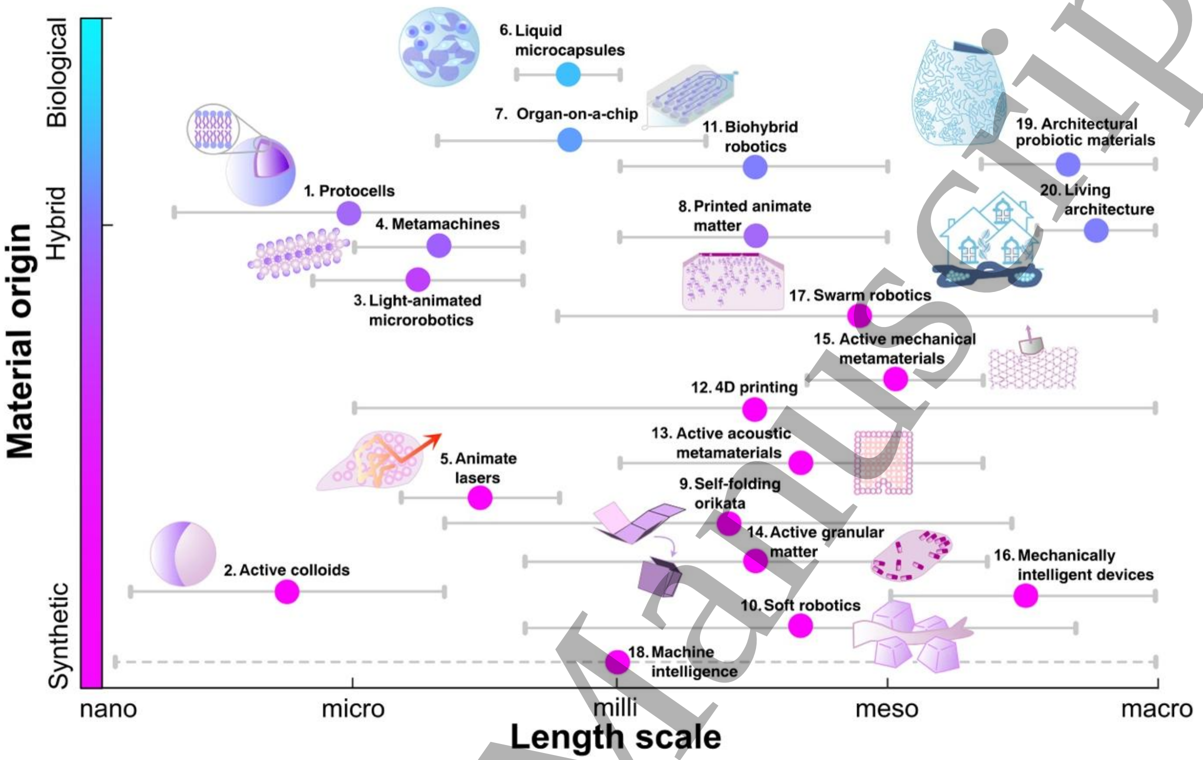

Figure 1 | Examples of animate materials to date. A plot showing the material origin (synthetic, hybrid or biological) versus length scale (from nanoscopic to macroscopic) for the different animate systems discussed in this roadmap, numbered based on how they appear in the table of contents (roughly as a function of scale and foundational relevance to understand following sections). In the roadmap, animacy is defined as the cumulative level of activity, adaptiveness and autonomy of a system. Only biological materials (not represented here) can be considered fully animated to date. The colour code (the position along the *y*-axis) highlights the material origin: most systems are fully artificial (synthetic), while some incorporate biological elements to different extents (hybrid). For each system, we represent the typical sizes of the final materials rather than those of their building blocks: we show both average size (coloured dot) and possible size range (horizontal lines). Spanning all scales, machine intelligence (Section 18) does not have a physical size (dashed horizontal line rather than solid), but it is a useful tool to design other systems at all scales and increase their level of animacy.

Animate materials are a novel class of potentially transformative artificial materials reproducing key properties of living systems [8]. They are not alive but are defined according to the **three principles of animacy**, being active, adaptive and autonomous [8]. By being **active**, they can transform energy available to them in the environment to perform tasks and work, such as motion, growth, communication, etc. Their **adaptive** nature means that they can individually and collectively sense, process and respond to environmental changes and stimuli, often exhibiting emergent behaviour. Finally, being **autonomous**, they can initiate behavioural changes based on a certain internal degree of information processing (which may or may not include memory) without external monitoring or control by human agents. The combination of these three properties sketches a future where materials are more efficient, resilient, and sustainable with the capabilities for, e.g., multitasking, self-regulation, self-healing, and even evolution. Currently, examples of these materials are being developed at all human-relevant length scales (**Figure 1**), from molecular assemblies (see, e.g., **Section**

1: Protocells) to urban ecosystems (see, e.g., **Section 20: Towards living architectures**): some materials are mainly artificial (see, e.g., **Section 2: Active colloids**, **Section 14: Active granular matter** and **Section 18: Machine intelligence**) while others hybridize biological materials with synthetic ones more (see, e.g., **Section 6: Liquid microcapsules**, **Section 7: Organ-on-a-chip**, **Section 11: Biohybrid robotics** and **Section 19: Architectural probiotic materials**), hitchhiking on natural properties to improve animacy of human-made systems.

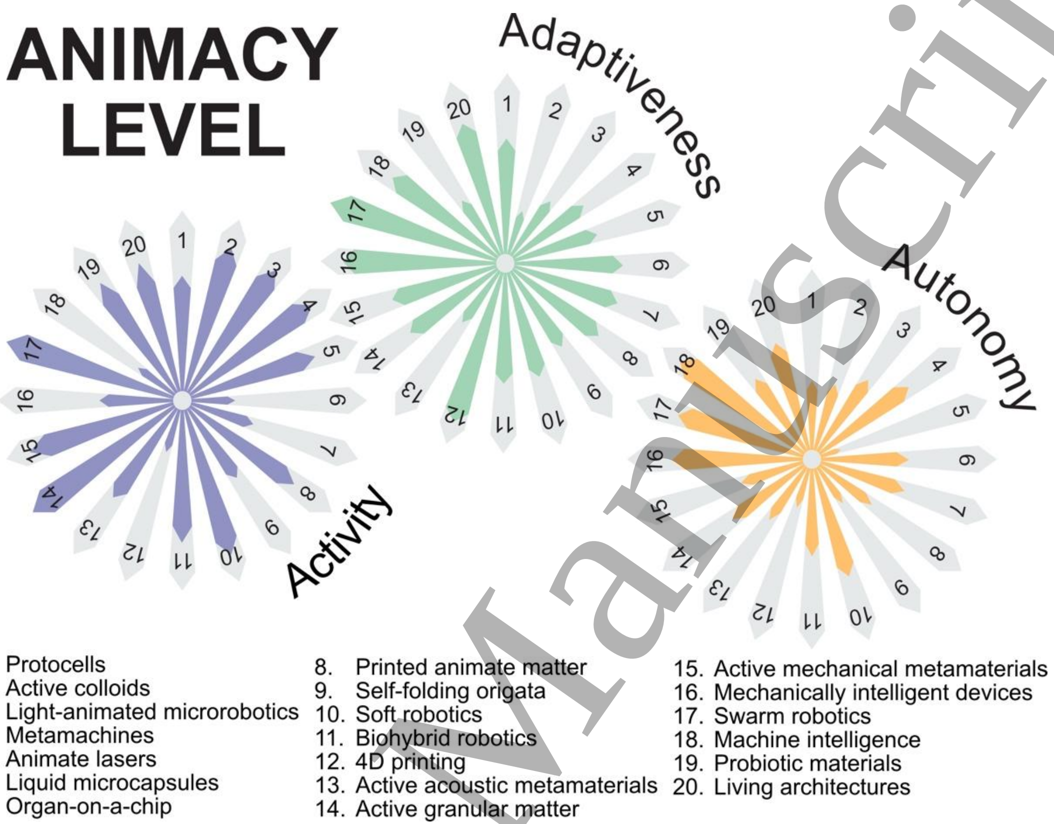

Figure 2 | The three properties of animacy. The three polar plots sketch our jointly perceived level of development for each principle of animacy (i.e., activity, adaptiveness and autonomy) for each system discussed in this roadmap. The polar coordinate represents the various systems, while the radial coordinate represents the level of development (from low to high) that each system shows in the principle of each polar plot. Ideally, within a generation, all systems will fill these polar plots to show high levels in each of the three attributes of animacy. For now, only biological materials (not represented here) can be considered fully animated. In general, most artificial systems to date show an average level of overall animacy lower than biological systems, with mesoscopic robotic systems (e.g. **Sections 16: Mechanically intelligent devices** and **Section 17: Swarm robotics**) typically scoring higher in the three principles due to the possibility of programming them directly. As can be expected, due to the miniaturisation problem, overall animacy levels tend to decrease going from the macroscopic scale to the smaller scales. The polar plots highlight the fact that efforts from the research community have not been equally divided to improve the three properties of animacy. Of the three principles, activity has seen more development on average, followed by adaptiveness and, finally, autonomy that lags behind the other two properties. While activity and adaptiveness have improved thanks to material engineering, autonomy is more difficult to achieve as it requires, e.g., computation to be implemented. This task is notoriously difficult when moving from macroscopic systems to smaller length scales due to current limitations in miniaturization. Interestingly, some systems discussed in this roadmap have mainly seen development in one property of animacy and score relatively lower on others: for example, **Section 2: Active colloids** and **Section 5: Towards animate lasers** score relatively high on activity; **Section 12: 4D printed systems** stand out for adaptiveness while **Section 18: Machine intelligence** jointly for adaptiveness and autonomy. For each system, the overall level of animacy is cumulatively given by all three properties. As a word of caution, our perception transpiring from these polar plots is not meant to be prescriptive but rather a starting point for future discussion and development.

To date, indeed, only living materials score highly under all three principles as these typically led to competitive evolutive advantages, while materials created through human agency typically lag behind their natural counterparts in at least one core principle, with exceptions being mesoscopic and macroscopic robotic systems such as **Section 16: Mechanically intelligent devices** and **Section 17: Swarm robotics** (**Figure 2**) [8]. For example, **Section 2: Active colloids** and **Section 5: Towards animate lasers** score relatively high on activity but are still limited in adaptiveness and autonomy, while **Section 18: Machine intelligence** shows high levels of autonomy and adaptiveness but fare lower in terms of activity. Miniaturising animacy presents particular challenges due to issues in scaling components (e.g. actuators, sensors, memories, processing units) and functionalities to smaller scales. Nonetheless, worldwide research effort on the topic of animate materials is ever growing driven by both the fundamental and applied challenges they represent. On the more fundamental aspect, developing and studying animate materials can shed light on the physics of living systems. On the more applied side, these materials hold great promise to revolutionize our technology in diverse sectors, including medicine, robotics, and infrastructure towards a more sustainable future. It is therefore a matter of time until artificial, fully animate materials will leave the realm of curiosity-driven research to start contributing to human technology. In the next decade, we could already see some first, simple applications of animate materials, such as targeted drug delivery (**Section 1: Protocells**), artificial tissues and organs (**Section 6: Liquid microcapsules** and **Section 7: Organ-on-a-chip**) as well as a range of novel robotic systems (**Section 10: Soft robotics**, **Section 11: Biohybrid robotics** and **Section 17: Swarm robotics**). We can however expect more impactful, game-changing applications to appear on a generational scale providing that this type of research keeps being supported and funded, from autonomous microscopic tools for sensing, therapeutics and diagnostics (**Section 2: Active colloids**, **Section 3: Light-animated microrobotics**, **Section 4: Metamachines** and **Section 5: Towards animate lasers**) to fully sustainable and autonomous buildings (**Section 19: Architectural probiotic materials** and **Section 20: Towards living architectures**).

This roadmap consists of a series of twenty authoritative perspectives that capture the current state of research in animate materials in different disciplines (Figs. 1-2). We organised them roughly based on average system's size and by their foundational relevance to understand following sections, with the caveat that many sections (e.g., Section 9: Printed animate matter, **Section 9: Self-folding orikata**, **Section 10: Soft robotics**, **Section 11: Biohybrid robots**, **Section 12: 4D printed systems**, **Section 14: Active granular matter**, **Section 17: Swarm robotics**) span across several scales. By no means intending to be an exhaustive list, we highlight representative areas where the concept of animate materials has found (consciously or not) application by driving advancements in materials science and has helped our understanding of living matter. We start discussing **Section 1: Protocells**, nanoscopic and microscopic compartments laying the foundations to synthetic life. A key challenge in the study of these systems is understanding dissipative self-organization at the microscale. This challenge is shared with **Section 2: Active colloids**, microscopic particles exhibiting autonomous motion that are building blocks for bioinspired functional devices and materials. Examples are described in **Section 3: Light-animated microrobotics**, **Section 4: Metamachines** and **Section 5: Towards animate lasers**. There is a similar drive to obtain biologically inspired functional materials at larger scales up to millimetre and centimetre lengths. Our roadmap highlights applications in tissue engineering and manufacturing with three sections on **Section 6: Liquid microcapsules**, **Section 7: Organ-on-a-chip** and **Section 8: Towards printed animate matter**. The aspiration to shape-shift autonomously is explored in **Section 9: Self-folding orikata**, where structures transform based on stimuli, in **Section 10: Soft robotics**, using flexible materials for lifelike movements and functionalities, in **Section 11:**

Biohybrid robotics, a class of soft robots combining synthetic and biological components, and in **Section 12: 4D printed systems**, where manufactured materials change over time in response to their environment. Our roadmap then examines mesoscopic systems that, like their smaller counterparts (e.g., **Section 1:Protocells** and **Section 2: Active colloids**) are also concerned with concepts of dissipative self-organization, such as **Section 13: Active acoustic metamaterials**, **Section 14: Active granular matter**, and **Section 15: Active mechanical metamaterials**, where, respectively, non-reciprocal wave-matter interactions, particle dynamics and shape-changes lead to counterintuitive science and mesoscopic functionalities. **Section 16: Mechanically intelligent devices** builds on these ideas to facilitate environmentally adaptive individual robots that spontaneously integrate sensing, computation and locomotion. This concept, known as physical intelligence, is also at the core of other robotic systems encountered in the roadmap (**Section 10: Soft robotics** and **Section 11: Biohybrid robotics**). Scaling up from individual components to collective intelligence, **Section 17: Swarm robotics** presents decentralized systems of simple robots mimicking biological swarms. The emergence of spontaneous collective "intelligent-like" behaviours is shared with other robotics examples encountered earlier in the roadmap: **Section 3: Light-animated microrobotics**, **Section 4: Metamachines** and **Section 14: Active granular matter**. Swarm intelligence is also a natural precursor to **Section 18: Machine intelligence**, where AI-driven decision-making further enhances animate materials at all scales with adaptive and predictive functionalities. Our roadmap culminates in the integration of living systems with materials at architectural scales. **Section 19: Architectural probiotic materials** introduce living microbes into the built environment, allowing for self-regulation and adaptation to support human health. Finally, **Section 20: Towards living architectures** generalise these concepts to entire buildings and infrastructures that evolve, self-repair, and respond to their environment and the climate.

Our roadmap embarks on a journey through this dynamic landscape, charting pathways across disciplines and length scales relevant to human experience, from nanotechnology to robotics, from synthetic biology to artificial intelligence, from metamaterials to living architectures. In each section, connections to other closely relevant topics are highlighted via direct references identified by the contributing authors. We summarize these connections as a connectivity graph in **Figure 3**, which reflects how experts across the field understand the conceptual links between topics. Notably, many connections are already established, reflecting the community's growing awareness of shared ideas and challenges. However, the graph also reveals that many interactions remain confined to similar scales or related disciplines.

With this roadmap, we aim to highlight common challenges and opportunities emerging in the design of animate materials at all scales without being dismissive of the unique challenges and opportunities emerging in each discipline and length scale. A recurring theme across contributions is that animate materials represent a convergence of physics curiosity, chemical and biological insights and engineering ingenuity. The field fosters the creation of materials with unprecedented functionalities and potential applications, some of which are already within reach in the next decade. To realise this overarching goal, a concerted effort across disciplines and scales is needed. Efforts to develop animate materials have often been siloed, focusing mainly on specific systems and scales in isolation or getting inspiration from closely related systems and disciplines (Fig. 3), such as for protocells (**Section 1**), robots (**Sections 10, 11** and **17**), or living architectures (**Sections 19** and **20**). While this proximity-based inspiration is a natural starting point, the field must now broaden its scope. Many analogous questions and technical challenges resonate across multiple scales, systems and disciplines, even if they manifest differently depending on the context. Artificial intelligence (**Section 18**) offers a concrete example of a cross-cutting tool that is already informing multiple scales, from guiding the behaviour of swarms and robotic systems (**Sections 10, 11, 16** and **17**) to optimizing molecular design in protocells and active colloids (**Sections 1** and **2**). Similarly, concepts in robotics (**Sections 10, 11, 16** and **17**), such as autonomy, sensing, and adaptability, are beginning to influence smaller-scale systems (**Sections 3, 4** and **5**) that cannot yet implement computation directly but can mimic intelligent behaviour through clever material design.

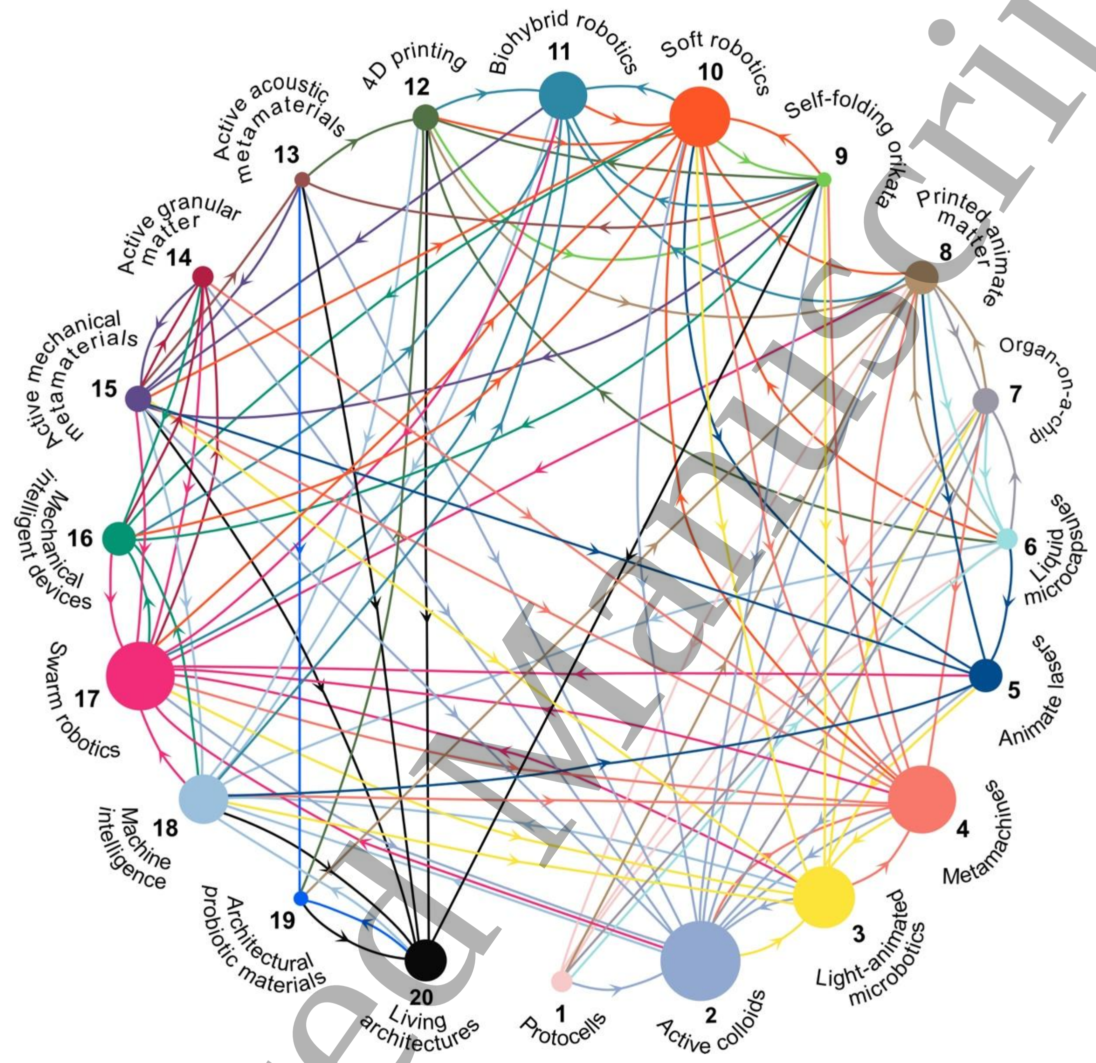

Figure 3 | Connectivity graph between roadmap sections. Each node represents a section of the roadmap, with directed links indicating references made from one section to another, as perceived by the contributing authors. Node size reflects the number of incoming references, and colours are used solely for visual clarity. Rather than offering an objective measure of importance, the graph captures the collective perception of conceptual links within the field. It reveals a rich network of connections already recognized by researchers, while also highlighting opportunities to strengthen ties, particularly across disciplinary boundaries. This visual map underscores the importance of fostering dialogue and collaboration across scales and domains to unlock the full potential of animate matter.

To fully harness the potential of animate matter, we must actively promote dialogue and collaboration across currently disconnected areas. Shared open challenges include: understanding, modelling and controlling dissipative self-organization and complexity emerging from animacy; miniaturizing its components, scaling up and deploying laboratory prototypes to real-life applications; defining a unified language to discuss animate materials; fostering opportunities for interdisciplinarity; promoting cross-fertilization of ideas across systems; and weighting the ethical, environmental and socioeconomic implications of developing animate materials. Developing shared frameworks and extending ideas and methods beyond disciplinary boundaries will be crucial to move from isolated achievements toward fully coherent implementation.

Key for the advancement of the field is the coordination of multiscale research efforts aimed at integrating and combining concepts and approaches from different systems and scales. The emergence of complex functionality in biological systems relies on the existence of intercommunicating hierarchical structures, from molecules to entire ecosystems via the formation of, e.g., macromolecules, cells, tissue and organisms [9]. Reproducing this multiscale approach in synthetic animate materials requires the development of interconnected hierarchical levels that can communicate and, if needed, store information effectively across scales. Succeeding in this task within the next generation of scientists and engineers paints a not-so-distant future with the creation of new animate materials presenting a hierarchy of structures and functions, thus unleashing the full scientific and technological potential of this class of materials and fulfilling their promise for animacy in terms of, e.g., self-regulation, self-healing, and even evolution.

While this is a grand aspiration for the future, there is no plain sailing ahead. The feasibility of this roadmap's projections unavoidably depends on socioeconomic factors that are difficult to predict at the time of writing such as industrial investment priorities, regulatory landscapes as well as socioeconomic and ecological uncertainties. Nonetheless, the academic and technological developments suggested in this roadmap are guided by existing global initiatives, such as The United Nations Sustainable Development Goals (SDGs). These goals provide a crucial framework for aligning this roadmap's aspirations for animate matter with pressing global needs, thus remaining both scientifically ambitious and practically relevant. Priority areas for animate matter include "Good Health and Well-being" (SDG 3), "Affordable and Clean Energy" (SDG 7), "Industry, Innovation, and Infrastructure" (SDG 9), "Sustainable Cities and Communities" (SDG 11), "Responsible Consumption and Production" (SDG 12), and "Climate Action" (SDG 13). With favourable alignment between academia, industry and policy makers in the next decade, animate materials could start serving as a critical enabler for a range of global challenges, such as:

- **Circular economy**. Driven by resource scarcity, extended producer responsibility regulations, and net-zero carbon commitments, the transition to a circular economy requires the development of materials that are self-repairing, biodegradable, and energy efficient. Animate matter could provide new solutions, e.g., from packaging with bioengineered orikata (**Section 9**) and 4D printed materials (**Section 12**) that degrade on demand, reducing plastic pollution, to the construction industry with self-healing probiotic materials (**Section 19**) that repairs cracks using microbial activity, reducing maintenance costs and emissions.
- **Personalised medicine and aging populations**. The demand for automation is increasing due to aging populations and labor shortages in healthcare and manufacturing. Robotics-driven eldercare solutions are gaining traction, highlighting a need for adaptive, soft, and safe materials that can interact with humans (**Sections 10** and **11**). Active drug carriers (**Sections 1** and **2**), shape-morphing prosthetics (**Section 10**), bio-responsive implants (**Sections 6** and **8**), and self-repairing synthetic tissues (**Sections 6** and **7**) could revolutionize medical treatments. Wearable biosensors made from printed animate matter (**Sections 7** and **8**) could enable real-time health monitoring, supporting preventive medicine and telehealth initiatives.
- **Climate resilience**. Animate matter offers the potential to create, develop and evolve materials that have the capacity and intelligence to respond to current and impending climatic and ecological changes. For example, chemotactic nanobots (**Sections 1** and **2**) could speed

up environmental cleanup efforts, addressing challenges like water contamination and marine pollution. Conversely, climate-adaptive building materials and living architectures (**Sections 19** and **20**) could provide resilience to future challenges including pandemics, global warming and biodiversity loss.

Finally, the animacy framework of this roadmap focusing on active, adaptive and autonomous materials is not meant to be prescriptive. We hope it will serve as a flexible framework for this emerging field defining a common language that can guide development across disciplines and length scales. As we embark on this multidisciplinary journey, we invite researchers, engineers, and visionaries alike from diverse backgrounds to join us in shaping the future of animate materials in a socially responsible and sustainable manner. Together, we can unravel the mysteries of living matter, harnessing its principles to create a new generation of materials and systems that are not merely passive objects, but active symbiotic participants in the vast fabric of human life and society.

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01 – Protocells

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Status

The mystery of the origins of life involves understanding and harnessing the structural and functional requirements to transition from non-living to living matter. Protocells are primitive compartments (assembled from prebiotic components) considered precursors to living cells [1]. Synthetic protocells provide a unique and versatile platform to investigate fundamental aspects (e.g., interactions between building blocks, environmental requirements) and design simple life-like functionalities. These artificial systems also hold promise for short-term applications such as nanomedicine (drug delivery, biosensing) and longer-term developments such as energy harvesting, tissue engineering (see also **Sections 6, 7** and **8**) and environmentally friendly materials.

Protocells are spatially confined nano- or micro-compartments (100 nm – 100 µm) emerging from the self-assembly of different (macro)-molecules. Compartmentalization establishes chemical environments separated from their surroundings (**Figure 1.1A**). The simplest protocell models are membrane-less droplets (e.g., coacervates and emulsions), forming distinct microenvironments through liquid-liquid phase separations, akin to intracellular organelles known as biomolecular condensates. Coacervates formed by attractive interactions within or between polymers, surfactants or biomolecules (e.g., nucleotides, peptides) [2] can encode chemical functionalities specific to their composition and serve as dynamic reactors when formed and dissolved under external stimuli (e.g., temperature, pH, light). The minimalistic synthetic analogues of cell membranes are membrane-bound protocells [3], believed to have evolved from coacervates [4]. These vesicle-like structures, typically formed by bilayers of amphiphilic lipids or polymers that spontaneously self-assemble in water (and/or assisted via double emulsions and hydration methods), allow for compartmentalization and encapsulation of biomolecules with selective permeability for environmental exchange mimicking cell membranes properties.

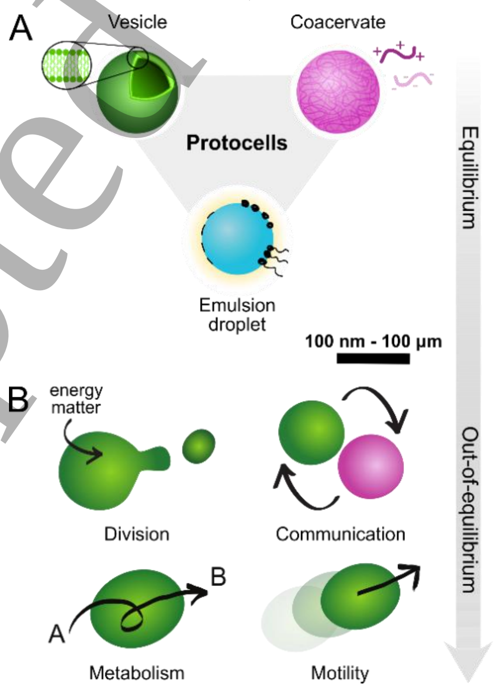

Figure 1.1 | Incorporating out-of-equilibrium properties in protocell design. (**A**) Schematic representation of the main models for protocellular compartments, including coacervates, emulsion droplets and vesicles. (**B**) Out-of-equilibrium processes characteristic of life-like protocells, including self-replication, communication, metabolic activities and motility.

The primary focus of protocell research is understanding and predicting the assembly and stability of the required minimal building blocks. However, recent efforts have expanded to out-of-equilibrium processes (**Figure 1.1B**), driven by intake of environmental energy and matter – a crucial step in transitioning to autonomous, self-sustainable units [5]. While reaction cycles, growth, self-replication and chemical communication are achievable through materials design approaches, physical transformations (e.g., self-propulsion or morphogenesis) still mostly rely on external actuation. The development of self-propelled protocells (e.g., active coacervates [6] or lipid vesicles [7,8]) mirrors cellular dynamics and their interactions with environmental cues, potentially offering insights into survival strategies of early pre-cellular units.

Advances in hybrid protocells, combining lipid vesicles with proteinosomes or coacervates, mimic the complex hierarchy of high-evolved living cells. This structural organization enhances spatially localized biochemical processes but also allows the combination of incompatible reactions within the same vessel together with their temporal orchestration. Sophisticated protocells have recently shown morphogenetic capabilities [9], especially when integrated with energy-sustaining bacterial components.

Current and Future Challenges

Creating life-like protocells using simple architectures poses a significant challenge, requiring solutions to key issues in their adaptive, active, and autonomous nature:

- **Stability.** Despite their structural simplicity, environmental perturbations (e.g., pH, light, temperature) might affect protocells' long-term stability, limiting their use in experiments and applications (e.g., oxidation of phospholipids, coalescence of coacervates). Yet, environmental changes are crucial to trigger certain minimal life-like processes. Understanding the relationship between stability and spatiotemporal evolution is vital, especially for implementing functionalities in non-equilibrium conditions.
- **Autonomous vs actuated.** The formula for self-regulation remains a complex puzzle driven by thermal forces and external stimuli. Unlike living cells that move, divide and continuously replace components to maintain integrity, protocells might reach a static state after self-assembly without external actuation. The challenge lies in designing self-regulating 'factories' via either continuous matter intake or internal machineries that produce their components, regenerate their structure and maintain their functionalities. The design of non-equilibrium processes based on dissipative (or transient) self-assembly and -disassembly remains an open challenge.
- **Chemical programming.** Integrating multiple (bio)chemical processes to achieve autonomous behaviours and developing a transcription-like machinery pose major challenges. This requires chemical compatibility amongst multiple components and managing cross-reactivity. Compartmentalization is essential to regulate these parameters, by allowing selective permeability and solubility. Yet, spatial localization can affect the reactivity of chemical species (e.g., due to crowding or interactions with soft interfaces). Moreover, linking molecular content with structural characteristics might mimic genotype-phenotype correlations, but specificity and variety of building blocks and reactions are currently limited.

- **Motility.** Motion is ubiquitous to all living systems as a survival tool. Self-directed motion is related to crucial intercellular migration or protocell interactions. These autonomous and spatial-dependent dynamics involve intricate exchanges of matter and energy (see also **Section 2**). Designing efficient motility mechanisms and understanding how softness and structural adaptation to dynamical stress affect protocells remains untapped.
- **Protocell interactions**. Understanding and replicating the communication and physical interactions between protocells, such as chemical signalling or fusion, involve high levels of physicochemical understanding of all elements involved. This includes studying competition for resources and predatory/cooperative behaviours among protocells. In this context, interactions between membrane-bound and membrane-less droplets are gaining increasing attention.
- **Reproducibility.** While nanoscale compartment production is rather optimised, cell-sized protocell fabrication methods are not achieving uniform composition, size, and geometry. This precision is essential for robust statistical studies across large samples. On one hand, microfluidic techniques – despite their popularity – suffer from their sensitivity to chip fabrication. On the other hand, template-assisted methods are not fully reliable to control size or encapsulation of colloidal or molecular units. Consequently, the variability in experimental approaches complicates reproducibility and hinders scaling protocells reliably for advanced applications.

Advances in Science and Technology to Meet Challenges

While actuated cell-like compartments (e.g., nanovesicles) are employed in technological and medical applications such as drug delivery, protocells with minimal self-regulated processes are mainly utilized as models to investigate fundamental life-like mechanisms rather than as fully autonomous systems. Short-term protocell research focuses on developing self-sustaining systems capable of energy conversion, regenerative cycles, and autonomous growth (<10 years). These efforts lay the foundation for adaptive, life-like systems with transformative applications in medicine, environmental sustainability, and materials science (on longer timelines, i.e., >10-20 years), addressing societal challenges like carbon capture, biofuel production, plastic waste management, tissue engineering, and antimicrobial solutions.

To meet these challenges, we propose the following technological and scientific approaches:

- **Building blocks design.** The rational design of novel building blocks is crucial for integrating advanced chemical networks into protocells to achieve life-like processes (e.g., chain reactions in membrane-bound compartments, molecular self-replication, motion, dissipative self-assembly). Key is the development of new molecules and building blocks that can initiate and maintain out-of-equilibrium processes. This involves accepting that prebiotic compositions are not fully replicable and the need to explore alternative systems. The use of enzymes presents a powerful chemical tool in that direction. Enhancing the performance and compatibility of enzymes through directed evolution could expand the range of functional chemical modules that can be integrated within protocells. Additionally, organic chemistry is crucial in developing unique and novel abiotic – synthetic – molecules that perform similar functions to prebiotic ingredients.
- **Conceptual and experimental frameworks.** Integrating conceptual models into experimental design might help identify and create combinations and interactions of building blocks for engineering self-regulated protocells. Assembly Theory [10] and its predecessors quantify the degree of selection in an ensemble of evolved units and identify molecular biosignatures that could lead to life-like compartments. The emergence of systems chemistry [11] also provides

valuable insights for designing dynamic chemical networks in complex systems composed of multiple interacting components and understanding how molecular interactions give rise to life-like behaviours (e.g., out-of-equilibrium assemblies, autocatalysis), which are essential for advancing protocell research.

- **Tool development.** Microfluidics is a well-established, high-throughput production method and environmental control platform (e.g., through light or local pressure). Intrinsically, this technique is capable of extensive parameter screening and optimization, which can be time-consuming and beyond current manpower capabilities. Developing microfluidics-automated reactions mimicking 'digitalization chemistry' approaches (i.e., based on chemical programming languages and automatized robotic platforms) might help screen an otherwise impossible condition range. Artificial intelligence is a valuable emerging tool to analyse vast amounts of data and predict possible outcomes from experimental information on protocell design.
- **Protocol standardization.** Due to the sensitivity of protocells to environmental changes and protocol variations, online platforms for sharing data and protocols are crucial to facilitate the unification of results, leading to parameter standardization otherwise difficult to control in individual laboratories (e.g., humidity and solvent quality). Extending experimental efforts to alternative environments (e.g., high-pressure settings or microgravity in sounding rockets or parabolic flights) can offer novel approaches to understanding the impact of gravity and pressure on the formation and evolution of protocells.
- **Knowledge sharing and training.** Establishing graduate programs focused on this topic and fostering interdisciplinary training through doctoral networks are critical for advancing the field and ensuring effective knowledge transfer. International collaboration is equally essential, with coordinated efforts from scientists, funding agencies, and organizations such as synthetic cell initiatives. The latter unite multidisciplinary environments under shared objectives, which have successfully driven innovation and secured impactful funding opportunities.

Concluding Remarks

The study of protocells is pivotal in understanding the transition from non-living to living matter, marking a significant advance in bioinspired materials, especially by integrating in- and out-of-equilibrium processes. Protocells, considered as precursors to complex cells, offer insights into the fundamental interactions of molecular building blocks within controlled environments. This research is key to understanding the assembly, stability, and evolution of these minimal units towards autonomous systems. Challenges in protocell research include achieving stability under environmental changes, designing self-regulating systems, and integrating multiple chemical functionalities. These efforts aim to replicate life-like behaviours, such as motility, communication, growth, and replication, mirroring the dynamics of living cells and offering insights into early life forms. The development of sophisticated protocells, capable of morphogenesis and integrated with energy components, represents a step towards complex architectures and life-like behaviours. This field extends beyond understanding the origins of life, by also contributing to the development of microscale materials with unique, self-sustaining features across synthetic biology, soft matter, systems chemistry, and biophysics. While significant advances have been made, challenges in sustainability, self-regulation, and evolutionary capabilities remain, making protocell research a rich area for future scientific exploration, with potential long-term applications in energy harvesting, environmental remediation, catalysis and biomedicine.

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02 – Active colloids

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Status

Biological microswimmers have evolved over millions of years to perfectly adapt their swimming mechanisms to the low Reynolds number conditions dictated by their small size. Physicists have been fascinated by various aspects of them over the last century, leading to seminal work such as the postulation of the Taylor sheet [1], Purcell's interpretation of "low Reynolds number life" [2] and Anderson's work on phoresis [3]. In the early 2000s, researchers were intrigued by the idea of artificially recreating the ability of these biological micro-entities to move at the microscale.

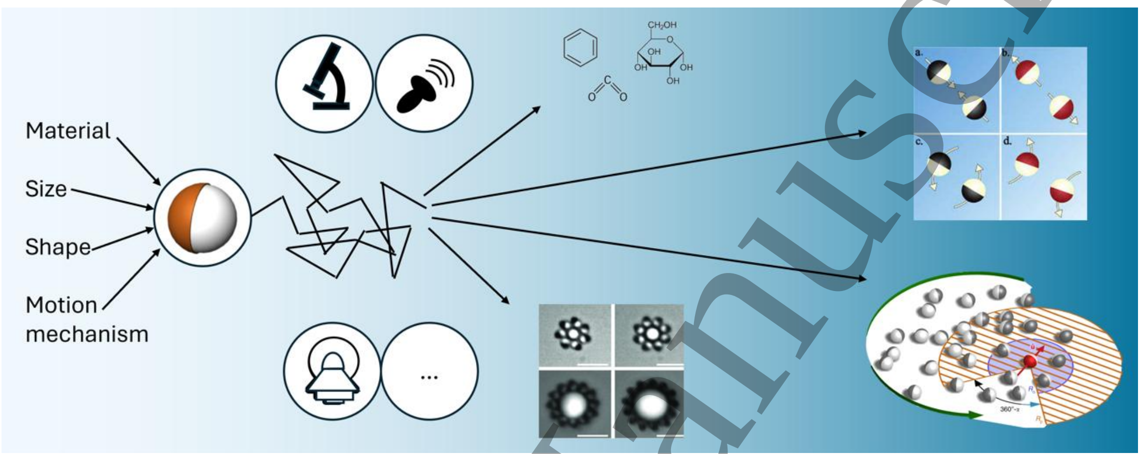

Figure 2.1 | Influencing and detecting emerging behaviours in active colloids. (Left) The swimming behaviour of active colloids is influenced by several factors such as material, shape, size and motion mechanism. (Middle) Detection is largely dependent on the environment, with optical detection being the simplest although it relies on transparent environments; ultrasonic or magnetic properties extend the range of imageable environments, and new alternatives are constantly being developed. (Right) Beyond controlling the motion properties (from diffusion to ballistic), the various fuel sources (first arrow from the top), the interactions between individuals (second and third arrow from the top) and larger groups (third and fourth arrow from the top) can lead to promising emerging behaviours. Insets (clockwise from the top): fuel sources; pair interactions reproduced from [4], use permitted under the CC-BY 4.0 licence; colloidal swarm reproduced from [5], use permitted under the CC-BY 4.0 licence; cogwheels reproduced from [6], use permitted under the CC-BY 4.0 licence.

Along with pioneering experiments with bimetallic rods, a theoretical paper postulated the active motion of a sphere with a catalytic patch. Subsequently, the first self-propelling colloidal spheres were proposed using an inert particle half coated with platinum that moved autonomously when placed in a hydrogen peroxide solution. This spherical, reliably moving model system (known as a Janus particle) allowed closer interaction between theory and experiment, leading to the exploration of different behaviours and the generation of a number of different modelling approaches able to capture different aspects of experimental observations. Specific proof-of-concept applications have appeared in fields as diverse as sensing, biomedicine and environmental remediation. In parallel, the active matter community began to explore different material and fuel combinations for artificial microswimmers, providing a broader insight into a range of swimming mechanisms and their limitations. These experimental realisations comprise a large size range from a few nanometres for enhanced Brownian systems up to several micrometre-sized structures. These investigations, progressing in parallel with theoretical advances, have not only demonstrated the versatility of these experimental systems but have also deepened our understanding of self-propulsion at the microscale. Progress has been made on the fabrication of active colloids using different materials by masking, phase separation, self-assembly, microfluidics, and chemical modification. These materials allow harvesting a plenitude of energy sources which influence the motion mechanism (both the translational and rotational motion of particles), increase biocompatibility, control states, speeds and motion modes and control interactions, all crucial properties for real-world applications.

In more recent years, active colloids have been challenged by a variety of stimuli and have been integrated with digital technologies. For example, an artificial computer vision model for active colloids has been proposed to observe the consequences of different visual cones on collective interactions [7]. Looking towards applications beyond colloids and the obvious drug delivery, biomedical uses depend on imaging independent of optical visibility. If visibility is impeded by particle size, dynamics light scattering (DLS) and other scattering techniques have become essential. For larger microrobots alternative imaging strategies using ultrasound, acoustic techniques or magnetic resonance can be used to extract information about positions, behaviours and speed of the active particles [8]. However, real-world industrial applications of active colloids, including microscale sensors, advanced control systems, and artificial intelligence, are yet to be developed.

Current and Future Challenges
Challenges for active colloids include:

- **Systematic comparisons.** One of the major challenges that will help move the field of active colloids from isolated knowledge to full understanding is to perform proper **comparisons between different active colloidal systems**. Changing propulsion mechanism, shape, and material affects many individual and collective behaviours (**Figure 2.1**, see also **Sections 3** and **4**) but experimental studies that evaluate these effects are sparse because unfortunately, this type of study is not highly valued in the scientific community due to a lack of innovation. As a result, such studies are much more difficult to fund and publish, and the field is still far from reaching out to industrial partners who would contribute to a broader body of knowledge. Approaches such as interlaboratory comparisons, which would lead to greater standardisation and cross-comparability of results (e.g., FDA approval, goals, funds), have been discussed but not yet implemented. Similarly, at the level of understanding certain phenomena that have often been observed for one type of microswimmer, studies across the spectrum comparing shapes and swimming mechanisms are largely lacking.
- **Advanced materials**. A major challenge, which has gained momentum as the community has grown and expanded beyond physics, is **the integration of 'new chemistry'** and a wider range of materials to increase the flexibility and options available to experimental systems, hand in hand with increased ecological awareness and biocompatibility, especially for biomedical and environmental applications.
- **Digitalization**. Although the first steps towards digital control have been taken, the integration of **digital features and computational capabilities** is still in its infancy. While it is desirable to increase the computing capacities of artificial active matter, new strategies must be developed because the integration of traditional transistor-based computing facilities on colloids has been very limited due to size constraints, mostly non-planar morphology and frequent imperfections of colloidal particles compared to traditional *in-silico* components. This is exemplified by the strategy for information storage, which uses magnetic switching in percolated iron films previously deposited onto the colloids [9]. While alternative computational modes have begun to take shape for biologically active materials [10], their artificial analogues are starting to take their first steps [11].
- **Swarms**. A future challenge that seems to be very closely related to applications is to look at **larger collectives** and model behaviours across scales (see also **Sections 3** and **4**) [12]. While a single micromotor might provide enough signal for sensing, most cargo delivery or

remediation applications will require more than an individual microswimmer to perform a given task. Therein, not only the emergence of complexity is posing a challenge, but also the sheer volume of data to handle from large numbers of individuals, their trajectories, spatial distribution, etc. (see also **Section 17**).

Advances in Science and Technology to Meet Challenges

To elevate research on active colloids from a curiosity-driven domain to a technology contributing to our economies and unlocking potential to solve global problems using microrobotics, a few advances are still required to face the current and future challenges:

- **Imaging**. While advances in microscopy have and continue to make tremendous impact for visualisation of small features, improvement in processes and techniques such as advanced particle image velocimetry to detect flows and innovative markers and signalling can continue to enable new levels of understanding, providing more detailed and dynamic insights into the behaviour of microswimmers (biological and artificial ones). To increase the visualisation of active colloids, teaming up with adjacent areas such as the biomedical field can lead to the implementation of techniques such as MRI or PET. It remains to consider that microfluidic systems (MEMS and NEMS) can already operate without direct monitoring (see also **Section 7**), which might be an aspiration for active matter applications as well [13].
- **Automation**. Better and more extended integration of technology (including moving stages and smart detection mechanisms, online-coupling, feedback and remote control) can improve the digital control and processing of active matter at the interface with computation and allow for real-time manipulation, data collection and evaluation. The combination of this fascinating area of research and digital requirements will contribute to increase the digital literacy of traditionally less exposed STEM areas such as biology and chemistry.
- **Advanced manufacturing**. Improved synthetic and fabrication capabilities in nanotechnology will allow for advanced design of materials with highly specific functionalities. Additive manufacturing techniques, including stop flow lithography and a broad range of 3D printing techniques, can contribute to broadening the available materials and enhance their functionalities and capabilities [14,15].
- **Interdisciplinarity**. A significant challenge that is less technological and more cultural is the collaboration between different disciplines. While research on active colloids and microswimmers has risen as a trans-disciplinary field of research, enabling and facilitating further knowledge transfer among disciplines to avoid 're-inventing the proverbial wheel' is of crucial importance and will ensure a more holistic approach to solving cross-disciplinary research problems.

Concluding Remarks

In conclusion, the fascination of creating artificial or robotic capabilities on the microscale, on par with nature's toolbox on this scale, is currently inspiring many scientists from different disciplines around the world. To fully realize the potential of active matter technology, a few steps towards routine studies, standardisation and enhanced reproducibility are necessary to create not just amazement but trust and acceptance among the different industries. Within the next generation, we could see real-life applications of active colloids emerge in sensing, drug delivery and environmental remediation, where proves of principles have already been demonstrated. Thinking forward, the far-from-equilibrium nature of active colloids could enable them to adapt their response to changing local environmental conditions when delivering their function. Closer interactions with advanced techniques for AI (**Section 18**), computation, enhanced manipulation, control strategies and image analysis will require effective knowledge transfer mechanisms but have the potential to unlock precision microrobots acting as a collective to perform the most intricate tasks on the microscale.

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03 – Light-animated microrobotics

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Status

Robots are man-made machines that can be programmed to perform tasks autonomously. Usually, a robot needs two main components: a decision-making system informed by external data and actuators to execute planned actions. While miniaturized robotic systems at the millimetre or centimetre scale have been successfully employed in biomedical applications such as endoscopy and surgery, untethered microscale robots have the potential to operate at the level of individual cells [1]. This could enable automation into laboratories built on microscope slides (lab-on-chip) or facilitate operations in previously inaccessible areas of the human body. Due to their small sizes, synthetic microrobots cannot yet incorporate complex decision-making systems and rely on external computers for sensing their environment and computing responses. As for actuation, fuel and controls should be provided wirelessly to enable remote control of the microrobots while operating in physically inaccessible environments. A solution is direct manipulation with non-contact forces (e.g., magnetic, electrical, optical or acoustic). Although these systems are usually referred to as microrobots, micromanipulation is probably a more appropriate definition when both control and force generation are external. Conversely, self-propelled microrobots integrate remotely controllable active components that can generate forces using locally available energy (see also **Section 2**). If microrobots are to execute complex and precise tasks, such as lab-on-a-chip sorting and cargo delivery, their movements must be directed accurately and independently. Light is an ideal carrier of both energy and control instructions delivered with high resolution in space and time [2]. Here we focus on a class of microrobots that can be remotely controlled by light using a variety of physical and biological mechanisms to convert photon energy into motion (**Figure 3.1**):

- **Optical and optoelectronic micromanipulation.** Optical actuation can be direct, i.e. through radiation pressure exerted by focused laser beams (optical tweezers). Multiple holographic traps can be used to grab, move, and rotate complex 3D-printed polymeric structures, e.g., for indirect live-cell manipulation [3]. Alternatively, by using photoconductive substrates as light-reconfigurable electrodes, strong electric field gradients with controlled spatiotemporal profiles can manipulate microscopic objects by dielectrophoretic forces [4].
- **Light-deformable materials.** Light-driven microrobots can be also built from softer polymeric materials with strong mechanical response to light. These are typically hydrogels or liquid crystal polymers that swell or deform upon light-induced local temperature changes. These microrobots can perform a variety of mechanical actions, like gripping and swimming, through shape deformations dictated by a dynamically structured illumination [5].
- **Light-controlled biological motors**. Motile cells can be used as biological propellers within microfabricated synthetic chassis. The use of light-driven proton pumps enables the selective powering of spatially separated bacteria. Modulation of bacterial thrust on different parts of a micromachine enables the execution of complex manoeuvres (see also **Section 4**) [6].

These microrobots are generally fabricated with sub-micron resolutions using 2D or 3D printing photolithography techniques, such as two-photon polymerization, and are mainly composed of epoxy-based photoresist materials (hard microrobots), or light responsive hydrogels and liquid crystal polymers (soft microrobots).

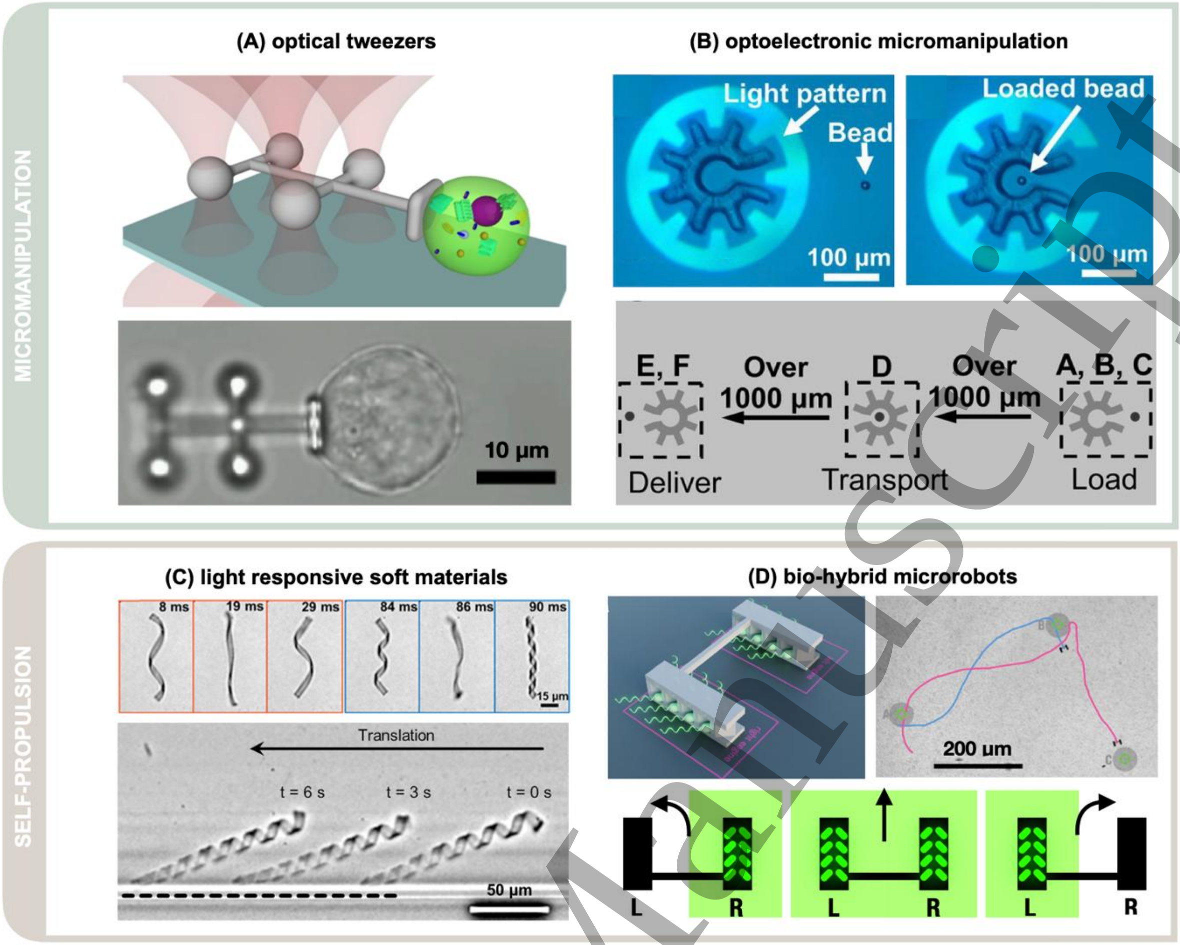

Figure 3.1 | Examples of light-actuated microrobots. (**A**) A 3D printed microrobot operated by holographic optical tweezers enables indirect manipulation of live cells. Adapted with permission from [3], Copyright © 2016, Optical Society of America. (**B**) A cogwheel shaped microrobot operated by optoelectronic tweezers delivers a colloidal cargo. Reproduced with permission from [4], Copyright © 2019, published by National Academy of Sciences. (**C**) Top panel: A soft hydrogel micro-robot undergoes large conformational changes triggered by laser light. Reproduced with permission from [7], Copyright © 2017, American Chemical Society. Bottom panel: Under periodic stimulation the helix can translate over a confining wall with a speed of 20 µm s^{-1}. Reproduced with permission from [8], Copyright © 2016, The Authors, published by Wiley-VCH GmbH. (**D**) Biohybrid microbot propelled by light-guided bacteria. A self-assembled microrobot consisting of a synthetic chassis and *E. coli* bacteria as propellers. A feedback loop running on an external computer navigates two microrobots through distributed checkpoints. Reproduced from [6], use permitted under the CC-BY 4.0 licence. Copyright © 2023, The Authors, published by Wiley-VCH GmbH.

Current and Future Challenges

Translating light-guided microrobots from the research laboratory to real-world applications poses several challenges:

- **Biocompatibility.** Probably one of the most stringent demands is to use technologies that are versatile and compatible with cellular environments. In this context utilizing electrical currents in dielectrophoretic actuation or high-power laser light may cause significant perturbations to cell physiology. On the other hand, using bacteria as propellers poses potential contamination risks. Finally, switching from epoxy-based photoresist to biodegradable materials will be crucial for health and environmental issues [9].
- **Friction.** Cell media are often salty, so that electrostatic repulsion is screened and strong nonspecific adhesions (e.g., van der Waals) give rise to irreversible sticking. In addition, an

often poorly controlled macromolecular composition of the environment causes tethering and increased friction. Even under ideal chemical conditions, sliding on a flat substrate involves a significant amount of shear that can result in high viscous drag and low velocities.

- **Noise resilient navigation strategies.** Brownian noise, combined with the inherent randomness of any microscopic propulsion mechanism, results in stochastic dynamics and the need for constant feedback to counteract deviations from planned trajectories.
- **Cooperation.** Implementing interactions between multiple microrobots is also important to amplify functional throughput or even to create higher-order functionality that exceeds the capabilities of a single microrobot [10] (see also **Section 17**). In biological communities, such as microorganisms or flocks of birds, physical interactions and chemical signalling between individual entities are critical to facilitate complex tasks such as navigation, predation and survival. Swarms of microrobots will need interactions to avoid collisions during parallel control and to be programmed for seamless collaboration on a common task.
- **3D navigation.** Most of the light-driven microrobotics developed so far is limited to 2D motions over a substrate while the possibility of navigating 3D environments could really help move the first steps out of the microfluidic chip and into real-world microenvironments. 3D navigation would also avoid sliding on the substrate, reducing friction and sticking risk.
- **Embedded control.** The main limitation of light driven microrobots is that they require a clear optical access to be operated, which poses a significant challenge for *in-vivo* uses due to the limited light penetration in biological tissues. Their 'sensing' capabilities are actually based on global imaging and processing by a central control computer. It will be a major challenge to equip these microrobots with integrated sensors that can detect physical or chemical signals from the environment and calculate a mechanical response.
- **Scalability.** Many microrobots with 3D structures are fabricated with two-photon polymerization techniques, where the fabrication time increases linearly with the number of microrobots and that are therefore not particularly suitable for mass production.

Advances in Science and Technology to Meet Challenges

Meeting these challenges requires scientific and technological advances:

- **Improve light-to-force conversion efficiency.** Improving actuation efficiency is crucial for successfully implementing collaborative schemes that involve simultaneously controlling large numbers of microrobots with relatively low optical power. This is essential to avoid compromising the viability of biological samples and the accuracy of manipulation. Biological motors show superior efficiency when compared to synthetic systems. With only a few nanowatts of optical power, bacteria expressing the light-driven proton pump proteorhodopsin can generate piconewton forces through flagellar propulsion. Synthetic systems, however, can generate stronger forces that are best suited to overcome friction, sticking and noise.
- **Understand and exploit friction.** A clear analysis of friction and sticking problems of microfabricated structures sliding on solid substrates is still lacking. A comprehensive study that incorporates both molecular and hydrodynamic interaction aspects could provide the necessary elements to select the best materials and geometries to build microrobots that maintain a high mobility in any biologically relevant media. Alternatively, friction could be exploited for new locomotion strategies such as walking [5].

- **Implement cooperativity and autonomy.** Optical control allows the implementation of effective interactions through feedback control loops. In light-activated colloids, effective interactions can be attractive or repulsive and even mimic animals' visual perception [11]. This approach could prove valuable in shaping collective behaviours within swarms of self-propelled microrobots (see also **Section 17**). However, precise knowledge of the location of the microrobots and their surroundings by the central computer may not always be guaranteed, as in the case of *in vivo* applications. Advancing towards the full autonomy of microrobots requires integrated sensors. One potential solution could come from an interdisciplinary collaborative effort involving synthetic biology. Within biohybrid microrobots, engineered cells can serve not only as actuators but also as sensors and processors of external signals [12]. Approaches borrowed from the Metamachine technologies described in **Section 4** could be used to implement purely mechanical sensing and couplings between microrobots.
- **Machine learning for navigation.** The machine learning advancements anticipated in **Section 18** could aid in developing more robust navigation strategies for complex biological environments characterized by spatial and temporal inhomogeneities, such as obstacles and fluid flows. Approaches based on reinforcement learning seem to be particularly promising, although most studies are only theoretical or conducted on simplified experimental settings [13].
- **Advanced 2D microfabrication.** Scalable solutions could come from alternative ways of using 2D lithography, which can parallelize microfabrication much more easily than two-photon polymerization. Grayscale lithography offers a faster solution for the creation of embossed (2.5D) microstructures. Alternatively, soft 2D microstructures can be designed to fold into a 3D shape in response to specific stimuli [5].

While speculative by nature, some of these advancements are framed within current technological trends and industrial imperatives, ensuring a forward-looking, yet realistic perspective on their feasibility and development pathways.

Concluding Remarks

Capable of generating stronger forces and with a higher level of control, optical and optoelectronic micromanipulation techniques are still more effective and reliable than semi-autonomous microrobots. However, the realization of autonomous units, which are minimally dependent on external control and power supply, offers more opportunities for innovation and applications that can go beyond the use in microfluidic chips. The path to realizing autonomous light-driven microrobots presents both exciting opportunities and significant challenges, potentially requiring more than a decade to overcome due to the necessity of breakthroughs across multiple scientific disciplines. The key to overcoming them lies in fostering an interdisciplinary collaboration that brings together experts in microfabrication, surface chemistry, synthetic biology, and control theory for noisy systems.

Acknowledgements

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04 – Metamachines

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Status

Machines are assemblies of parts that transmit forces, motion and energy to one another in a predetermined manner. Their development thrust the industrial revolution, unleashing technical progress with important societal and environmental impact. By converting energy sources into work, machines expand human abilities beyond physiological limits, such as lifting enormous weighs or covering large distances at rapid speed. Specialized machines (or mechanisms) are combined and directed by a computational unit to form a machine of variable complexity, whether a blender or a self-driving car. This approach shows great impact in the engineering of macroscale machines but hits conceptual bottlenecks when scaling down to the microscale. There, parts experience surrounding noise that can render robust placement challenging or the reading of signal needed for sensing elusive. In addition, micromachines carry limited resources that make conventional actuation and *in silico* computation beyond reach.

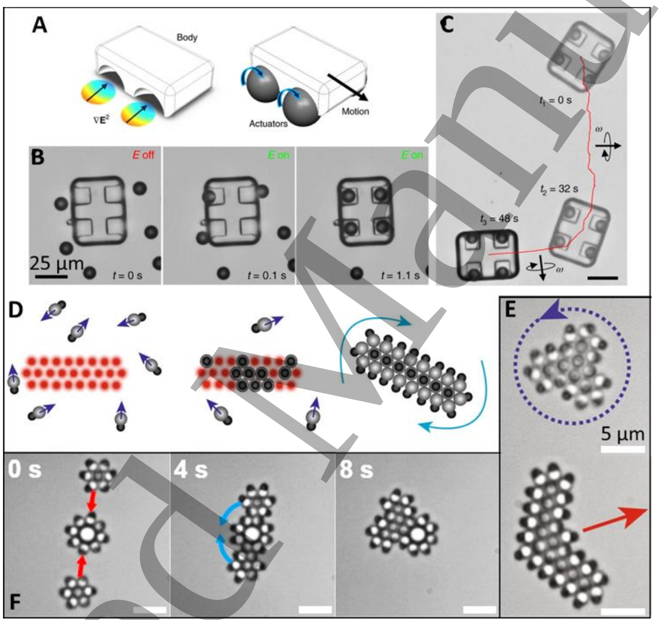

Figure 4.1 | Examples of synthetic metamachines. **(A-C)** Rigid template translated by colloidal micro-actuators. Reproduced with permission from Y. Alapan *et al.* [1]. Copyright © 2019, Springer Nature. **(A)** Dielectric forces program the self-positioning of particles in the designed chassis. These particles act as propelling wheels following application of a rotating magnetic field. **(B)** Self-assembly of the magnetic micro-actuators with the chassis thanks to the dielectric forces. **(C)** The direction of translation of the micromachine is controlled with the orientation of the rotating magnetic field. **(D-E)** Optically templated colloidal metamachines. (**D**) A pattern of optical traps constitutes a programmable 2D template to assemble a metamachine. Colloidal microswimmers position on the traps forming a metamachine that remains stable after removal of the optical traps. The metamachine is an autonomous machine with prescribed dynamics. Adapted from A. Aubret *et al.* [2], use permitted under the CC-BY 4.0 licence. Copyright © 2021, The Authors. (**E**) Top: Chiral metamachine rotating counterclockwise. Bottom: Axisymmetric metamachine displaying translational motion. Adapted from A. Aubret *et al.* [2], use permitted under the CC-BY 4.0 licence. Copyright © 2021, The Authors. (**F**) Parts of a machine self-position and lock to form a metamachine, showing elementary features of configurability. Adapted from Q. Martinet *et al.* [3], use permitted under the CC-BY 4.0 licence. Copyright © 2022, The Authors.

The inspiration from nature, which exhibits prototypical examples of functional and autonomous machines at the microscale, funds the concepts of metamachines, or machines made of machines [4] (**Figure 4.1**). *Metamachines are modular and functional microscale machines made of machines with* *the ability to compute, e.g. sense and respond to their environment autonomously.* As a result, metamachines have constitutive elements that are internally driven. They can be active colloids (**Section 2**) for purely synthetic metamachines [2] or responsive bacteria for hybrid metamachines (see also **Section 3**) [5]. The field of metamachines therefore appears as a complement to the field of conventional microrobotics. There, major advances were achieved, using monolithic structures that were powered externally. Microscopic walking robots [6] or reconfigurable micromachines [1] show important progress towards Feynman's original vision of "swallowing the surgeon". They however remain large (50-100 µm) and present limited modularity or autonomy. At the microscale, machines that respond to their environment require a design that departs from conventional robots (see **Section 17**), leveraging physical phenomena relevant at this scale, e.g. interfacial phenomena, to power mechanisms and sense. Practically, metamachines require microscale building blocks that consume fuel. They demand novel engineering approaches to assemble them in structures with meaningful functions and embedded computation capability.

Current and Future Challenges

To date, experimental realizations of metamachines are scarce, with shortcomings towards the ultimate goal of an autonomous and functional machine. We briefly present here pioneering results, highlighting their advantages and the drawbacks to motivate future challenges.

Self-assembled metamachines currently use a rigid 3D-printed template to position active agents to act as actuators [5]. This approach requires the fabrication of a complex chassis and relies on the self-positioning of active agents in adequate positions within it. This step of self-assembly is central but typically challenging with conventional colloidal building blocks, hindering progress. Advances will require tailoring interactions between building blocks to form specific architectures, potentially leveraging recent developments in patchy particles or DNA-origami [7]. Alternatively, metamachines can be assembled from pluripotent building blocks, i.e. components with multiple functionalities that can be selected by their environment. We recently demonstrated the powerful character of this approach, where the propulsion forces of self-propelled colloids were delicately balanced by the optical forces of an optical trap to position and trap active colloids onto a controllable 2D template. Such templated structures remained stable after the removal of the optical traps thanks to non-equilibrium interactions providing cohesion to the overall assembly. Those non-equilibrium interactions lead to propulsive forces responsible for the dynamics of the metamachines. They could form small colloidal machines, typically below 10 µm, with embedded dynamics, i.e. self-spinning microgears, whose chirality could be set by optical vortices, or translational rods. These metamachines show elementary features of configurability, e.g. self-positioning parts into larger and dynamical structures [3], and respond to light gradients.

In effect, important progress remains to be achieved notably targeting the following features:

- **Emergent dynamics.** Currently, metamachines lack internal dynamics and emergent features, e.g. oscillations or self-replication, that are landmarks of non-equilibrium systems. To this end, they will need feedback mechanisms. One avenue would be to embed them with computational units, a difficult task at the microscale. An alternative route is to leverage "passive" interactions, such as the deformation of soft materials or the alignment of particles in shear flow to sense the environment, perform feedback and unveil emergent dynamics [8].

- **Reconfigurability.** Currently, metamachines lack the ability to reconfigure and adapt their shape or function to a varying environment. These advances would constitute a significant step towards the realization of metamachines that compete with living organisms.
- **Collective Dynamics.** A salient step will be to embed interactions to orchestrate the response of multiple metamachines into collective dynamics. For example, we could think hypothetically of self-oscillating metamachines that would self-replicate to form a synchronized collection of cilia able to transport fluid at large scales!

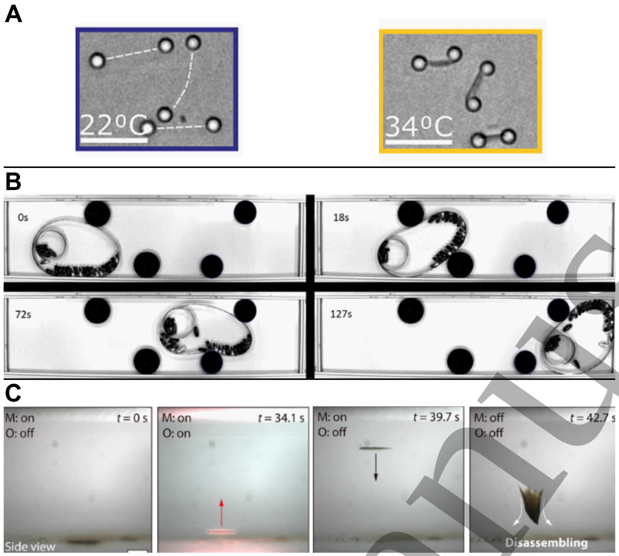

Figure 4.2 | The future of metamachines. (**A**) Composite colloids with responsive components. Silica colloidal dimer linked by a thermoresponsive hydrogel. Brightfield images of the colloidal dimers at 22°C and 35°C. Scale bar: 10 µm. Adapted from S van Kesteren *et al.* [9], use permitted under the CC-BY 4.0 licence. (**B**) Smart robots from flexible scaffolds. Photographs of the superstructure resulting from the self-organization of centimetre-sized robots enclosed scaffolds moving through obstacles and carrying a load. From J. F. Boudet *et al.* [10]. Reprinted with permission from AAAS. (**C**) Fluid dynamic colloidal collective navigates in 3D. Driven by a rotating magnetic field, sedimented ferrofluid iron colloids self-assemble into a dynamic colloidal collective. The optical field triggers the generation of convective flow through photothermal effect, allowing the 3D navigation of the colloidal collective. The M and O labels indicate respectively the status of the magnetic and optical field. The red and black arrows show the direction of displacement of the colloidal assembly. Scale bar: 1 mm. Adapted from M. Sun *et al.* [11], use permitted under the CC-BY 4.0 licence.

Advances in Science and Technology to Meet Challenges

Meeting these goals requires stepping up the current state of basic science and technology (**Figure 4.2**). In particular, we highlight three directions in different contexts that hint at possible developments that would be beneficial to the success of metamachines:

- **Deformable parts**. Compliant structures will provide additional degrees of freedom, that can be leveraged to compute and respond to environmental constraints [10]. Self-organization and reconfiguration of metamachines with deformable parts can enable complex tasks such as going through a constriction or moving a load (see **Section 10**).
- **Multiple materials**. Metamachines and their ability to reconfigure would benefit from flexible and responsive building blocks, that replace the current monolithic chassis. Similar blocks have been recently made available by progress in micro- and nanofabrication techniques. Composite metamachines, made of different materials, would benefit from the combination of their different physical properties to realize multiple and complex functions by decoupling parts for propulsion, actuation and sensing.
- **3D navigation**. To date, metamachines and their functions have been limited to two dimensions, so has their navigation. For either medical or environmental applications, metamachines will have to navigate in a three-dimensional complex environment and be

biocompatible. A collection of ferrofluidic iron colloidal particles self-assembled into a dynamic colloidal collective thanks to the application of a rotating magnetic field. This fluid architecture was then controlled using the convective flows arising from heating by a focused laser beam [11], These convective flows allowed the structure to overcome gravity and navigate in three dimensions, by lifting the colloidal collective. This example of metamachine is however millimetric and a comparable implementation at microscale remains elusive. It nonetheless highlights how soft and reconfigurable machines could displace in a three-dimensional environment, responding to external control.

Concluding Remarks

Metamachines is a nascent field aimed to complement the current developments in microrobotics with autonomous and responsive colloidal machines. Its success will hinge on the use of smart(er) materials in nano- and microfabrication, allowing responsiveness to the environment and flexibility. In coming years, we envision that metamachines will be endowed with advanced properties, e.g. reconfigurability, self-replication or oscillatory behaviour, ultimately providing a flexible platform for bottom-up assembly of hierarchical structures.

Acknowledgements

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JPhys Condensed Matter (2024) ####

05 – Towards animate lasers: Bioinspired lasers with active matter

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Status

The invention of new optical materials and lasers has always been sought after for technological progress and the creation of new applications. Small lasers, for example, made from single nanodisks [1] and microspheres [2] led to the development of 'biolasers' that could attach and function inside biological tissues/cells, spurring research activity in cell tagging, imaging and even targeted treatment inside the body. However, developing lasers that can reliably function in complex dynamic environments, like in an organism, is challenging, as it requires precise control over the position and orientation of individual components.

One solution is to build lasers out of disordered structures, utilising multiple scattering for light trapping and active manipulation (**Figure 5.1**). Such type of lasers, termed random lasers, are free from rigid cavity designs and, hence, can better maintain their performance in dynamic environments [3]. Random lasers, which are usually in the order of 10 to 100 micrometres in size, have been made using strong scattering optical materials such as photonic glasses, semiconductor powders, and colloidal particles. These are typically static and hard to tune. In contrast, the recent use of animate matter – that can respond autonomously to its environment [4] – allowed for the dynamic synthesis and control of a random laser. This is an exciting development, as the self-organisation of animate matter opens new possibilities to build complex artificial optical metamaterials and devices.

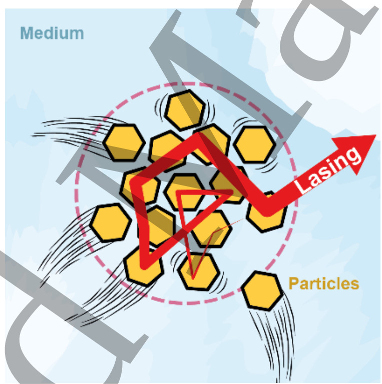

Figure 5.1 | Self-assembled random lasers. Schematic showing light amplification in a colloidal solution with scattering particles and laser dye. Dense clusters formed by self-assembly enable random lasing to occur.

Lasing is an important functionality for animate materials, whose potential is yet to be exploited. The first steps towards realising active lasers were focussed on manipulating the properties of the structure during fabrication, with fixed architectures afterwards. For instance, the dynamic assembly of semiconductor nanorod lasers was demonstrated under an external electric field [5]. With the tendency of the nanorods to align with the electric field in the solution, nanorod superstructures with tuneable orderliness could be deposited on the substrate with corresponding tuneable lasing or amplified spontaneous emission (ASE) thresholds.

Recently, active colloidal random lasers built via self-assembly with additional functional controllability were demonstrated [4]. By incorporating Janus particles (see also **Section 2**) for thermo-osmotic attraction, colloids in a dye solution were assembled into clusters surrounding a Janus particle. The threshold for random lasing was reduced by the enhancement of scattering in the cluster, thus enabling random lasing under optical excitation. Together with the active control of particle dissipation, the laser was controlled adaptively with reversible and reconfigurable lasing behaviours.

This recent advancement in active random lasers suggests the possibility of achieving programmable animate lasers that can autonomously adapt to their environment.

Current and Future Challenges

Many challenges remain to turn active matter lasers and biolasers into practical technologies. Meeting these challenges will open opportunities for novel applications in medicine and industry. For example, active lasers could be used inside the body for novel targeted cancer therapy or in microfluidic devices to provide controllable coherent light sources with small-footprint for lab-on-a-chip experiments. Key challenges are discussed below:

- **Lasing materials**. Materials development for active lasers in complex systems requires consideration of many factors, including viscosity, size, density, solubility, hydrophilicity, and surface functionality. Furthermore, pH, toxicity, and carcinogenicity must also be considered for use in a biological environment. All these considerations significantly constrain the material choices and make it challenging to realise low-threshold, small-footprint active lasers.
- **Manipulation speed**. Future active lasers will require rapid manipulation of their components to respond faster to the stimuli from the environment. The current active lasers constructed using thermal gradients are limited to an assembling speed of tens of minutes [4], which is far slower than changes in a dynamic environment. Important laser functionalities, such as fast signal modulation and beam steering for wavelength multiplexing, are also still missing in active lasers and will require substantial development.
- **Adaptive behaviour**. One of the major targets in the active laser community is to realise programmable and autonomous lasers that can self-organise, react, cooperate, and adapt to the environment like biological materials. This would require responsiveness from the system to sense environmental changes and feedback mechanisms to reconfigure its structures. This is an extraordinary function which has not yet been implemented in any photonic structure. These challenges are shared with those of active colloids (**Section 2**) and swarm behaviour in light-animated microrobots (**Section 3**) and collective efforts are required to achieve self-adapted lasers that can change their photonic/lasing properties in response to environmental stimuli.
- **Safety and ethical issues**. Developing active lasers for medical applications can enable unprecedented functionalities. However, the approval process would involve lengthy animal and clinical trials. Therefore, safety concerns and ethical issues also need to be addressed when developing active laser technologies for practical applications.

Advances in Science and Technology to Meet Challenges

The future development of active lasers will require advances in the gain material as well as in the active control of the self-assembly process and of the interaction between the elements in the swarm. Specifically,

- **Lasing materials:** Materials play a crucial role in active laser performance. Low-index contrast materials hamper the lasing process by reducing light confinement. Recent advancements in nanophotonics have achieved nano/micro-particles with various high refractive indices, such as perovskite-SiO_2 nanocomposites [6] and inorganic semiconductors [7]. These nanoparticles are biocompatible and intrinsically combine high optical gain and strong-scattering properties, which are desirable for assembling random lasing swarms in dynamic environments. Lasing systems can also implement gain both in its units (e.g., fluorescent beads) and environment (e.g., perovskite nanocrystals in solution [8]) and incorporate materials with ultra-high refractive indices (e.g., Germanium or artificial metamaterials [9]) to achieve highly confined, small-volume active lasers.

- **Active control methods:** Additional driving forces could be exploited to realize faster responding active lasers. Optical, electric or magnetic fields could improve material assembly as well as swarm formation, rapidity and flexibility. Photo-induced accumulation and depletion of a colloidal assembly on a conductive substrate shows the potential to achieve faster responding laser swarms with assembly times under a minute [10]. In addition, collective structures with varying shapes and sizes can be formed, for example, by exploiting electric fields in metal or dielectric colloids [11]. Implementing these faster and more flexible assembly schemes in active laser systems could lead to programmable swarming that can not only adapt and operate in a fast-changing environment, but also actively change the lasing properties in the environment.
- **Swarm interactions:** To realise truly autonomous and life-like swarming lasers, achieving self-monitoring of the particle motions is crucial. If the swarm motion is driven externally, possibilities for control and mobility remain limited. For an ideal laser swarm, individual units should be able to "communicate" by sensing other units' changes and adapt to the overall swarm motion (see **Section 17**). **Figure 5.2** illustrates this concept. With the target set for the laser swarm (e.g., by introducing chemical or temperature gradients), individual laser units assemble while simultaneously sensing their environment to guide the whole laser swarm to the target collectively and maintain the lasing properties and functionalities on the way. The interactions between the laser swarm and its environment are a critical part for enabling its automation. Sensing and signalling could be boosted by optical antennas with the capability to emit and receive directional signals from neighbouring swarms or obstacles. Although many implementation challenges are still awaiting to be addressed, learning how to engineer the driving mechanisms of the laser units and their coordination could enable active lasers to adapt to their environment and become truly programmable and autonomous.

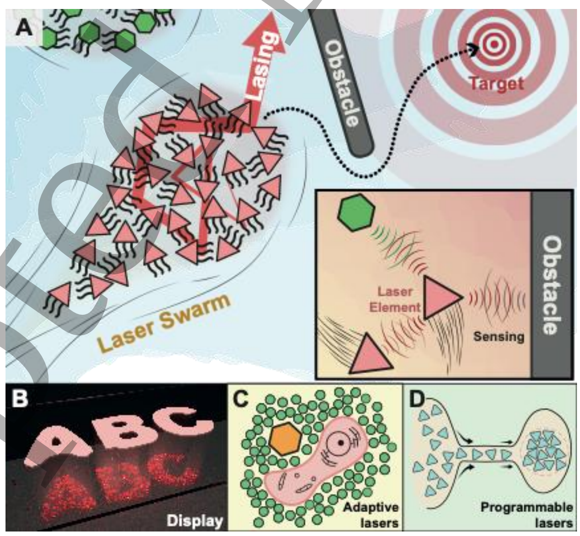

Figure 5.2 | Swarming lasers. (**A**) Illustration of an autonomous active laser. Laser units form a laser swarm through sensing and signalling to generate collective motion with lasing functionalities. The laser swarm can respond to environmental changes and be guided towards the target by introducing potentials. The examples of the laser swarms' possible applications, including (**B**) displays, (**C**) adaptive biological lasers, and (**D**) programmable lasers.

Concluding Remarks

The development of active lasers is still in its infancy, with only a few architectures blending active matter concepts with nano-/micro-laser systems. However, the first success in manipulating active laser properties suggests new laser functionalities that can be realised in dynamic systems. With further development in tackling challenges such as laser materials, swarm manipulation, and environment interactions, active programmable lasers in dynamic systems could be achieved. Solving the common challenges in animated colloids would fast-track the development of animate lasers, and potentially maturing within 30 years. This could enable exciting applications for realising novel functionalities in complex and biological environments, such as biological sensing, signal processing, and non-conventional computing.

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JPhys Condensed Matter (2024) ####

06 - Liquid microcapsules: Life within confined liquid microenvironments

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Status

Life finds expression through a diverse array of liquid compartments. This phenomenon extends across various length scales, from the micro- to the macroscale, featuring entities such as lysosomes, animal cells, embryos, zebrafish eggs, or the mammalian amniotic sac. Cells also utilize membranes to sculpt liquid and functional compartments, mirroring the sophisticated organizational principles observed in the human body, where organs meticulously fulfil specific functions. Within tissue engineering, researchers aspire to replicate the intricacies of natural biological systems to fabricate complex 3D microtissues. For example, researchers have successfully compartmentalized basic components to develop artificial cells [1] (see also **Section 1**). Cells have also been encapsulated within hydrogels to obtain tissue-like constructs such as myocardium or epithelium organoids. [2-3]. Inspired by nature, a cell encapsulation system was realized, serving as an authentic bioreactor supporting the autonomous development of microtissues [4].

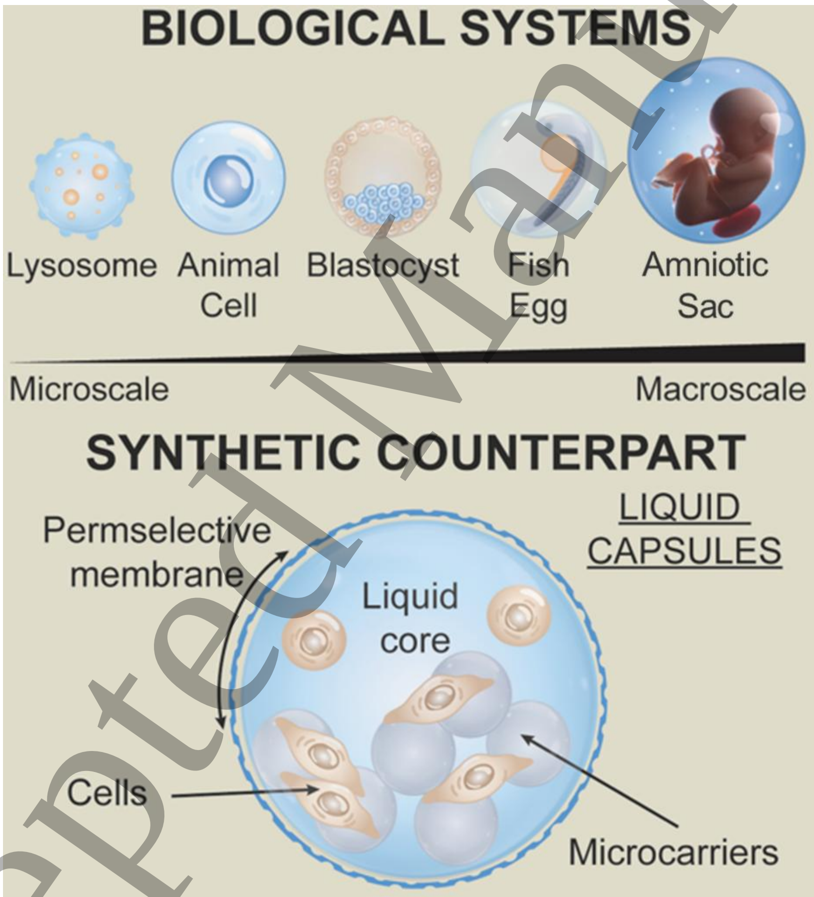

Figure 6.1 | Biological and synthetic liquid compartments. Liquid capsules as intricate synthetic constructs, drawing inspiration from the diverse liquid compartments prevalent in nature.

These liquid capsules, with typical sizes between 800 µm to 1 mm, contain (i) a permselective membrane, wrapping the liquid content, (ii) microcarriers for cell adhesion alongside (iii) the cells themselves (**Figure 6.1**). The membrane facilitates the exchange of vital biomolecules (e.g., nutrients, oxygen, growth factors, and cytokines) throughout the 3D construct. Microcarriers play a pivotal role in supporting cell adhesion, proliferation, and differentiation, particularly beneficial for adherent cell types. They also support the encapsulation of suspension cells, faithfully recreating an environment that closely mimics their natural surroundings. The unique fluidic environment enables the orchestrated development of dynamic flows, optimizing the interaction of cells with microparticles for the creation of living matter. Besides working as a specialized bioreactor, these liquid microcapsules, by enhancing the precision of *in vitro* tissue-engineered constructs, are envisioned also as a promising alternative to conventional scaffolds. The membrane works as a selective barrier against the intrusion of immunoglobulins and immune cells and prevents the dispersion of the core contents into peripheral regions of the body upon implantation. Furthermore, liquid capsules demonstrate excellent injectability, facilitating their delivery by minimally invasive procedures. This pioneering system, already tested *in vivo*, emerged as a versatile cell-encapsulation solution for diverse applications, including bone, cartilage, and bone marrow tissue engineering [5-6]. Such kind of systems can also be used to create human embryoid bodies and functional cardiospheres with a very precise morphological control [7].

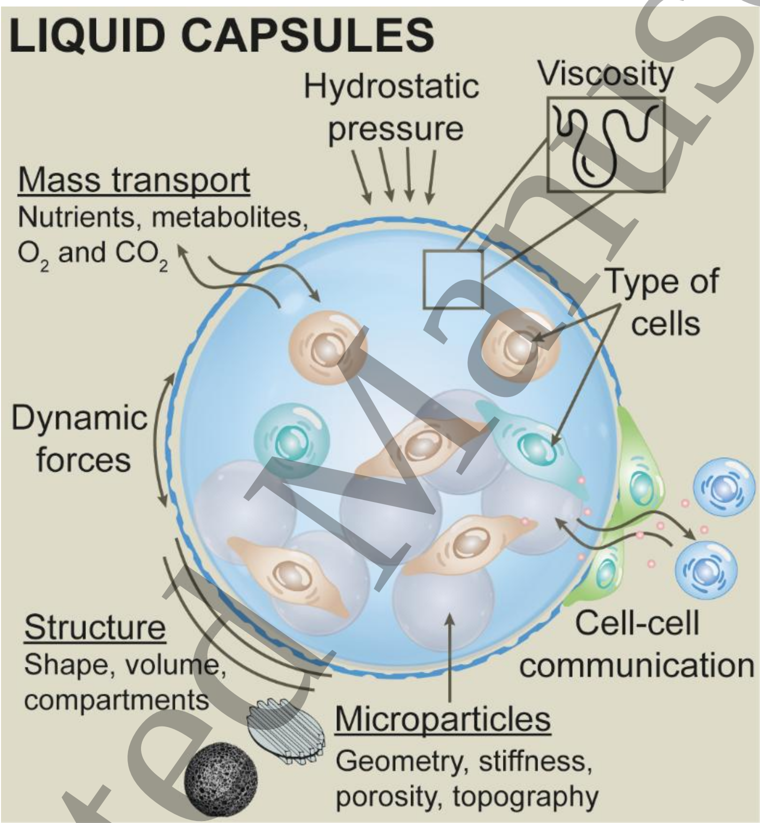

Figure 6.2 | Liquid microcapsules. Liquid capsules function as specialized bioreactors, offering the potential for the independent manipulation of various parameters tailored to specific applications and objectives.

Current and Future Challenges

Developing the next generation of bioreactors and scaffolds requires careful consideration:

- **Vascularization.** Prioritizing *in vitro* vascularization prepares tissues for successful *in vivo* integration. Remarkably, liquid capsules (Fig. 6.1) enable the self-regulated organization of cells, primarily orchestrated by the cells themselves, presenting a compelling advantage in directing the differentiation of stem cells without external biochemical factors. Nevertheless, a significant obstacle persists within the liquid capsule strategy, namely the establishment of vascularization. Despite noteworthy advancements, establishing a fully functional vascular network within these capsules remains a central focus and a persistent challenge in the field [8].

- **Coculture.** The introduction of an inflammatory environment alongside growing tissue is essential to mimic mammalian host responses. To mitigate these challenges, various co-culture systems have been conceptualized, including the encapsulation of mesenchymal-derived stem cells, macrophages, and endothelial cells. This approach not only enhanced the release of angiogenic factors but also elicited a regenerative immunomodulatory response [8].
- **Process monitoring.** A pivotal step for advancing tissue engineering outcomes involves the continuous monitoring of the bioreactor. Utilizing advanced imaging and sensing techniques facilitates the real-time, non-destructive evaluation of cell fate and tissue growth in the complex 3D environment, establishing the foundation for the automated control of the bioreactor. One of the advantages of liquid capsules lies in the semi-permeable membrane, which permits the passage of proteins released by cells, enabling their detection and measurement in the surrounding culture medium without compromising the integrity of the capsules.
- **Scale-up.** Scaling up these micro-units is another aspect to bear in mind. One approach is to incorporate these micro-units within hydrogels. Alternatively, the outer membrane of capsules can be functionalized, introducing adhesion sites conducive to the formation of larger structures [9]. This innovative approach involves a dual building block system, where microcapsules demonstrate the capability to generate microaggregates of cells and microparticles within the liquefied core, and simultaneously, these microcapsules can be assembled by cells to create macroscopic, more complex 3D structures [9].

Advances in Science and Technology to Meet Challenges

Various strategies can be explored to address the primary challenges of the field. While current liquid capsules demonstrate remarkable potential in orchestrating the development of microtissues, future advancements must steer towards more sophisticated and forward-looking solutions:

- **Processing methodologies.** There is still a need to develop new methodologies to produce such hybrid liquified objects. From a first generation of capsules, involving the preparation of temporary hydrogel templates coated with polyelectrolytes using the layer-by-layer technique [4-6], we can now fabricate such compartments using a one-pot method involving the complexation of oppositely charged polyelectrolytes in aqueous biphasic emulsions [8], thus involving more sustainable processing routes, using non-organic solvents and operations at normal temperature/pressure.
- **Versatility of the capsule's ecosystem.** Each liquid unit possesses the versatility to harbour distinct living matter, including both suspension and adherent cells, derived from multiple sources, such as human-based and animal-based cells, or even microorganisms. Combining different cell phenotypes in varying ratios could offer a promising approach to enhancing vascularization and reducing heterotypic tissue formation.
- **Versatility of the conditioning parameters.** The quality of the generated tissues may also be upgraded by the independent manipulation of various parameters (**Figure 6.2**). For instance, precise control over hydrostatic pressure is possible, allowing the replication of native mechanical microenvironments. This control is an essential factor influencing the regulation of the differentiation of stem cells. Additionally, modifying the core viscosity by adjusting fluid composition, may enable the modulation of shear stress magnitude.
- **Design of the microparticles in the capsules.** Another notable possibility of guiding stem cell differentiation and improving vascularization could be the customization of microparticle characteristics, offering flexibility in the type of material, quantity, geometry, stiffness, porosity, and topography, or even incorporating specialized features for controlled drug release. The encapsulation of microparticles not only provides precise mechanical stimuli to

trigger the initial differentiation of stem cells towards controllable lineages but also expands the range of stiffness compared to hydrogels. The microparticles that are used to support the adhesion of cells can also be loaded with bioactive agents that could be released to the core of the capsules to have some biological effects.

- **Capsule culture in bioreactors.** Taking advantage of the liquid core, these capsules can be cultivated in dynamic environments like spinner flasks, providing mechanical stimulation that profoundly influences cell behaviour and response. Cells can sense the mechanical stimuli resulting from the agitation of the compartmentalized liquid within capsules, a characteristic easily customized by adjusting the rotations per minute of the culture flask. Moreover, the adjustment of other parameters, including pH, temperature, and oxygen levels, can be easily accomplished by altering the conditions of the culture medium, also owing to the properties of the membrane (see also **Section 7**).
- **Degradation control.** We can engineer the shell of the capsules to be degraded with time or upon some specific actions (including by some external stimuli or by the own action of the cells) – this would permit to use such systems as temporary compartments, where cells could explore outer regions upon the disruption of the capsule.
- **Other applications.** Another avenue worth exploring is the integration of engineered living materials for applications such as biosensing or sustained drug release, effectively managing the regulation of differentiation and vascularization [10].
- **Modularity and response to external stimuli.** In addressing the challenge of scaling up, liquid capsules offer a promising avenue as modular building blocks. One viable strategy involves leveraging bioprinting techniques to integrate these capsules into larger, more intricate structures (see **Section 08**) and with the capability to have controlled function in space and time (see **Section 12**). This could permit to extend the concept of 4D materials [11]. Due to the absence of a core, it is hypothesized that incorporating liquid capsules within hydrogel precursors can address the limitations associated with direct cell embedding, such as lack of direct cell-cell contact or limited diffusion of nutrients, while also reducing the amount of bioink required for such processes. Additionally, the application of magnetic and acoustic fields presents an opportunity to precisely arrange capsules, used frequently in controlling the position of cells and biomaterials [12], facilitating the creation of customized designs. The adaptability of this system extends to the modification of external features of the capsule, such as shape, compartments, or volume, easily achievable based on the chosen fabrication technique. While spherical systems are commonly utilized, there is a growing exploration of generating multi-shaped, intricate 3D structures to emulate the complexity of native tissues.

Concluding Remarks

The topic of liquified capsules is clearly within the context of the new field of living materials [10], and animate (hybrid) matter, where the form in which cells and microorganisms are integrated with materials truly dictates the general properties of the bioengineered system, including evolvability, self-organization, response to external stimuli and specific interactions with living systems. Such stimuli can include the application of external non-harmful fields such as acoustic, magnetic or light (see, e.g., **Section 5**). We predict interesting applications of such systems not only in advanced therapies, but also in the conception of in-vitro disease models (see, e.g., **Section 07**) to screen drugs and in the development of highly sophisticated sensors and actuators/soft robots (see **Section 10**), not only in the biomedical context but also to be used in industry or for environmental applications. Inspired by the intricate liquid compartments observed in nature, liquid capsules stand as a ground-breaking advancement in tissue engineering. Serving as animate matter and specialized bioreactors, these units facilitate reproducible and controlled variations of specific environments during the *in vitro* development of living tissues. Moreover, liquid capsules enable the simultaneous application of multiple stimuli, spanning from mechanical to biochemical cues. This unique structural design permits systematic investigations into the effects of these stimuli on cell functions and tissue morphogenesis, elevating the precision of *in vitro* tissue-engineered constructs. Like conventional bioreactors, liquid capsules allow independent manipulation of multiple parameters, being adaptable to sizes ranging from approximately 50 µm to 2 mm in diameter. This micro-scale versatility enables tailored mimicry of both the geometry and nature of mechanical and biochemical stimuli specific to the target tissue. The truly living nature of such systems permits a pure biological control of their structural and functional properties, which cannot at this stage be found in synthetic counterparts, such as protocells or artificial cells. Overall, liquid capsules represent a transformative approach, offering unprecedented control and adaptability in tissue engineering that holds great promise for advancing the field. Much effort will still need to go in using such unitary systems to bioengineer macroscale constructs by direct self-assembly bottom-up procedures (including biofabrication) or by external-field (e.g., magnetic, acoustic, shear) mediated organization. Such highly complex organizations with an intrinsic biological/living activity will be in the future much more explored in combination with machine learning and artificial intelligence (see **Section 18**) to explore the full capabilities of such hybrid multi-scale structures. Taking the interest of research groups and even companies on the general field of living material, we expect that engineered devices where properties are dictated by the machinery of cells and microorganisms could find applications in the next few years.

Acknowledgements
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07 – Organ-on-a-chip: Guiding cellular specialization with environmental cues in advanced cell cultures

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Status

Since emerging in the early 2000's, organ-on-a-chip technology has rapidly evolved, transforming the study of human biology and disease. These microfluidic-based devices house living, miniaturized 3D cell cultures at micro- to mm-scale, designed to replicate the physiological environment of specific tissues. By incorporating both parenchymal and non-parenchymal cells, these platforms aim to closely mimic organ physiology and pathology. The rapid growth of the field is fuelled by the integration of human-derived stem cells and microfabrication techniques, allowing precise control over tissue-specific microenvironments and spatiotemporal dynamics critical for cell specialization and maturation [1] (see also **Section 6**).

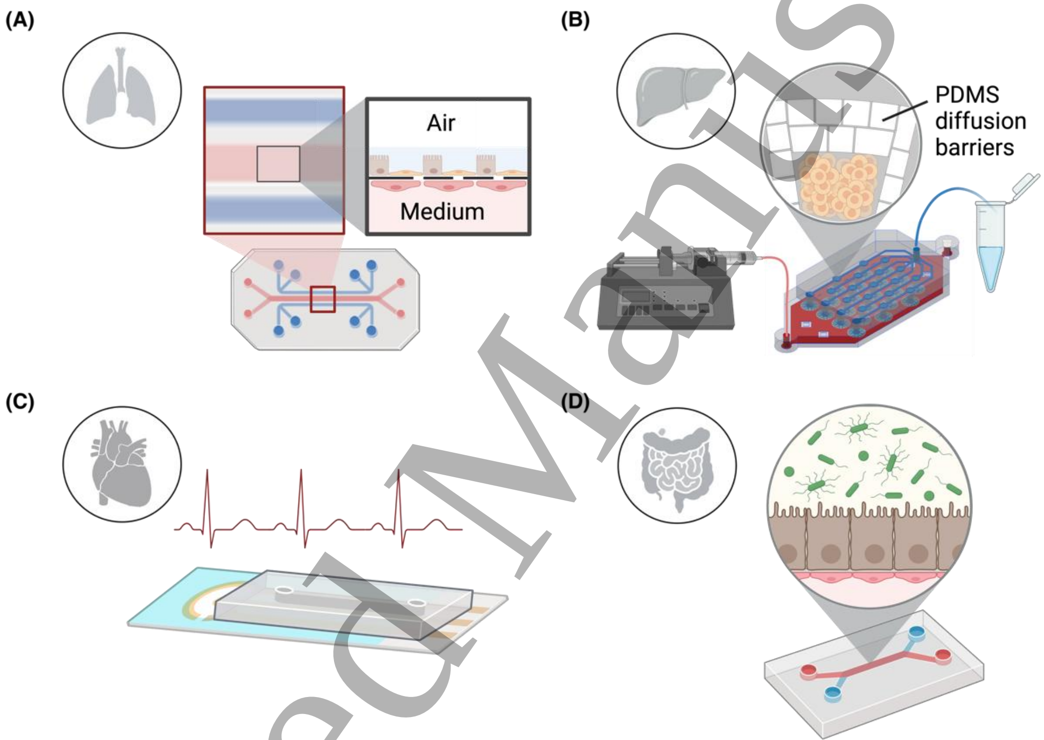

Figure 7.1 | Examples of four organ-on-a-chip platforms designed to replicate key physiological parameters of their respective tissue environments. (**A**) In the dual-layered lung-on-a-chip model, mechanical stretching (blue channels) facilitates physical conditioning of lung-specific cell co-cultures [3]. (**B**) The liver-on-a-chip (or liver-lobule-on-a-chip) incorporates diffusion barriers to mimic endothelial shielding, regulating blood flow-induced shear stress (red) to create an optimal environment for hepatocytes (blue and gray in inset). Adapted with permission from [4], use permitted by author of original publication. (**C**) The heart-on-a-chip employs electrical stimulation to promote cardiomyocyte maturation [5], while (**D**) the intestine-on-a-chip features an integrated barrier during fabrication, allowing for microbiome interactions [6]. Schematic generated with Biorender.

Although most cells in the human body exist in a 3D configuration, traditional 2D monocultures continue to dominate biological research. However, replicating the complex in vivo environment on a chip presents varying degrees of challenges depending on the tissue type. An ideal organ-on-a-chip design should integrate several key factors [2], such as co-culturing capabilities, controlled cell orientation (polarization), medium perfusion, and the use of primary or stem cell-derived cells instead of immortalized cell lines to enhance physiological relevance. In practice, organ-on-a -chip models typically incorporate only some of these features and, at best, are supplemented by physical conditioning (e.g., shear stress, strain, electrical stimuli) to promote cellular self-regulation, specialized gene expression, and functional maturation. These advancements are pushing organ-on-a-chip technology toward more accurate representations of human biology and disease states. For example, lung-on-a-chip systems often include mechanical stretching to mimic breathing [3], while liver-on-a-chip models account for hepatocyte shear stress by utilizing diffusion-based perfusion to provide a protective shielding effect [4]. Similarly, heart-on-a-chip platforms apply electrical stimuli to promote cardiomyocyte maturation [5], while intestine-on-a-chip models integrate barrier functions and microbiome interactions to reflect their native physiological roles [6] (**Figure 7.1**).

As organ-on-a-chip technology advances, increased funding, regulation, and innovation will drive its adoption. Looking ahead, the field could revolutionize drug screening by providing physiologically relevant human-based platforms, replacing animal models in alignment with the principles of 3Rs: refining research models to align with human biology, reducing reliance on animal testing, and replacing animal testing wherever feasible. A key future direction is the development of patient-derived cells, which hold promise for enabling personalized medicine, accelerating disease research, and advancing therapeutic discovery [1, 2].

Current and Future Challenges

Organ-on-a-chip models hold great promise, yet several challenges must be addressed for their full potential to be realized:

- **Cell choice**. Physiologically relevant cultures required replacing immortalized cell lines with primary cells or induced pluripotent stem cells (iPSCs). While primary cells closely resemble in vivo phenotypes, their limited availability, heterogeneity, and low throughput hinder reproducibility. iPSCs offer a scalable alternative but face clonal selection issues and variability in differentiation protocols, raising concerns about whether they fully mature into functional tissue-specific cells. Another challenge is optimizing a common coating substance that allows cells to form a 3D culture within the chip compartment, along with a suitable culture medium that replicates the intended microenvironment. Co-cultures per se may offer a solution, as their synthesized extracellular matrix and secreted compounds can help supplement and stabilize the shared media, though this introduces additional complexity in system standardization.
- **Tissue interaction**. Capturing systemic organ interactions remains a significant challenge. Multi-organ models, such as body-on-a-chip systems, offer a promising approach for studying inter-organ communication and reciprocal cellular responses, which are crucial for understanding complex disease progression, tumor development and metastasis, as well as metabolic and endocrine disorders. The involvement of immune system activity adds another layer of complexity to these models. One highly debated issue is the challenge of scaling. Accurately determining the realtive organ size ratios, perfusion rates, fluid volumes, and stimulus distribution is essential to ensure proper signaling and physiologically relevant responses [7].
- **Materials, instrumentation and protocols**. The diverse applications of microfluidic technology have led to a lack of standardized materials and fabrication methods, hindering reproducibility and cost-effective production. Variability in liquid perfusion systems and instrumentation for nutrient delivery and waste removal further complicates device handling, with protocols differing across laboratories. One material, polydimethylsiloxane (PDMS), has become a leading material in organ-on-a-chip studies due to its biocompatibility, gas permeability, optical transparency, and ease of fabrication via soft lithography. However, its hydrophobicity and porosity limit its use in drug research. Alternative polymers are more challenging to fabricate, while inert glass offers advantages but is difficult to customize for detailed designs.

- **Readout**. Traditional in vitro studies rely on endpoint assays, limiting time-resolved analysis. In contrast, organ-on-a-chip devices can integrate optical and electrochemical sensors for continuous monitoring of microenvironments and cellular responses. However, tracking parameters like pH and oxygen alongside metabolic features adds complexity and may disrupt cell homeostasis, leading to unreliable results. Automated feedback loops remain rare, as fundamental research studies rely on post-experimental time-lapse analysis, increasing repetition, time, and costs while limiting real-time understanding of cellular responses to stimuli.

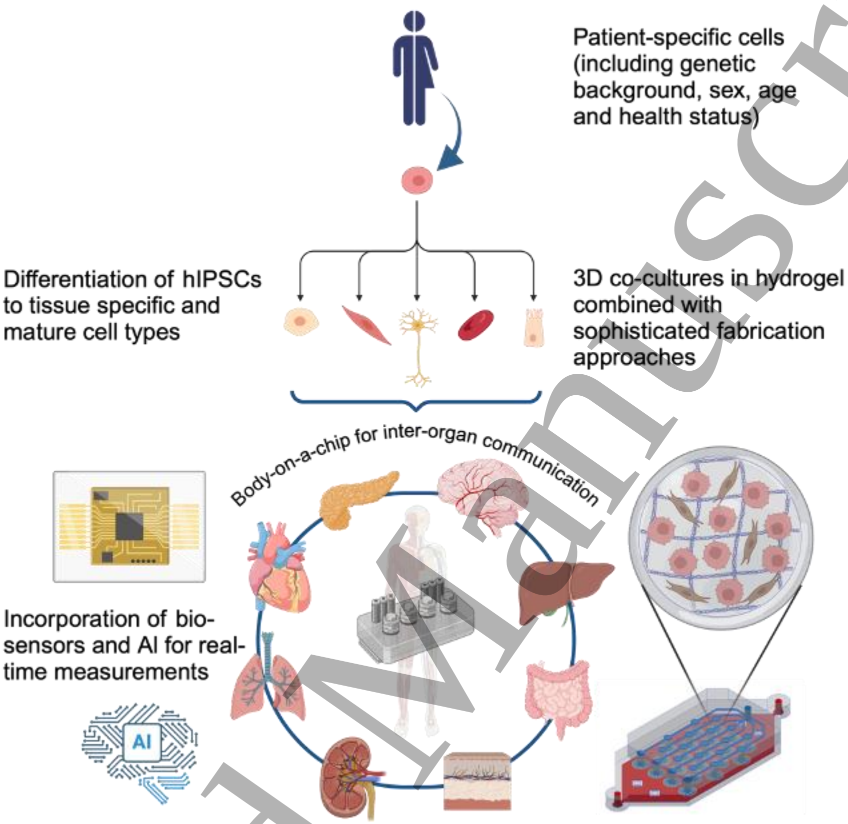

Figure 7.2 | Illustration of the potential integration of microfluidic organ-on-a-chip technology with iPSC-based approaches. Somatic cells, such as fibroblasts, are reprogrammed, karyotyped, and differentiated into specialized cell types using specific protocols. These cells are then ideally cultured in physiologically relevant 3D environments within an optimized extracellular matrix, hydrogel, or synthetic scaffold, maintained under tissue-specific conditions with controlled perfusion. Real-time readouts can be achieved through integrated biosensors and optical sensors compatible with the chip material. With advancements in machine learning and AI, feedback signalling between the platform and instrumentation enables dynamic modulation of the environment. Ultimately, this approach could lead to the development of full-body-on-a-chip or multi-organ-on-a-chip platforms, facilitating inter-organ communication for systemic control and deeper biological understanding. Such platforms hold promise for patient-specific drug development and testing, providing in vitro models for both healthy individuals and disease conditions. Schematic generated with Biorender. The liver chip (bottom right, as in Fig. 7.1B) is adapted with permission from [4], use permitted by author of original publication.

Advances in Science and Technology to Meet Challenges

The interdisciplinary field of organ-on-a-chip is evolving rapidly, integrating advancements in biomedical research, material science, sensor miniaturization, and imaging technologies. These innovations are shaping the next generation of in vitro cell culture systems, enhancing their accuracy and applicability across multiple disciplines. Key advances for the technologies would be:

- **Towards personalized medicine**. A significant step toward personalized medicine involves incorporating patient-specific parenchymal and non-parenchymal cells, including immune cells, into organ-on-a-chip systems. By integrating donor-specific genotypes, these models closely replicate a patient's in vivo environment, enabling precise disease modeling and drug testing. Achieving a full-body-on-a-chip system first requires the development of differentiation protocols for essential cell types, followed by the gradual integration of additional cell types. Advances in proteomics and gene transcription databases are refining these processes, making tissue engineering more reproducible and precise.

- **Biocompatibility and fabrication**. Optimizing scaffolds and coating matrices is critical to supporting multiple cell types. These materials range from extracellular matrix components and hydrogels to innovative options like spider silk. Controlling the microenvironment ensures that media composition, cytokines, and oxygen levels meet each cell's specific requirements. Since different cell types have unique growth conditions, adaptable materials and fabrication techniques are necessary. Material selection must balance biocompatibility, accessibility, and cost-effectiveness. For example, polydimethylsiloxane (PDMS) absorbs lipophilic compounds, making alternatives such as glass, thermoplastics, and biologically derived materials (like hydrogel-based bio-inks) more viable. Coupled with advances in optical printing, bioprinting [8], and laser-based fabrication, high-precision manufacturing methods [9] are improving chip architecture and tissue integration (see also **Sections 6** and **8**).
- **Integrated sensors and real-time data acquisition**. Advanced imaging techniques and biosensors enable real-time, non-invasive monitoring of cells and their microenvironments. Enhanced spatial transepithelial electrical resistance-based sensors provide localized permeability measurements, while 3D printing has improved the efficiency and affordability of microelectrode arrays. Multi-sensor integration is essential for body-on-a-chip platforms, allowing continuous tracking of inter-organ interactions. Additionally, probe-free imaging techniques, such as holographic microscopy and virtual staining powered by machine learning, facilitate long-term, non-invasive monitoring, streamlining data acquisition and conserving resources. Real-time data collection also enables intelligent microscopy-based feedback control, improving precision in dynamic tissue studies [10].
- **Sophisticated Body-on-a-Chip**. Body-on-a-chip platforms represent a cutting-edge advancement in organ-on-a-chip technology, allowing researchers to explore complex physiological interactions driven by dynamic inter-organ communication. These sophisticated systems mimic systemic circulation by incorporating microfluidic networks that not only supply essential nutrients and oxygen but also enable reciprocal molecular signaling between organs via cytokines and metabolites. Additionally, advanced microfluidic designs can generate biomechanical forces such as tissue-specific shear stress. Even dual-tissue multi-organ-on-a-chip platforms offer significant value in drug development, enabling researchers to assess therapeutic efficacy in target organs while concurrently evaluating potential toxicity in metabolically active tissues like the liver or kidneys. This integrative approach provides a more comprehensive understanding of drug metabolism and systemic effects. Incorporating multiple organ models is crucial for studying complex pharmacological processes and systemic diseases, as it captures intricate biological responses that single-organ systems cannot replicate. However, developing these multi-organ platforms poses considerable engineering challenges, particularly in maintaining physiologically relevant scaling ratios and functional relationships between organ units. Addressing these challenges is essential for advancing the field and developing more accurate, reliable, and personalized in vitro models [11] (**Figure 7.2**).

Concluding Remarks

Organ-on-a-chip technology represents a transformative shift in experimental approaches within biomedical research and pharmaceutical development pipelines. At the technological core, the microfluidic devices utilize specialized fabrication techniques to embed human living cells into an engineered environment mimicking key architectural and physiological features of organs and tissues. The result is an in-vitro model exhibiting complexity not achievable in conventional 2D cell cultures. As advancements in biomaterials, microfluidics, and cell culture techniques continue to refine organ-on-a-chip platforms, their potential to revolutionize medicine grows. In academic research, these systems provide unprecedented insights into infection dynamics, toxicity responses, and treatment efficacy through direct, species-relevant cellular observations. Simultaneously, the biopharmaceutical industry is integrating organ-on-a-chip models to enhance compound screening and drug efficacy testing, accelerating the development of personalized therapies tailored to individual patients. With strong pharmaceutical backing and AI-driven drug discovery rapidly identifying novel candidate molecules, the demand for physiologically relevant in vitro models is rising. Organ-on-a-chip systems play a crucial role in this transformation by improving preclinical testing and increasing the likelihood of drug candidates succeeding before reaching costly late-stage trials. Over the next decade, this technology is poised to revolutionize preclinical R&D by reducing failure rates and streamlining drug development pipelines. Notably, its ability to assess tailored carriers (see **Sections 1, 2, 3** and **4**) for cell-specific targeting enables on-chip evaluation of therapeutic strategies aimed at reversing or treating pathological conditions. Consequently, organ-on-a-chip platforms, among the most disruptive and transformative innovations, will play a pivotal role in shaping the future of healthcare in the 21st century. Finally, BoC-inspired designs could offer a powerful tool for assessing the toxicity of environmental pollutants while also addressing various sustainability challenges outlined in the Sustainability Development Goals. These include studying bacterial behaviour in antibiotic resistance, analysing planktonic interactions and their impact on aquatic life, and exploring microplastic interactions with biological matter in soil, ice, or water. With their miniaturized design, these technologies could provide valuable insights across multiple research fields.

Acknowledgements

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08 – Towards printed animate matter

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Status

The overwhelming majority of work on printed 'active' matter falls under the umbrella of bioprinting, which aims to recapitulate the physiological form and function of an organ for use in regenerative medicine or *in-vitro* modelling (see also **Sections 6** and **7**). A more niche, albeit rapidly growing area applies the advanced fabrication techniques used in bioprinting to incorporate active components into complex structures as working parts, producing a distinct class of materials: Printed Animate Matter ('PAM'). To be classified as PAM, systems must satisfy three criteria. First, they must have some sort of architected structure, either through fabrication or controlled self-assembly. Second, they must incorporate embodied energy or the means to convert energy from their surrounding environment; they do not simply relax to equilibrium. Third, they must consist of discrete, potentially autonomous building blocks that can collectively give rise to complex emergent behaviour. The typical size scale of these building blocks is on the order of 10 to 100 µm, with printed ensembles reaching millimetre-to-centimetre scales depending on fabrication method. Although the field is in its infancy, materials that satisfy some of the criteria of PAM have already had translational impact, attracting venture capital in the areas of synthetic biology (see also **Section 1**), structural colour, and soft robotics (see also **Sections 10** and **11**). Materials that satisfy all the above criteria have found laboratory-scale applications in stem cell culture, soft electronics, and ecological complexity modelling. We can expect further uptake and development within the next decade, with potential applications in environmental remediation and alternatives to hydrocarbon-derived plastics.

The most developed printed animate materials are tissue-like, droplet-based constructs built around droplet interface bilayers ('DIBs', **Figure 8.1A**) [1]. DIBs form when phospholipid surfactants adsorb to oil-water interfaces and zip together to form bilayers when two droplets are brought into contact. The resulting droplet-droplet adhesion enables the printing of complex structures comprised of thousands of droplets. Incorporation of nanopores into the bilayers enables size-selective, spatially defined communication between droplets. Incorporating hydrogels into the printed structures leads to remarkable robustness, enabling the fabrication of light-, heat-, or magnetic-field-responsive structures. More impressive still is the incorporation of living material and its interfacing with a synthetic component. Recently, a battery formed from a printed chain of ion-selective hydrogel droplets was connected to another chain of droplets containing neural progenitor cells [5]; the resulting electrical stimulus led to a marked change in cell behaviour.

Given its affordability, ease-of-use, and breadth of commercially available and open-source implementations, extrusion printing is the most popular platform for producing PAM. Using this approach, structures that incorporate diatoms, bacteria, and even mycelium have been made (**Figure 8.1B**) [2], with applications in pollution sensing, cellulose synthesis, and a remarkably resilient living synthetic skin. Extrusion printing naturally lends itself to the production of vascularised structures by writing fibrillar, sacrificial structures into shear-thinning, yield-stress support baths. This approach has been harnessed to produce animate materials ranging from wholly synthetic autonomous soft robots (**Figure 8.1C**) to vascularised, organ-like constructs comprised of aggregates of thousands of living cell spheroids [6].

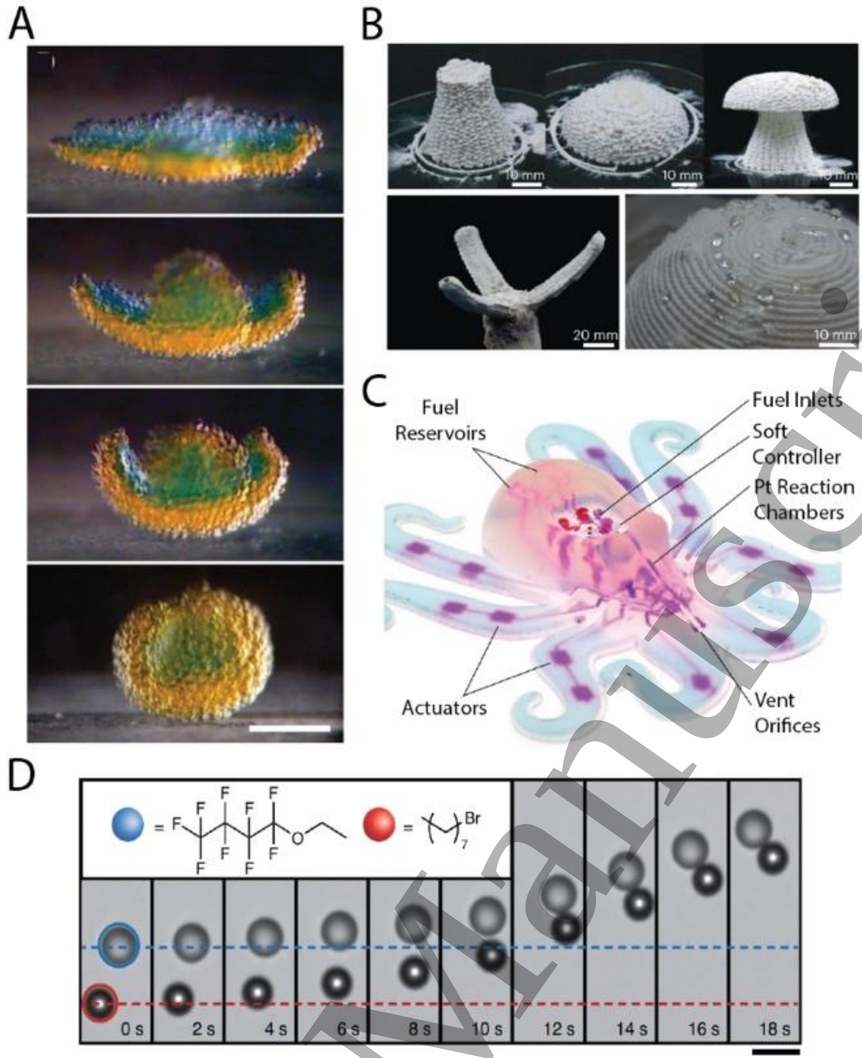

Figure 8.1 | Examples of printed animate matter or its building blocks. (**A**) Reconfigurable droplet-based constructs that change shape due to liquid flow between interconnected compartments. Scale bar, 200 µm. From Villar *et al.* [1]. Reprinted with permission from AAAS. Copyright © 2013, AAAS. (**B**) Living structures of mycelium made from inoculated, printed scaffolds. Scale bars: 10 mm in all images apart from lower-left, which is 20 mm. Reproduced with permission from Gantenbein *et al.* [2]. Copyright © 2022, Springer Nature. (**C**) An autonomous, soft robot that is driven from equilibrium by an incorporated power source. Reproduced with permission from Wehner *et al.* [3]. Copyright © 2016, Springer Nature. (**D**) Motility, chasing, and dissipative self-assembly in a system of two species of droplet. Scale bar, 100 µm. Reproduced with permission from Meredith *et al.* [4]. Copyright © 2020, Springer Nature. Note that only **B** and **D** satisfy all three criteria of PAM.

Current and Future Challenges

There several key challenges associated with further development of PAM, namely:

- **Building a Community.** The biggest barrier to developing the field of PAM is getting researchers in active matter, advanced fabrication, systems chemistry, and tissue engineering to speak to one another. The dialogue between 3D printing and tissue engineering has a long and successful history. By contrast, interactions between these areas and active matter are surprisingly infrequent; soft and active matter physicists still work too rarely with complex biological systems. Taking a loose definition of 'printing', the advanced fabrication community has been too slow to adopt holographic optical and acoustic tweezers. The main obstacles to intercommunity collaboration are the perceived expense of bioprinting methods, the perceived difficulty of building and using holographic optical and acoustic tweezers, and the fundamental focus of active matter work. The surge in recent years of cheap and open-source soft matter fabrication methods provides some wonderful opportunities to address this shortcoming.

- **Integrating Dissipative Systems and Advanced Fabrication.** Recent developments in systems chemistry must be integrated into advanced soft matter fabrication techniques. The last decade has seen huge advances in dissipative self-assembly, chemical reaction networks, and stimulus-responsive soft materials. PAM is a powerful setting for investigating what happens when dissipative chemistries that lead to active phase-separation, dynamic self-assembly, or quorum sensing are placed in a structurally complex setting. To maximise translational impact, the active matter community should look at the biocompatible hydrogels used in tissue engineering that incorporate stimulus-responsive cross-linking using biologically active moieties, host-guest interactions, or focussed ultrasound. There are a wide range of active, artificial cytoskeletons that have been incorporated into droplets and vesicles, although these systems are challenging to work with. Easier-to-use are the wealth of active droplets driven from equilibrium by encapsulated chemical compounds (**Figure 8.1D**). Droplets containing magnetic material, whether confined to a soft interface or encapsulated in the bulk, can exhibit highly controlled response to external fields and the emergence of dissipative structures.
- **Developing Design Heuristics.** The field needs to develop simple design rules that relate how complex behaviour emerges from active building block composition and fabricated structure. The protocell community (see also **Section 1**) already incorporates cells, biological machinery, and minimal mechanisms that reproduce biological phenomena into materials that are easy to integrate into advanced fabrication workflows. The active colloids community (see also, **Section 2**) has already designed a huge range of materials that are readily compatible with the printing methods presented here. Discovery-led work that investigates how ensembles of these materials behave when integrated into complex structures have the potential to inform design rules in the fields of metamachines (see also, **Section 4**), biohybrid robotics (see also, **Section 11**), and swarm robotics (see also, **Section 17**).

Advances in Science and Technology to Meet Challenges

To meet the previous challenges, some key advances are needed:

- **Open Hardware.** The proliferation of open-source modifications to fused deposition modelling (FDM) printers in recent years has led to remarkable innovations in chemistry, lab automation, and bioprinting. These advances have happened because of the affordability of FDM 3D printers (a good-enough model currently costs <£300) and the ease with which these setups can be programmed and modified. Most important has been the willingness of the 3D printing community to share its ideas, with knowledge exchange nucleated through hackspaces; the global proliferation of cheap, self-built bioprinters is a stand-out example of what happens when this approach works. While the adoption of self-built devices has been strongest in the extrusion printing community, recent growth in the publication of designs for droplet printers (**Figure 8.2A**) means this area is likely to see a similar surge soon. Such an approach must be taken to the wealth of other advanced fabrication techniques, especially optical methods such as digital light processing and stereolithography. Laudable efforts have already been made to facilitate broader use of holographic acoustic (**Figure 8.2B**) and optical manipulation (**Figure 8.2C**, see also **Section 5**), however the perceived technical barriers to uptake of these setups, particularly for 3D manipulation and fabrication, remain significant and their use is rather limited compared to that of modified FDM printers. Similarly, the community must embrace a willingness to share practical realities of techniques that go beyond the ‘Materials and Methods’ section, echoing the success of similar initiatives in organic chemistry (e.g., Not Voodoo) and the life sciences (e.g., OpenWetWare).

- **Autonomous Hardware.** The design principles of active systems and the collective emergent behaviour that they exhibit need to be better understood and reduced to heuristics. This Roadmap documents a great deal of progress in this area, but for translational impact the discipline needs formulation science as well as fundamental science. Automated and high-throughput methods that incorporate algorithms for accelerated or curiosity-driven exploration of parameter space could prove particularly powerful here. These approaches naturally lend themselves to PAM in which the printer itself plays an active role in the experiment; successful implementations of this concept have led to evolutionary droplet printers that can uncover a rich array of behaviour from a simple model system [10].
- **Multiscale, Multidimensional Characterisation.** Microscopy methods that couple spectroscopic analytical chemistry techniques to multiscale optical characterisation must be applied to provide insight into how processes are coupled across the wide gamut of length scales in PAM. Such techniques are already either in use or under development in the life sciences; the major challenge comes in implementing them without the need for expensive equipment and large-scale facilities. Similarly on a theoretical level, models that connect a systems chemistry approach with the structural evolution of soft cellular systems would enable bottom-up approaches to rationally designing synthetic animate tissues. These models must be simple and insightful rather than complicated and over-parameterised.

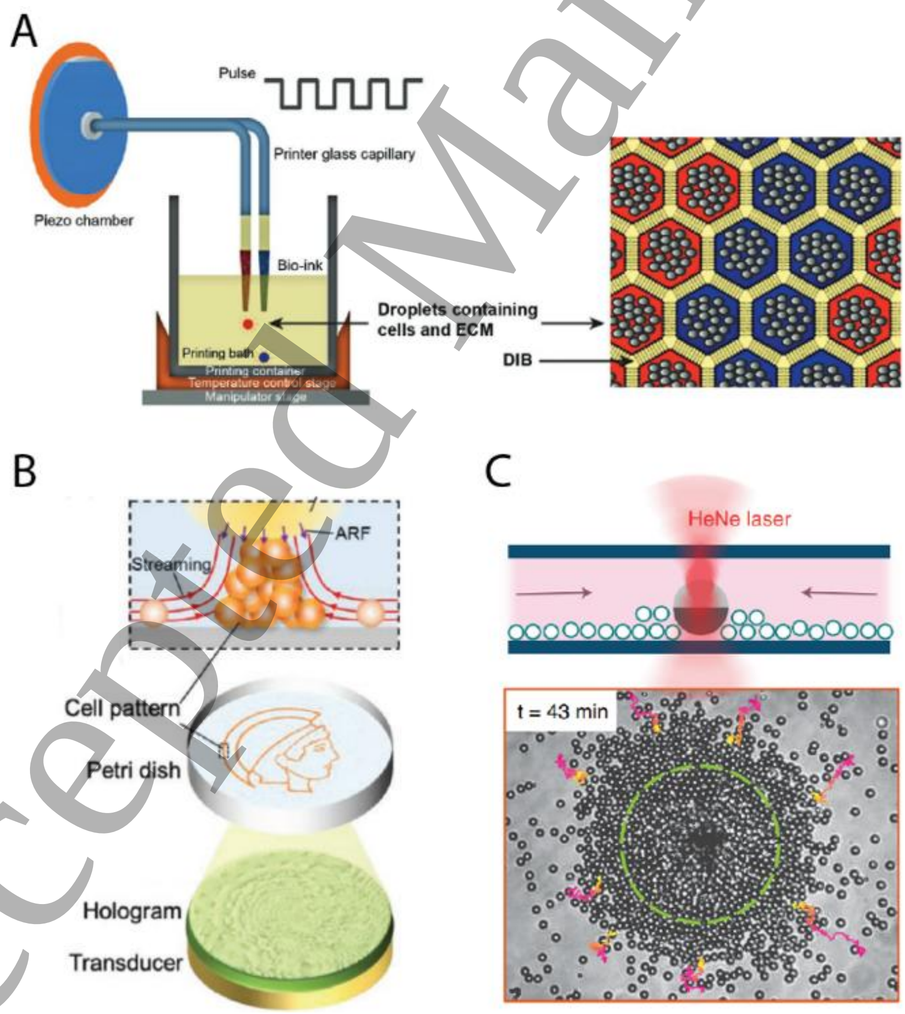

Figure 8.2 | Methods for fabricating printed animate matter. (**A**) Droplet deposition printing used to produce DIB-based synthetic tissues. Reproduced with permission from Zhou *et al.* [7]. Copyright © 2020, John Wiley and Sons. (**B**) Complex

patterns of living cells assembled using acoustic tweezers. Reproduced from Ma *et al.* [8], use permitted under the CC-BY 4.0 licence. (**C**) A self-building random laser that is nucleated by optical tweezing. Reproduced with permission from Trivedi *et al.* [9]. Copyright © 2022, Springer Nature.

Concluding Remarks

Printed Animate Matter brings together the principles of active matter and advanced fabrication to produce materials that draw inspiration from biological tissues. These materials are inherently cellular, consisting of individual, energy-converting building blocks that are arranged in an architected structure. The resulting systems are soft, reconfigurable constructs that exhibit complex, emergent, and programmable functionality. To drive this field forward, what is needed is more knowledge exchange and collaboration between the fields of advanced fabrication, active matter, systems chemistry, and tissue engineering. Active matter physicists must embrace chemically and biologically complex systems; recent efforts to understand the physical principles of confluent cell monolayers, multi-cellular algae, and even tissue spheroids are laudable, but still too rare. Tissue engineers must embrace unconventional fabrication techniques such as holographic optical and acoustic tweezers. Advanced fabrication researchers must embrace dissipative self-assembly to design materials that print themselves. Implementation of many of these ideas is already well underway, but the field has plenty of space for new entrants.

Acknowledgements

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09 – Self-folding orikata

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Status

The origins of origami are now obscured by time but are plausibly as old as paper itself. Recently, however, origami and kirigami, a related art in which one folds and cuts paper, have emerged as a powerful tool to manufacture and actuate three-dimensional shapes [1]. Unlike traditional 3D printing, in which a structure is built layer-by-layer, orikata – meaning "folded shapes" and which we will use to refer to both origami and kirigami – begins with a flat, patterned substrate which subsequently folds up into the target 3D shape [2]. Whereas 3D printing has been touted as a route towards rapid prototyping, self-folding structures can potentially be fabricated in bulk and in sizes that might otherwise be difficult to achieve. The field has advanced rapidly, and numerous examples of self-folding structures can be found in the literature with sizes from the micro- to macroscopic (**Figure 9.1**). The long experience of origami artists has provided a wealth of structures for use in engineering applications, including in soft robotics (see also **Sections 10** and **11**), deployable structures (see also **Sections 12** and **16**), architecture (see also **Section 20**), and metamaterials (see also **Sections 13** and **15**) [1], as well as in biomedical applications including drug delivery, stents, and new tools for surgery (see also **Sections 2, 3** and **4**) [3]. Technological advances have even enabled origami microrobots and devices that can fold and refold into many different shapes [4].

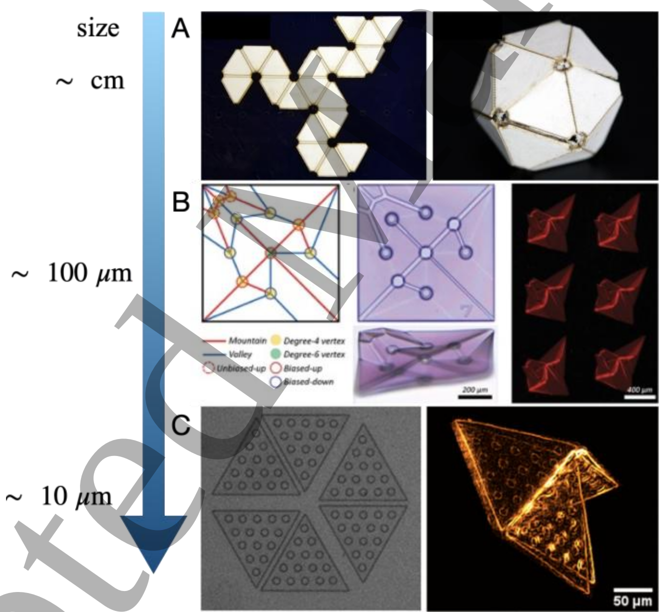

Figure 9.1 | Self-folding orikata spanning multiple scales. (**A**) Macroscopic shape memory composite by heating. Reprinted with permission from [4], Copyright © 2014, IOP Publishing Ltd. (**B**) Polymer trilayer folded by swelling. Reprinted with permission from [11], Copyright © 2019, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (**C**) Folding nanofilms. Reprinted with permission from [5], Copyright © 2020, American Chemical Society.

One question one might ask is whether there are any limitations to what shapes could be formed in this manner. Here, the answer is clearly no. First, there are algorithms to generate a fold pattern that can be folded into a given polyhedron from a single sheet of paper, though the results can sometimes be unwieldy [4]. Other algorithms produce origami tessellations [5], or kirigami structures [8] that approximate arbitrary shapes.

In recent years, however, several fundamental limitations of our understanding of self-folding orikata have become apparent. There appears to be a deep connection between the foldability of orikata with rigid faces and computation [9]. The foldability of orikata simplifies when faces can bend, but then the number of folding pathways grows exponentially with pattern complexity. Between these extremes, the energy landscapes of origami exhibit features of glassiness [10] and complexity that can prevent successful folding [11]. This proves a fertile ground for methods of physical learning, in which an origami material can be *trained*, because of material plasticity, to self-fold along a desired pathway. In physical learning as applied to origami, one looks for a local rule that changes the properties of the folds. Subsequently, one is training the origami to self-fold along the desired pathway much as one might train a neural network to recognize patterns [10].

Current and Future Challenges

The long history of origami means there is no shortage of fold patterns to exploit in new devices. There are challenges both to improve implementation of self-folding orikata and also fundamental associated with the physics of orikata, but all are within reach in the coming decade.

- **Improved material systems.** The range of cost-effective materials that can be used to drive repeated folding and unfolding must be increased. The challenges for these materials are to improve scalability of material platforms while also improving control over the angle of individual folds and the forces that drive folding.
- **Understanding kinetic constraints and foldability.** Another challenge for physics is to understand how to take advantage of kinetic constraints and energetics to program robust folding pathways, especially as complexity is increased. As in protein folding or self-assembly, self-folding orikata must find a target ground state in a high-dimensional, complex energy landscape. Orikata, however, also provide kinetic control over fold geometry and fold stiffness that can be used to hierarchically control the shape and complexity of that landscape. The rigidity of the faces relative to the folds, for example, can be used to tune the nucleation of metastable states and the depth of the deep valleys along which orikata are constrained to fold [11]. Orikata already display many hallmarks of complex physics: the multistability of origami structures can exhibit hysteresis, return-point memory, and other phenomena of complex dynamical response [12]. In greater than one dimension, one expects hysteretic elements to interact to unveil new phenomena, shedding additional light on the connections to computation and physical learning [9,10].
- **Understanding fluctuations and errors.** As origami structures shrink, they will be subject to additional random forces, either thermal motion or motion due to athermal, external driving. Surprisingly little is known about statistical mechanics and phase transitions in branched energy landscapes, but at small scales, the branched structure of the energy landscape [10] suggests that entropy will play a role in determining expected states of self-folding orikata. As one example, thermal fluctuations of structureless, thin sheets are believed to drive a crumpling transition; in the case of origami, whether and how this transition might happen is not clear.
- **Extending the range of deformations.** Origami often produces shapes by hiding extra paper wastefully. In addition to folding, however, one might imagine growing or shrinking the faces so that the vertices develop a small excess or deficit angle. This would be a discrete analogue to a non-Euclidean sheet (or 4D printing), in which the in-plane and out-of-plane stresses are frustrated to buckle into complex 3D shapes (see also **Section 12**). One can envision orikata that are connected into a non-flat topology either by self-assembly (**Figure 9.2**) or as a multi-layered structure that unfolds from flat to 3D as would a children's pop-up book. The interplay of topology, fluctuations, and folding remains uncharted.

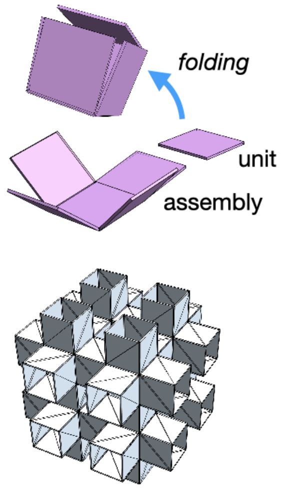

Figure 9.2 | Self-assembling tiles to generate complex or actuating structures. (Top) Self-assembly is an alternate pathway to forming complex origakata at the nanoscale. This can produce origami-like structures that cannot be folded from a flat sheet without gluing. (Bottom) A model of a triply-periodic orikata that can be formed with triangular units having the symmetry cubic symmetry. This cannot be folded from a flat sheet of paper but could be assembled from triangular units following simple rules.

Concluding Remarks

The use of self-folding orikata presents a transformative approach to manufacturing by enabling efficient, high-precision fabrication of complex 3D shapes from simple 2D templates. This method minimizes waste, reduces production costs, and enhances scalability, making it an attractive solution across industries. Self-folding orikata can enable the development of smart materials that dynamically adapt to climate and ecological changes by altering their shape, properties, or functions in response to environmental stimuli like temperature, humidity, or light. Moreover, the inherent adaptability of these techniques to micro- and nanoscale applications, combined with the biocompatibility of many foldable materials, opens exciting opportunities in personalized medicine. From deployable medical devices to innovative drug delivery systems, orikata-based designs could revolutionize packaging and transport of sensitive biological materials, ensuring safer and more efficient healthcare solutions. Beyond their potential to revolutionize manufacture, self-folding orikata raise critical, and fundamental, questions that highlight the relationship between geometry and elasticity. The basic science has progressed far enough to foresee the use of folding in many engineering applications. Yet, I have argued that there are also remaining questions that connect to physics, especially when coupled to actuation and motion. These questions speak to a need to further develop the technology and of continued theoretical development. Orikata constitute a new class of materials and structures for physicists to explore questions of energy landscapes, hysteresis, and fluctuations.

Acknowledgements

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10 – Soft robotics

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Status

A key challenge in robotics is to make robots interact with natural (unstructured) environments and with living beings effectively and safely. To this aim, animals exploit flexible, elastic, and soft tissues, relying on the inherent compliance and adaptability of their body structures. Many animals even have fully soft bodies or use fully soft appendages for extremely dexterous manipulation (e.g., the elephant trunk). This has inspired roboticists to develop a so-called *soft robotics* approach (**Figure 10.1**) [1], which could enable deformable and adaptable robots for applications in fields such as industrial manipulation of unknown or fragile objects (including fresh produce), collaborative assembly with human operators, search & rescue following natural disasters and climate change-related extreme events, as well as minimally invasive medicine [2].

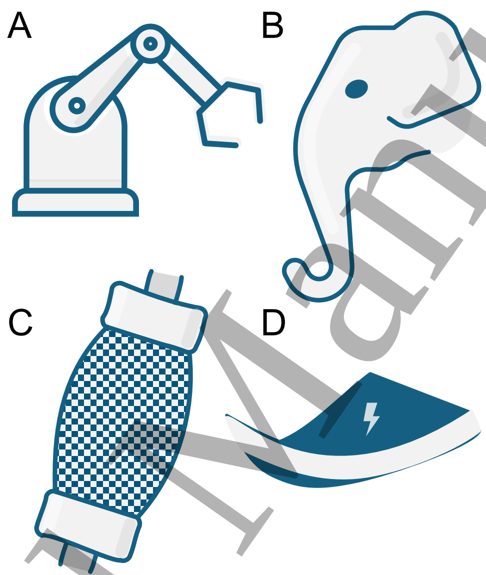

Figure 10.1 | From rigid to soft robots. (**A**) Traditional robotic manipulator with rigid links. (**B**) Example of nature as a source of inspiration for soft robots: the elephant trunk. Examples of soft actuators: (**C**) pneumatic artificial muscles and (**D**) dielectric elastomer actuators.

Soft robots can be defined as robotic devices that can interact with the environment with high compliance and deformability (see also **Section 11**) [3]. The term initially referred to robots with compliant joints or compliance control and has then identified with the shift from robots with rigid links to continuum robots that are inherently compliant, for instance by consisting of flexible or soft materials (e.g., elastomers and gels). The soft robotics approach thus consists of exploiting compliance and softness of (some of) the robot components to make them more easily and naturally interact with the physical world, without the need for controlling all movements with the highest precision.

In soft robotics, therefore, the distinction between the 'mind' and the body starts to blur. The soft robotics approach can help in making robots inherently adaptable and robust. In other words, it has the potential to make robots more autonomous and intelligent, exploiting the computational features of their bodies rather than just those of their 'brains' (see also **Section 16**) [4]. In this context, materials become key robotic components, not only because of their structural properties and role, but also, and especially, because they implement *functions*. Indeed, smart, stimuli-responsive polymeric materials can be used as soft actuators and/or sensors in soft robots (see also **Section 9**). The design of robots' body and 'mind' thus become intertwined, implementing the principles of *embodied intelligence* observed in living beings [5], leading to the proposal of the term *Physical Artificial Intelligence* (PAI), which involves the co-evolution of body (including morphology, actuation, and sensing) and control (see also **Section 16**) [6].

The soft robotics approach could lead to a new generation of life-like (soft) robots. Soft robots span in size from the metre scale (elephant trunk-like manipulators or growing robots) down to the sub-millimetre scale (soft microrobots) and can consist of pneumatic, elastomer-based bodies or of smart polymers and gels. Pneumatics is used for robots required to exert large forces and that can be connected to pressure lines. Small scale, integrated robots, which have tightest requirements on their tethering but are not required to generate large forces, can be realised with smart polymeric materials [7]. Moreover, the soft robotics approach is functional to the development of autonomous and intelligent small-scale robots (e.g., sub-millimetre robots known as microrobots) [8]. This represents a challenging test field as, given their size, small-scale robots cannot be assembled out of standard components and can greatly benefit from implementing robotic functions in the constituent materials (see also **Sections 3 and 4**). Indeed, in small-scale robots, the material *is* the robot.

Current and Future Challenges
Challenges for soft robotics include:

- **Modelling and control.** Unlike 'traditional' robots made of rigid metallic links and (most often) electromagnetic motors and sensors, which can be accurately designed, fabricated, modelled, and controlled, soft robots are (at least partially) made of soft materials, such as elastomers [9]. Whereas it is relatively simple to fabricate inflatable elastomeric actuators or pneumatic artificial muscles to make soft robots move, doing it with the accuracy and precision needed in many robotic applications is far from trivial. Modelling and controlling the behaviour of such soft robotic parts also presents additional challenges, related to the nonlinear and viscoelastic properties of the adopted soft materials. Model-free, data-based control approaches are thus taking traction in the field [10].
- **Actuation materials.** Despite the wide adoption of pneumatic actuators, soft robotics has stimulated (and has been stimulated by) research on smart and active materials that can work as soft actuators and artificial muscles or as soft sensors. They include Electro-Active Polymers (EAPs – e.g., Dielectric Elastomer Actuators) and other stimuli-responsive polymeric materials (thermo-responsive, photo-responsive, or chemo-responsive – e.g., hydrogels and Liquid-Crystal Elastomers). Nonetheless, no smart material is currently able to meet all the specifications required to a general-purpose soft robotics actuator, and the choice of a smart material as actuator depends strongly on the specific implementation.
- **Distributed intelligence.** In addition, if a material responds to environmental stimuli and conditions, rather than to provided control stimuli, they can act as sensors and actuators at the same time, implementing *reactions* to the environment. Indeed, an opportunity and challenge for soft robotics is the progressive decentralization and distribution of 'intelligence' to the different materials and parts of the body (see also **Section 16**). These reactive behaviours are of particular interest for small-scale soft robots, which must have a simple, electronics-free architecture and can make use of reactive materials to achieve some level of autonomy [8].
- **Power.** Powering soft robots could also prove particularly challenging, especially if untethered operation must be achieved. Indeed, almost no soft power sources or batteries exist, and smart material actuators can have peculiar input requirements (e.g., very high voltages).

Moreover, in the most widespread case of soft robots actuated by pneumatic artificial muscles, a source of compressed air must be used, which is difficult to integrate on board and is thus often off board. Especially when untethered operation is required, energy efficiency becomes an issue, as most soft smart polymer actuators are highly inefficient.

- **Life-like bodies.** Finally, the abilities to grow, self-heal and degrade in the environment are pursued to make soft robots even more adaptable, resilient, and sustainable [11]. Durability of most soft materials is inherently lower than that of metals, which becomes an issue in applications in harsh environments (search and rescue) or extending over long periods of time (exploration). Nonetheless, even in other cases, the performance of soft robots could worsen over time due to a deterioration in material properties.

Advances in Science and Technology to Meet Challenges

To meet the challenges mentioned above, these advances are needed:

- **High-performance smart polymers actuators.** Enhancing the actuation (or, in general, functional) performance of stimuli-responsive polymeric materials, as well as their practicality, could greatly benefit soft robotics. Higher forces, deformations, or frequencies might be needed to match the performance of natural muscles. Moreover, lower power consumptions/higher efficiencies, as well as extended durability would significantly enhance the practicality of such materials and make them a standard choice as soft robotics components.
- **Soft robotics components.** Efforts are also needed to improve the integrability of smart polymeric materials' components, by providing practical and standard ways to interface them with the rest of the robot, e.g., with power supplies and controllers. Developing easy-to-assemble, or even plug-and-play, soft robotic components based on such materials could boost their translation from material science to robotic applications.

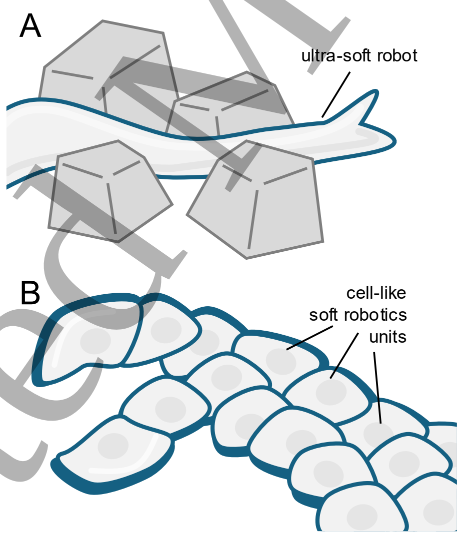

Figure 10.2 | Future advances in soft robotics. (**A**) Improvements in responsive materials and new designs can lead to enhanced soft robots able to grow and squish, and to navigate complex environments autonomously. (**B**) Multi-agent soft robots could be developed consisting of basic functional units akin to biological cells.

- **New designs and ultra softness.** Improving responsive/smart materials for soft robotics components could indeed enhance (soft) robots. Further benefits could come from new design and fabrication methods, as well as from innovative actuation, sensing, and control approaches, that could lead to even softer (or *ultra-soft*) robots able to dramatically change their body shape, growing or squishing, and thus moving in extremely cluttered environments and narrow openings (**Figure 10.2A**).

- **Cell-like active units.** Moreover, the field could be revolutionized by the realization of active/autonomous matter units akin to cells – the fundamental units of living beings. These could implement functions such as active deformations and movement, interact with each other and with the external environment, consuming energy already available in the environment or purposedly provided. These functional active units should self-assemble and self-organize, while it should be possible for their collective dynamics to be steered or controlled by input signals (**Figure 10.2B**). This will require a major shift in the design, construction, and operation of (soft) robots, with the potential advantage of drastically improving the robots' robustness and adaptability. The units could consist in centimetre-scale electromechanical devices based on standard rigid materials that collectively behave as a soft body robot [9-10], or could themselves be soft and squishy (and perhaps small) as natural cells, possibly consisting of enclosed suspensions of self-propelled particles (see **Sections 2**) or other active matter systems (see also **Sections 3, 4** and **5**).
- **Sustainable and biodegradable materials.** Finally, responsive and active materials that, in addition to providing functionalities and performance, are not harmful to the environment and could instead degrade safely after the robots' life are highly needed to make (soft) robots sustainable. This will also be necessary to develop biomedical soft microrobots that could operate and then biodegrade inside the human body.

Concluding Remarks

Soft robotics has had the merit of providing a new paradigm in robotics, shifting the focus from highly-precisely fabricated and controlled components to the exploitation of the intrinsic compliance of soft materials to achieve high adaptability to the environment. This has required the contribution of roboticists, material scientists and engineers alike. Although soft robotic components (e.g., soft grippers or pneumatic actuators) have become widely used and already found specific real-world applications, there is still a long way to go for fully soft robots. These must prove their full potential, with performance and operability better than, or at least on par with, traditional robots. In the next decade, this is likely to happen for specific applications for which soft robots can be better suited than traditional robots, such as manipulation of unknown objects, including fragile ones, and medicine (compliant interaction with body tissues). In addition, further evolution of soft robotics based on advances in responsive materials and active matter could lead to completely novel capabilities and open application opportunities that are completely precluded to traditional robots. A specific application field in which a new generation of soft (micro)robots could play a major role is that of minimally invasive medical robotics, which present challenges for the movement of the robot, its intimate interaction with delicate tissues and its end of life.

Acknowledgements

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11 – Biohybrid robotics

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Status

Advances in robotics have actively contributed to reducing human labour needs in agriculture, manufacturing, and shipping [1]. New robotic tools have led to advances in medical interventions, including targeted drug delivery and robot-assisted surgery [2]. Cutting-edge mobile robots are being tested for applications in search-and-rescue and reconnaissance (see **Section 17**) [3]. However, there are still many challenges in developing soft, safe robots with the adaptability, behavioural flexibility, and robustness seen in animals (see also **Sections 10** and **16**). The ability to achieve these capabilities in robotics would enable robots to be deployed in a wide range of applications where the current rigid state-of-the-art robots currently pose risks, such as in healthcare, ecological monitoring, and environmental repair. To overcome these problems, a growing area of research is investigating the concept of biohybrid robots, which are robotic systems that combine living organisms or biological cells and tissues with synthetic components. Biohybrid robots are composed of a synergistic combination of organic and synthetic systems, with the organic components often taking the role of structure, actuator, sensor, or control [4,5,6].

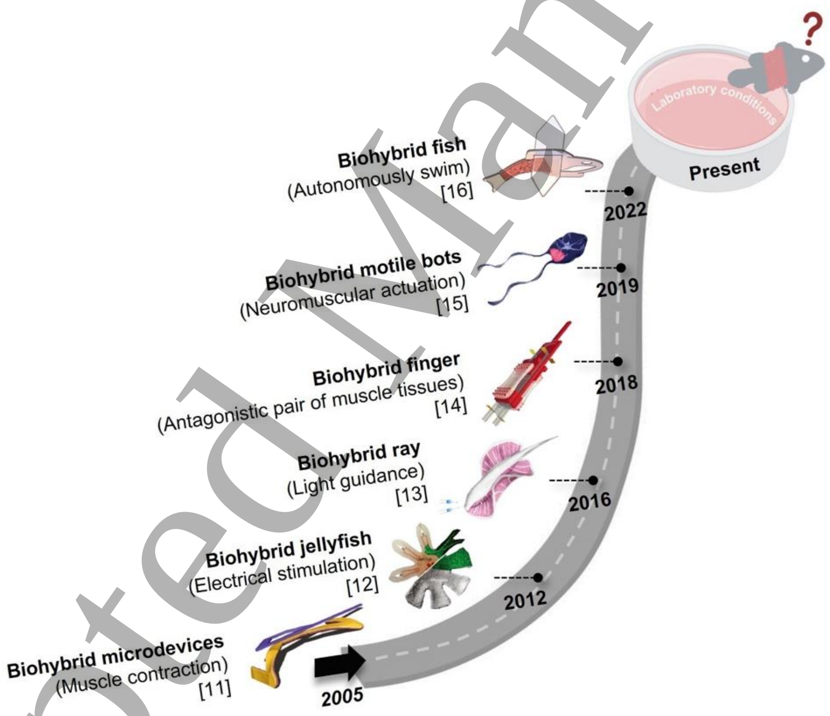

Figure 11.1 | Time evolution of tissue-based biohybrid robots. Schematic overview of a brief history of tissue-based biohybrid robotics. Adapted in part from open access reference [10] under CC-BY 4.0, and with permission from primary sources: biohybrid microdevices reproduced with permission from [11], Copyright © 2005, Springer Nature; biohybrid jellyfish reproduced with permission from [12], Copyright © 2012, Springer Nature; biohybrid ray from [13], reprinted with permission from AAAS, Copyright ©2016, AAAS; biohybrid finger from [14], reprinted with permission from AAAS, Copyright © 2018, AAAS; biohybrid motile bots reproduced from [15] under CC-BY-NC-ND with authors' permission – permission must be obtained from the authors before further reuse; and biohybrid fish from [16], reprinted with permission from AAAS, Copyright © 2022, AAAS. Additional graphics were created using Biorender. Webster-wood, V. and Seok J. (2025) https://BioRender.com/h81u145.

Representative biohybrid robots are mainly categorized into micro-organisms, tissue-based biohybrid robots, and cyborgs [5]. Although biohybrid robotics shows great promise for creating future robotic solutions that are adaptable, sustainable, soft, and biocompatible, many challenges to applying these approaches beyond basic research remain. Each category of biohybrid robots faces its own unique challenges. Therefore, in this section, we will discuss the current and future challenges and directions to overcome the current limitations in tissue-based biohybrid robotics, which can enable biomimetic movements such as walking, grasping, and swimming by external stimulation at the millimetres to centimetres scale (**Figure 11.1**).

Current state-of-the-art tissue-based biohybrid robotics research has focused on fabrication, material selection, and recently, sensing and controls. Fabrication approaches for tissue-based biohybrid robots can be categorized as top-down and bottom-up methods [7]. In top-down methods, natural tissues are explanted and used on the robot with the advantage of maintaining the mature tissue hierarchy. In contrast, bottom-up methods start by cultivating small organic units, which can be designed to fit the desired shape of the robot. Commonly, flexible elastomers and hydrogels are used as the body, and the robot is co-assembled with cast or 3D-printed tissue for the biological component [8]. True robots exhibit a sense-plan-act cycle in which they sense the world around them, plan motions and tasks, and act in response. Only recently have tissue-based biohybrid robots begun achieving sensing and basic motion control [9]. However, their current capabilities in this realm still fall short of traditional robots. Therefore, integrated sensing, motion planning, and actuation are important focus areas for enhancing biohybrid robots.

Building on this state-of-the-art and overcoming existing challenges in biohybrid robotics will allow tissue-based biohybrid robots to move beyond the laboratory. In the following sections, we present existing challenges in tissue-based biohybrid robotics and suggest research needed to overcome them. By focusing on the fabrication, achieving a sense-plan-act cycle, and improving the longevity of biohybrid robots, researchers can move the field towards the long-term goal of biohybrid robots that outperform synthetic counterparts by leveraging living materials to improve adaptability, and energy efficiency, or sustainability [5]. Achieving these goals will allow biohybrid robots to safely monitor and repair fragile environments, whether that be in medical settings within the body or environmental settings where they could be deployed *en masse* to monitor changing climates without posing a risk to the ecosystem should they be lost or damaged.

Current and Future Challenges

There are several key challenges facing the development of biohybrid robots which should be focused on in the coming years:

- **Fabrication.** Both top-down and bottom-up fabrication methods face challenges in creating biohybrid robots. For top-down methods, it is challenging to maintain tissue functions after explanation from the animal, to resize the pre-designed structure, and to connect the tissues to the robots robustly. In bottom-up approaches, the biological cells self-assemble based on their surrounding environment to form the final tissue. Therefore, bottom-up approaches allow embedding functional organic components more precisely on the biohybrid robots than top-down methods. However, manufacturing reproducibility, and, therefore, functional performance reproducibility, is difficult to achieve when fabricating systems with biological components, which are apt to remodel surrounding hydrogels and adapt or change in response to environmental cues. Current fabrication practices are also bench-scale, often creating only a few robots at once. Scalable manufacturing of these devices for future commercial deployment faces many challenges, including the need for production of large quantities of cells, precise spatial patterning of cells and extracellular matrix proteins, and sterility requirements throughout production.

- **Sense-Plan-Act.** Sensing, whether of internal states or external features, remains a substantial challenge in biohybrid robots due to the relative sizes of sensors to detect relevant cues and the small payload of existing biohybrid robots [6]. In addition, sensors that require complex signal processing are challenging to package appropriately for integration with other biohybrid components. Using biological components directly as sensors, such as optogenetic sensing of light, is one way to overcome these challenges, yet it restricts the types of cells that can be used due to the need for genetic tools. For autonomous biohybrid robots, motion planning is needed for behaviours more complex than feed-forward walking, gripping, swimming, and pumping. However, controlling cell-based actuation is challenging due to stochasticity in actuator response and structure. To date, external electrical or optical triggers activate most biohybrid motions [10], which limits translation beyond the lab. Much of the research in tissue-based biohybrid robots has focused on actuation. While small and soft robots have been demonstrated using muscle-based actuators, a key challenge is that the low structural integrity of the muscle tissue can lead to structural instabilities and even tearing of the actuators. This mechanical limitation, combined with low force, limits the design space available for current biohybrid tissue-based robots.
- **Life support:** Sustaining many of the components within biohybrid robots as they move in the real world is difficult. Living actuators require highly specific temperature requirements, ambient sugars for energy, and mechanisms for the removal of accumulated wastes, all while maintaining sterility. Also, it is difficult to accurately check the status of the biohybrid robot during deployment to assess tissue health, making controller design challenging as controllers must adapt to actuator fatigue or damage and manage energy and waste needs.

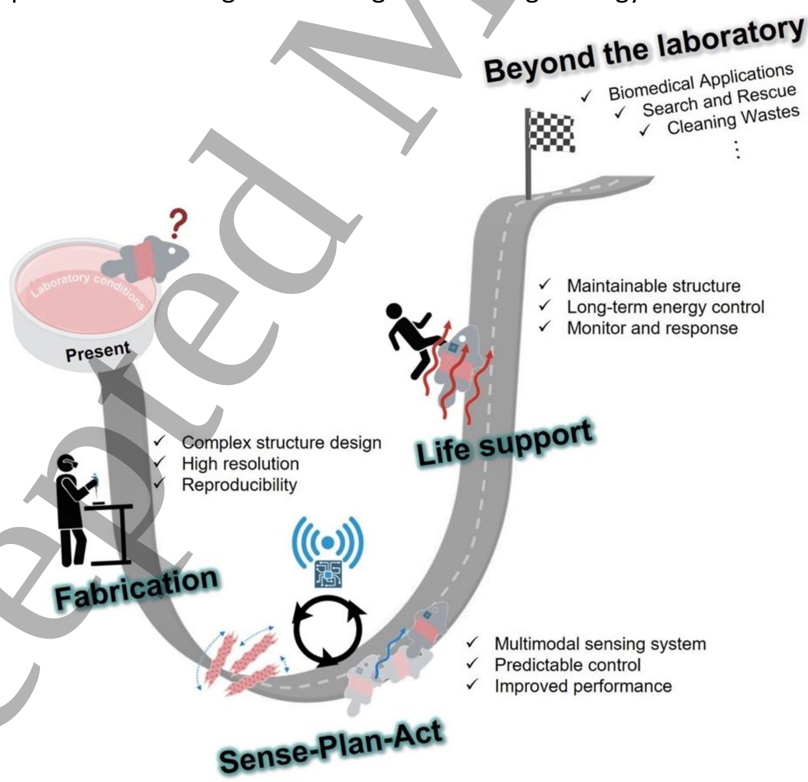

Figure 11.2 | The future of biohybrid robots. Roadmap of future research areas needed to overcome existing challenges in translating biohybrid robots beyond the lab. This figure was created in part using Biorender. Webster-wood, V. and Seok J. (2025) https://BioRender.com/h81u145.

Advances in Science and Technology to Meet Challenges

Creating reproducible and deployable tissue-based biohybrid devices will require several advances in fabrication, sensing, motion planning, controls, and reliable interfaces between actuators and robots:

- **Fabrication.** In creating biohybrid devices, achieving high fabrication resolution and reproducibility is important. Reproducibility of the biohybrid robots can be improved by developing platforms for quality control at the fabrication stage, which will be critical for expanding the design and realization of complex biohybrid robots in the coming years.
- **Sensing.** At the sensing level, new approaches are needed to integrate multimodal sensing into biohybrid robots. Such systems should enable internal state sensing and fusion of multiple external sensing modalities. However, such capabilities will need to be light or biological to not overload bioactuator payload capabilities. Integrated motion planning will require energy-efficient algorithms and lightweight computational platforms [5]. One area for future research is to leverage biological neural networks, or brain-inspired algorithms, to mimic the sensing behaviours and capabilities found in natural systems (see also **Section 18**). Preliminary proof of concept devices leveraging this approach have begun to appear in the literature [17].
- **Controls and Planning.** To generate autonomous behaviour, once motion planning is performed, that signal must be transmitted to actuators. Although actuation has seen the largest focus in tissue-based biohybrid robotics, substantial research is still needed to achieve autonomy. Therefore, research should focus on improving the robustness and reliability of biohybrid muscle-based actuators for predictable control.
- **Actuator Interfaces.** The interfaces between bioactuators and the surrounding robot structure must be improved to eliminate stress concentrations. This research can leverage ongoing research in myotendinous repair. The development of future bioactuators need not be limited by what nature has achieved. For example, novel multi-material muscles could combine conductive materials with cells to improve actuator performance or signal transmission across actuators, or new approaches in cellular engineering could be leveraged to enhance the force capabilities of individual cells. Recent research is laying the foundation for such approaches through the integration of novel materials and biohybrid actuators [18]. Given the complexity of integration needed to achieve these goals, advances will likely occur for each subarea in the coming years, but full integration may require longer time-scale investments.

On longer research horizons, to move biohybrid robots beyond the lab, the development of novel housings optimized to provide the correct mechanical properties, protection from the elements, energy harvesting, nutrition, or even oxygenation are needed. This will likely require substantial research in enabling technologies over the coming 5-10 years before integration into biohybrid robots.

Concluding Remarks

Biohybrid robotics research is growing across the biomedical, ecological, environmental, and engineering fields. A broad array of current research has focused on biohybrid robot's structural fabrication and functional control. However, several key challenges remain to allow biohybrid robots to move beyond the lab (**Figure 11.2**), including: (i) the realization of heterogeneous biohybrid structures through reproducible and predictable fabrication methods with a high resolution; (ii) complex sensing, motion planning, and actuation using biologically derived materials; (iii) using autonomous cellular systems in complex environments beyond the laboratory. To solve these challenges, interdisciplinary research, multidisciplinary training programs, and collaborative research support are critically needed.

Acknowledgments

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12 – 4D printed systems

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Status

4D printing has been attracting increasing attention since the concept was proposed in 2013 [1]. 4D printing is based on 3D printing technology but involves transformation over time in response to additional stimuli. Initially, it was defined as "4D printing = 3D printing + time" [3]. However, the concept has undergone evolution in recent years: the shape, structure, properties, and functionality of a 3D-printed object can change after being triggered by external stimuli such as temperature, light, pressure, pH, and water. Such transformation should be controllable and predictable, such as being programmed to trigger at a desired time or within a specified time range. The temporal and spatial scales have evolved over time as well. For example, slow transformation due to natural growth can fall into 4D printing category as well.

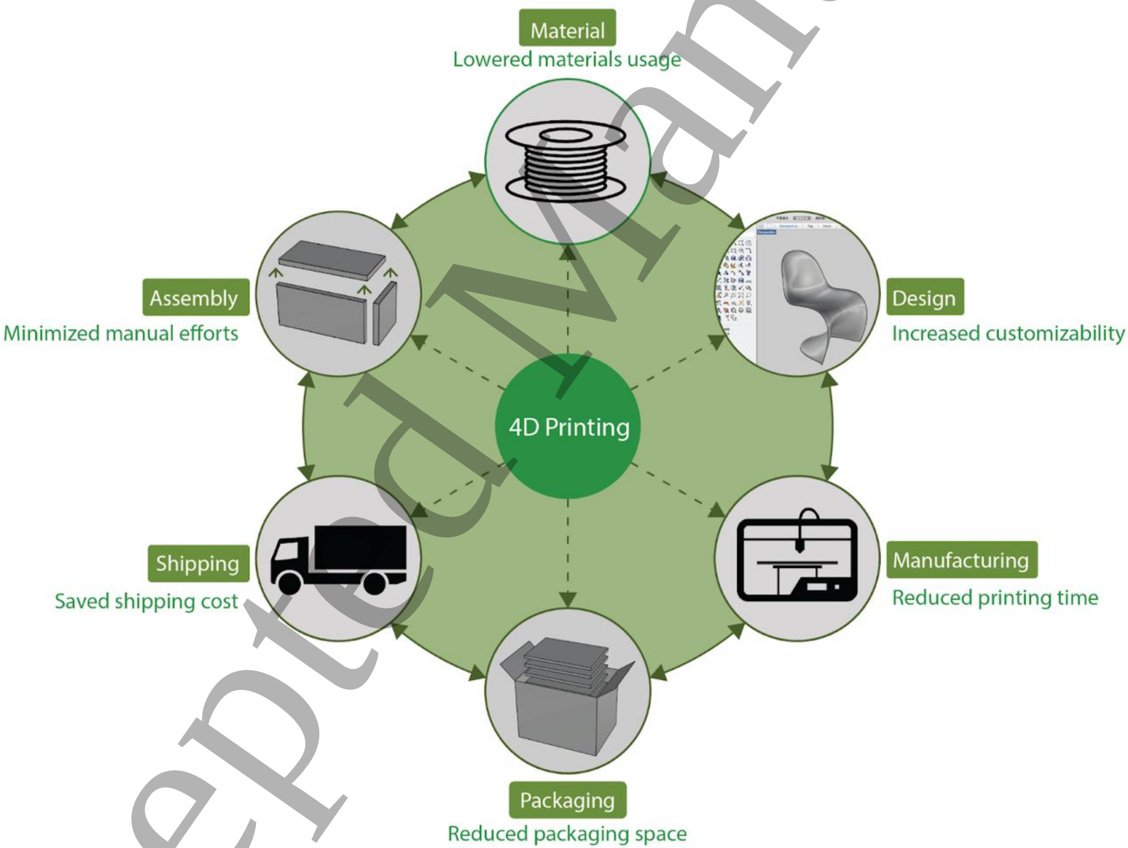

Figure 12.1 | A schematic envisioning a green and circular manufacturing pipeline enabled by 4D printing. 4D printing can be used to save costs and time, increase customizability, reduce energy consumption, minimize manual effort, and improve efficiency throughout the entire life cycle of products, including material selection, design, manufacturing, packaging, shipping, and assembly. Initial artwork credited to Guanyun Wang.

By designing and preprograming the structure of smart materials, 4D printing allows animate materials to be 3D printed [4] including various shape-changing behaviours, such as bending, folding, twisting, and surface curling [4] (see also **Sections 8** and **9**). Sequential shape-changing behaviours have also been extensively studied to explore more complex behaviours and functions. These dynamic changes allow the printing of complex and responsive animate materials that can adapt to environmental conditions or user requirements [3].

The transformative properties of 4D printed materials, including self-assembly, self-adaptability, multi-functionality, and self-repair, exceed those of traditional 3D printed materials [8]. 4D printing has the potential to revolutionize manufacturing because of the bespoke geometries it affords which brings benefits such as reduced manufacturing & assembly, reduced transportation, reduced waste, increased customization, and more environmentally sustainable products (**Figure 12.1**).

This innovative technology could be utilized to create highly customized and adaptable solutions in various fields such as aerospace, biomedicine, human-computer interaction, soft robotics (see also **Sections 10** and **11**), and electronics [2]. The size of 4D printing can range from micro to macro according to applications. While 4D printing is still in its early stages as a technology, it is growing rapidly, attracting attention from both interdisciplinary academia and various industries. The technologies of additive manufacturing, stimulus-responsive materials, and related mathematical modelling are under active research and contribute to the growth of 4D printing.

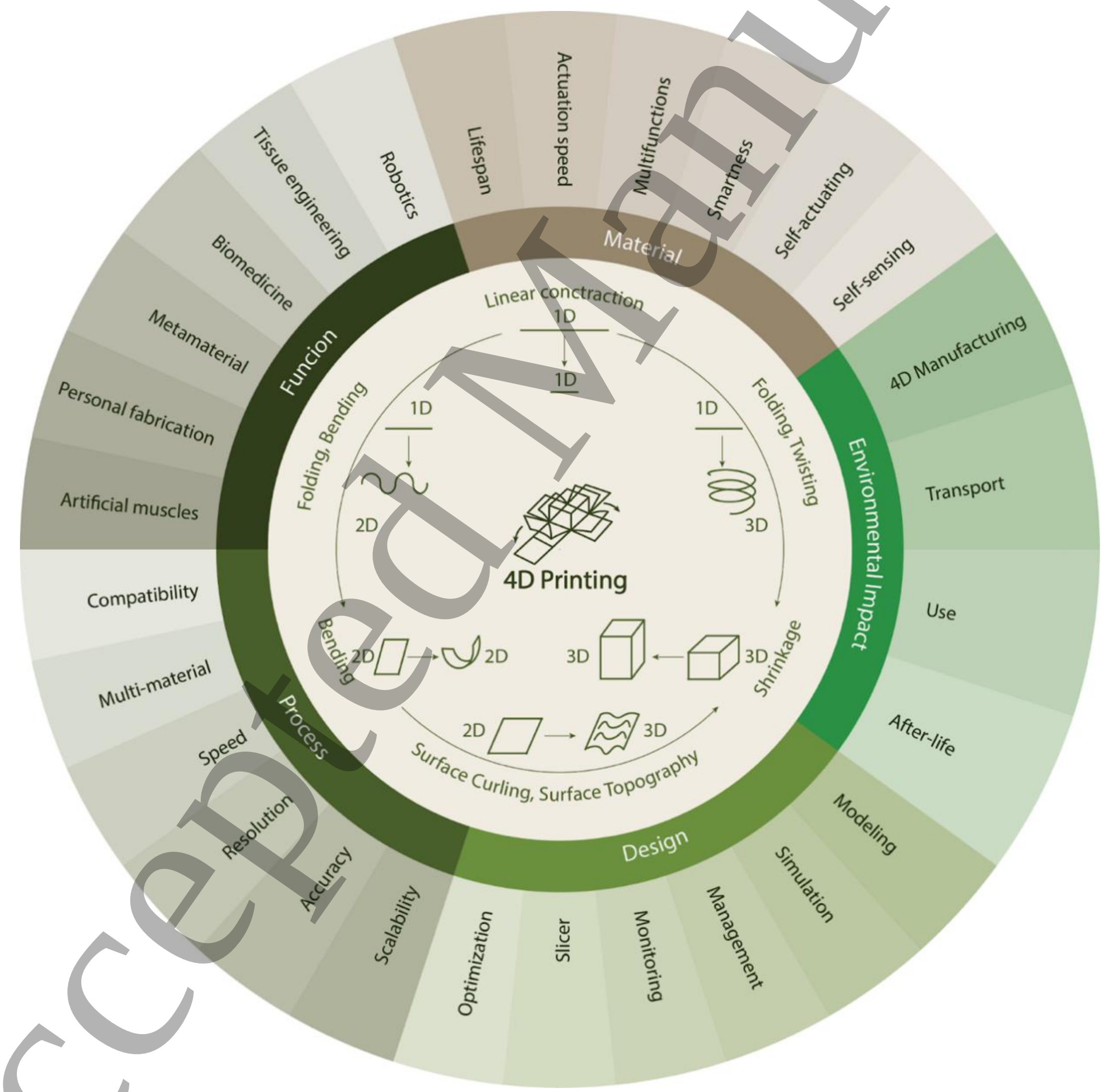

Figure 12.2 | A schematic showing the important challenges of 4D printing that must be addressed for the technology to reach its full potential. These cover material, function, process, design space, and environmental impact.

Current and Future Challenges

Current 4D printing faces several challenges, including material development [4], process, design, function, and environmental impact (**Figure 12.2**).

- **Material**: The majority of 4D printed materials are polymers and elastomers (tensile strengths of 1 – 100 MPa and densities of 1000 – 2000 kg/m^3) [11] or biomaterials (100 – 1000 kg/m^3 and similar strength). It is rarer to find ceramics and metals (2k - 20k kg/m^3) being 4D printed. The properties of smart materials, such as printability, multifunctionality, multiscale structure, mechanical robustness, actuation speed, and lifespan, all influence their ability to be successfully 4D printed [2]. For most shape-changing polymers, only one-way shape change is allowed. Although there are materials that permit multi-cycle shape changes, most 4D printed structures cannot fully return to their original shapes. Additionally, designing materials that change shape sequentially and respond to multiple stimuli remains a challenging issue.
- **Process**: Material compatibility with 3D printing technology is crucial, requiring directly printable materials that integrate seamlessly with existing technologies. The ability of a printer to accurately and efficiently produce materials with complex structures is essential for the advancement of 4D printing technologies. Regarding 4D printing facilities and technology, factors such as printing accuracy, resolution, speed, multi-material compatibility, and overall material compatibility are crucial [5]. Additionally, current research mostly focuses on layer-by-layer stacking printing. There are still challenges in direct and freeform printing of 3D structures, reducing undesired shape changes during the printing process, and conducting conformal 4D printing on existing non-planar surfaces. Moreover, the portfolio of materials that can be successfully 4D printed is still small.
- **Design**: Developing models and computational design tools increases the efficiency of the 4D printing process compared to manual path planning. The goal of the forward simulation is to describe final shapes from material specifics and stimuli (forward design), while inverse design focuses on deriving print paths or structures from desired outcomes [4]. Simulating the dynamic shape change, often within a multi-physics context, is non-trivial. Moreover, current research falls short in modelling the time-varying behaviour in 4D-printed composite structures. Further development of 4D printing design tools is needed to optimise material properties, printing techniques, and structural considerations. Additionally, the usability of the design tool is important, ensuring that it is accessible for a diverse range of end-users.
- **Function**: Applications of 4D printing, leveraging its self-assembly, self-adaptability, multi-functionality, and self-repair capabilities, have been developed across various interdisciplinary fields. 4D printed products find applications in personal fabrication [10], human body systems such as artificial muscles, implantable biomedical micro-devices, soft robotics (see also **Sections 10** and **20**), living architecture (see also **Section 20**), and wearable sensors [2]. The need for these technologies is driven by strong societal, climatic and economic factors. For instance, the ability to dynamically respond to the damage caused by storms through self-repair, restoring function and reducing associated labour costs.
- **Environmental impact**: Although crucial, the environmental impact of 4D printing across its life cycle has been insufficiently discussed. Its unique materials, processes, and lifecycle behaviours significantly differ from those of traditional manufacturing methods [9]. However, this also presents opportunities to design a green manufacturing cycle that can lead to greater energy savings compared to conventional manufacturing methods (Figure 12.1). The main hurdles include optimizing manufacturing to reduce waste and energy use, designing for

efficient transportation and use, and ensuring end-of-life strategies such as recyclability and biodegradability [9].

Advances in Science and Technology to Meet Challenges

The following five advances are needed to develop 4D printing into a technique that can be used reliably to produce animate materials.

- **Material**: Recent studies concentrate on the printing of both single and multiple shape-changing materials as well as composites [6]. Shape memory polymers (SMPs), hydrogels, actuating materials such as liquid crystal elastomers, and composite materials such as magnetic elastomer composites are commonly utilized materials in the field of 4D printing [8]. Multimaterial 3D and 4D printing, utilizing a variety of materials such as polymers, metals, ceramics, and biomaterials, enable shape programmability and enhances part quality by altering materials between layers, thereby surpassing traditional manufacturing techniques [7]. Developing materials with varied properties, durability, and rapid response capabilities will enable the creation of customised objects to meet diverse needs of product manufacturers and withstand various environments. Meanwhile, multi-stimuli responsive and self-computing materials are desirable for making multifunctional objects.
- **Process**: In recent years, various manufacturing methods and facilities have been utilized and further developed to enhance 4D printing, focusing on improvements in printing speed, resolution, and greater material compatibility. These methods encompass extrusion-based techniques such as Fused Deposition Modelling (FDM) as well as inkjet and Direct Ink Writing (DIW) [5] and photopolymerization methods such as Stereolithography (SLA) and Digital Light Processing (DLP). Advanced machines that combine multiple printing parameters are crucial for making heterogeneous printed structures [8]. Furthermore, the customized functions of 4D printed objects can be enhanced by utilizing various printing methods to print multiple material systems. Additionally, 4D printing can be extended to 4D manufacturing, incorporating not only printing process but also diverse manufacturing techniques that can manufacture flat objects which can consequently morph into 3D with additional energy stimuli [9]. Other 4D manufacturing techniques include laser cutting, 2D jetting, layer lamination, etc.
- **Design**: Advancements in predictive methodologies and simulation capabilities are paving the way for the automated design of 4D printed objects, guided by predefined material compositions, attributes, and shape models. Various modelling methods, including simplified geometrical models, the spring-mass system, the 1D elastic rod, the multi-physics finite element model, and data-driven surrogate models, have been developed [4]. Furthermore, advanced machine learning techniques are being utilized to enhance simulation predictions and fast design tools (see also **Section 18**). In the future, advanced software that can be used with different machines and integrated with various hardware should be developed to improve efficiency and coordination.
- **Function**: Applications of 4D printing, leveraging its self-assembly, self-adaptability, multi-functionality, and self-repair capabilities, have been developed across various interdisciplinary fields. 4D printed products find applications in autonomous robotics, personal fabrication [10], human body systems such as artificial muscles, implantable biomedical micro-devices, and wearable sensors [2]. These applications contribute to increased efficiency, reduced human labour, and decreased costs in real-world settings. Future application development needs the convergent mindset of engineering, science, and design thinking. It's crucial to identify the true needs in real-world settings where 4D printed objects can outperform current methods.

- **Environmental impact**: Holistic design guidelines are emerging [9]. These guidelines aim to provide a unified workflow for considering sustainable design practices, addressing the environmental impacts of morphing matter throughout its lifecycle, including 4D manufacturing, transport use, and end-of-life. For example, renewable resources should be used while considering the products' desired functions [9]. Moreover, advances in science and technology, like digital fabrication and AI-based computational design, can improve 4D printing efficiency by optimizing energy consumption and design processes.

Concluding Remarks

4D printing, an evolution of 3D printing, introduces dynamic, time-responsive elements to objects, allowing them to change shape, properties, and functionality in response to stimuli. However, challenges such as material development, process optimization, design complexity, functional application, and environmental impact remain. Addressing these requires advancements in smart materials, printing technologies, mathematical modelling, and sustainable practices. Despite these hurdles, the potential for self-assembling, adaptive, and multifunctional structures positions 4D printing as a transformative force in manufacturing. Considering that the development of 4D printing is closely related to the mature technology of 3D printing, we are likely to see 4D printing used in products such as furniture, electronics or biomedical devices in the next decade.

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13 – Active acoustic metamaterials

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Status

Acoustic metamaterials have received significant attention since the early 2000s due to advances in materials science, micro- and nanotechnology, and physical modelling. Acoustic metamaterial systems can steer, control, and manipulate sound waves in ways that are not possible with conventional structures. Historically, band gaps in periodically arranged atomic lattices have inspired the development of photonic and phonic crystals, where the lattice constants are on the order of the electromagnetic and acoustic wavelengths, respectively [1]. However, the large wavelengths of acoustic waves in the audible range (centimetres to metres) led to large and bulky phononic designs.

The emerging field of acoustic metamaterials overcame this limitation by allowing lattice sizes much smaller than the acoustic wavelength (size range of millimetres to centimetres) and expanding their application in acoustic waveguides and acoustic imaging. Since the first experimental realization of acoustic metamaterials, called locally resonant sonic materials [2], several local resonators have been developed, such as Helmholtz-based [3], or membrane-based resonators [4], which provide unconventional, overall bulk modulus and system's mass density. Despite the great progress of these unit-cell resonators, their designs rely on passive and linear systems with fundamentally limited bandwidth, which hinders their applicability in practical time-variant applications, such as noise pollution in urban and natural environments as well as climate-responsive infrastructure (see also **Sections 19** and **20**).

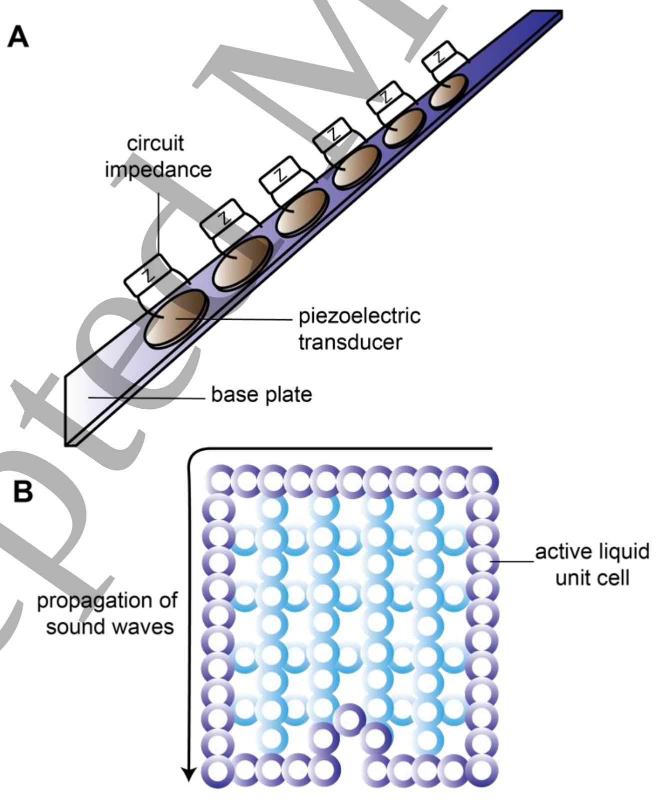

Figure 13.1 | Schematics of two active acoustic metamaterials. (**A**) Active acoustic metamaterial using external electric field through piezoelectric unit cells [5]. The piezoelectric local resonators can tune the stiffness of the host structure and tailor the acoustic wave propagation behaviour. (**B**) An animate acoustic metamaterial consisting of active liquid unit cells, enabling

topological acoustic property [9]. The liquid unit cells control the propagation of sound and enable topological insulators which are immune to structural defects. The high-density active particles in the unit cells are shown in dark blue and low-density active particles are shown in light blue.

Active acoustic metamaterials (**Figure 13.1**), in contrast to passive acoustic metamaterials, use external control (e.g., electric, light, or magnetic field) or the material's adaptive and active energy absorption properties (e.g., active colloids as animate materials, see **Section 2**) to tune the effective material properties of the structure, enabling a wide range of on-demand acoustic wave manipulation. Notably, the adaptive nature of active acoustic metamaterials and animate materials positions them to address urgent ecological challenges, such as climate-related changes in environmental noise and infrastructure resilience. Engineered acoustic metamaterials could serve as both advanced wave-control platforms and responsive technologies for pressing global challenges.

The most common active unit cells are electromechanical systems, piezoelectric materials, and electrically loaded loudspeakers [5]. The active elements can dynamically tune their properties in response to changes in the acoustic waves, expanding their applications in rapidly changing noise environments. Another interesting subclass of active acoustic metamaterials is non-reciprocal acoustic metamaterials, encompassing a variety of unidirectional wave phenomena [6]. These include acoustic isolators and circulators, topological insulators and edge states, spatiotemporally modulated media, and one-way waveguides. The non-reciprocal acoustic metamaterials often exploit time-reversal symmetry breaking, allowing unique capabilities for unidirectional propagation of sound waves (e.g., isolation, circulation, and robust transport along edges) that are immune to the backscattering caused by structural imperfections and perturbations in the material. As such, they have enabled the creation of acoustic diodes and isolators, topological insulators, one-way mirrors, and circulators, spanning their application in biomedical ultrasound, targeted therapy, architectural acoustics, and vibration control [6].

Current and Future Challenges

Regarding real-world applications, active acoustic metamaterials face challenges regarding their practical applicability. Future developments should build on the existing industrial progress and include new design, fabrication, and control methods, as well as theoretical modelling developments, as outlined below:

- **Fabrication and Scalability.** One of the primary concerns is the fabrication and scalability of these metamaterials, which are crucial for their widespread adoption. However, these metamaterials currently suffer from high costs and complex production methods. Furthermore, the performance of acoustic metamaterials is frequently constrained by their frequency bandwidth. In particular, those that rely on locally resonant unit cells typically exhibit inherently narrow frequency bandwidth properties, which restricts their applicability across various frequency ranges in noisy and broadband acoustic spectra. Another challenge is the passive nature of many acoustic metamaterials, which suffer from a combination of material's viscous energy loss and thermal losses. Therefore, addressing these inherent material losses is a vital area of ongoing and future research.
- **Design and Modelling.** Conversely, active acoustic metamaterials offer enhanced dynamic range and tunability across a broad frequency bandwidth. Nevertheless, their practical implementation remains complex, requiring the development of simpler designs to facilitate their use in real-world settings. Moreover, the design and fabrication of specialized forms, such as topological and non-reciprocal acoustic metamaterials, entail intricate processes that significantly increase costs and hinder scalability. The physical dimensions of some acoustic

metamaterials also restrict their suitability for compact environments due to their considerable dimensions and bulk, on the order of metres. Integrating these materials into existing conventional systems presents additional challenges, notably impedance matching issues, which complicate their practical deployment. Moreover, translating theoretical and numerical models into experimental setups is a non-trivial task that requires meticulous adjustment and validation.

- **Robustness.** In the emerging field of topological acoustics – the study of materials and structures that allow sound waves to propagate along their edges and isolate sound inside them – independent control and mechanical biasing of individual lattice structures present significant engineering challenges. Topological acoustics differ from the classical study of surface acoustic waves (SAWs) [7] primarily in how the propagating modes are protected and shaped by topological invariants. Unlike SAWs that can be scattered or reflected by small imperfections, topological edge states are robust to defects and disorder. This robustness stems from the non-trivial band structure in topological systems, preventing backscattering and localizing propagation along interfaces or boundaries. Thus, while both phenomena involve surface-bound wave propagation, topological acoustics provides enhanced immunity and control that classical SAWs do not possess.
- **Dimensionality.** The majority of current research in topological acoustics has focused on airborne sound with longer acoustic wavelengths, while studies on sound waves in solids, especially in three-dimensional structures, are still lacking [8]. This is attributed to the ease of airborne sound manipulation and measurement as well as low acoustic energy loss in certain distances compared to the propagation of sound waves in solid medium. However, for biomedical applications, frequencies in the ultrasound range are preferable, indicating smaller footprints of acoustic metamaterials in the range of microns to millimetres. Furthermore, despite the advances in three-dimensional fabrication technologies, most research has concentrated on two-dimensional designs, such as metasurfaces, likely due to their relative ease of production. Moving forward, a shift towards more extensive research on three-dimensional metamaterial structures, enabling the control of sound propagation at different directions, is crucial to fully leverage the capabilities of acoustic metamaterials in diverse biomedical and environmental applications.

Advances in Science and Technology to Meet Challenges

The following advances in active acoustic metamaterials are needed to overcome the challenges:

- **3D Fabrication.** The recent advancements in three-dimensional (3D) additive manufacturing have significantly facilitated the fabrication of intricate three-dimensional architectures for acoustic metamaterials. This technological progress has facilitated the integration of theoretical and computational designs with experimental applications, thereby enhancing the translation of complex models into tangible, functional materials. As the ease of use of 3D printing techniques as well as 4D printing (**Section 12**) continues to improve, there is a growing necessity for an increased focus on 3D metamaterials research over traditional 2D metasurfaces. This could further expand the potential applications and effectiveness of these materials.
- **Novel Materials and Structures.** To address the limitations of current acoustic metamaterial systems, recent efforts have focused on refining unit cell designs to achieve targeted sound absorption—ensuring energy is converted where and how it is intended—while minimizing unwanted losses (e.g., random scattering or damping outside the target frequency band) that do not contribute to the beneficial absorption mechanism. This distinction between controlled, desired absorption and unnecessary dissipation is critical for optimizing

metamaterial performance. Consequently, this research field requires the investigation of novel materials and structures, such as active colloids (**Section 2**) and shape changing active mechanical metamaterials (**Section 15**), with low-loss profiles which could enhance the overall functionality of acoustic metamaterials.

- **Adaptive Control**. The field of active materials represents an intriguing avenue for the advancement of acoustic metamaterials. These materials employ active control mechanisms, such as electromechanical transducers, to facilitate adaptive and reconfigurable properties within the structures, allowing for precise control of mechanical deformations triggered by electrical energy inputs. This approach is exemplified by research on animate matter, where the propagation of topologically protected sound modes in metamaterials made from active liquids—fluids comprising self-propelled particles (see also **Section 2**)— was explored [9]. Such animate materials can support unidirectional sound waves and establish topological order, enabling sound to travel without backscattering, even in the presence of obstacles or disorder.
- **Biomedical Applications.** Finally, there is a shift in material research towards the design of solid acoustic metamaterials within fluidic media, such as underwater environments, where acoustic contrast is less pronounced. One such innovation is the use of air bubbles as locally resonant unit cells to create promising underwater acoustic metamaterials suitable for medical ultrasound applications [10]. The direct applications of these materials are being explored in fields such as transdermal drug delivery. In this context, pyramidal lattice structures have been used to create localized acoustic streaming around sharp edges, thus enhancing the diffusion of transdermal drugs [11]. These developments illustrate the transformative potential of active acoustic metamaterials in a variety of practical applications.

Concluding Remarks

In conclusion, active acoustic metamaterials stand at the forefront of innovative materials science, offering unprecedented capabilities in sound wave manipulation through their unique design and composition. The development of these materials has progressed from passive, narrowband systems to more dynamic, actively controlled structures, and animate materials that can actively absorb energy and adapt to various acoustic environments. These advancements are largely attributable to significant breakthroughs in micro- and nanotechnology, as well as theoretical and computational modelling. Despite these strides, challenges in scalability, fabrication costs, and integration into existing systems persist, limiting their broader application. Looking ahead, the focus is shifting towards refining 3D additive manufacturing techniques to enhance the practical deployment of these materials. Innovations in unit-cell design and material properties aim to reduce losses and increase functionality, facilitating their use across a wider array of applications, from architectural acoustics to biomedical ultrasound. Additionally, the exploration of non-reciprocal and topologically protected acoustic waves promises new dimensions in sound control, potentially revolutionizing how active acoustic metamaterials are utilized in everyday environments. The ongoing research and the next-decade development in this field are poised to not only overcome existing limitations but also to unlock a myriad of new possibilities for acoustic manipulation and application in animate matter.

Acknowledgments

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14 – Active granular matter

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Status

Granular matter denotes a very large ensemble of similar small elements that are however not small enough to be ruled by Brownian motion and equilibrium statistical mechanics. The typical size of granular particles spans in the sub-millimetre to centimetre range. In active granular matter, each granular element of the ensemble can convert some input energy into motion in which friction and shocks are the main sources of dissipation. The development of active granular matter can be traced back to the 2000's with first active grains powered by vertical vibrations [1,2] and then individually powered granular robots [3]. The dominant studied situation was directional motion, which relies on various self-propelling mechanisms for granular particles with head-tail asymmetry. As an example, we can mention cylinders with a non-symmetrical mass distribution [1]. Interestingly, these particles are geometrically symmetrical but, under vertical vibrations, they have a rectified drift velocity towards their lighter side. In the case of granular robots [3], the particles asymmetry comes from their shape with tilted legs that converts the vertical jumps of the robot to a horizontal drift. With typically hundreds of such particles interacting in a confined environment, collective states such as clustering and flocking can emerge. These states are the results of aligning interactions at the scale of particle-particle interaction and assemblies of self-propelled grains typically show transitions between disordered gas-like states at low densities and ordered collective states at higher densities. Active granular particles are also used to mimic vehicular or pedestrian traffic [4]. This can be achieved by placing active particles in a track with a bottleneck and, depending on the particle density, different regimes of congestion are obtained.

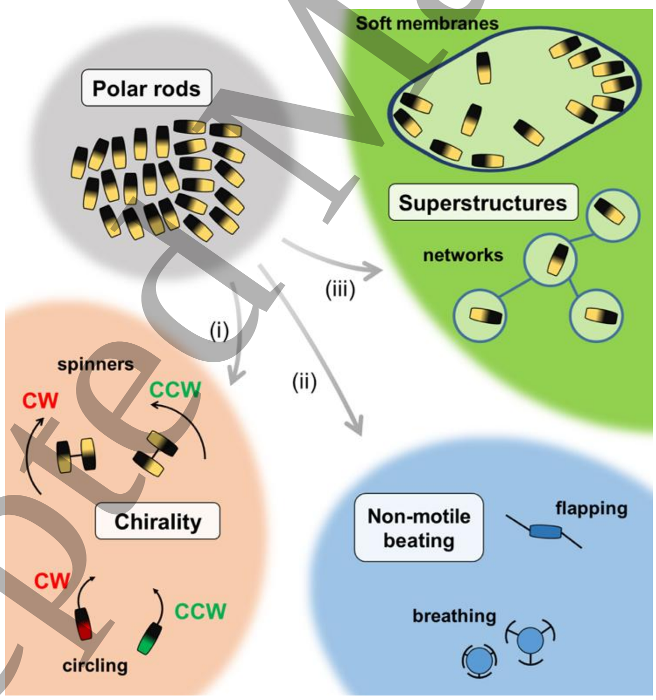

Figure 14.1 | Perspective for active granular matter as animate matter. At first, active was mostly referring to self-propelled elements such as polar rods and disks with a persistent directional motion. More recently, activity beyond translational motion was studied with (i) rotational activity for chiral active matter and (ii) non-motile active particles with body deformation decoupled from the centre-of-mass motion for the individual particles. Structures using granular active elements as building blocks are also proposed (iii) to form more complex animate objects.

In the context of animate matter, the specificity of active granular matter is the simplicity of the granular elements that contrasts with the complexity of the collective regimes observed. If we put aside the active mechanism, granular particles are easy to find in nature and laboratories. The granular interaction phenomenology at the macroscale is however not so simple due to the non-smooth properties of contact interaction. First, the collisions are very short-time events with sudden change in the velocity of the particles. Second, friction between grains or walls can induce transitions between sticking and sliding regimes.

Because the granular interactions are repulsive, the collective states typically appear and persist for sufficiently large densities under the influence of steric effects. Elongated particles are more likely to have strong aligning interactions but, even with self-propelled particles of circular shapes, the interplay between collisions and friction of the moving particles also leads to velocity alignment and flocking.

The interaction of active granular particles with walls is an important aspect of the individual and collective particles' dynamics. Because of the aligning interaction, and depending on confining geometries, self-propelled particles can be guided, jammed or trapped. The collisions with boundaries can also enable the formation of clusters of particles even for moderate densities.

Current and Future Challenges

Challenges for granular matter include:

- **Chirality**. Granular matter offers the possibility to explore activity beyond linear motion – a topic of great interest with further potential for the future. Recently, chirality has attracted much attention in active granular matter [5] (**Figure 14.1**). A chiral active particle can be a spinner, i.e. a particle self-propelled into a rotating motion or a particle moving on a circular trajectory, which can be viewed as a combination of directional motion and body rotation. Rotation necessarily implies the existence of two-particle types, clockwise (CW) and counter-clockwise (CCW). Consequently, chirality brings a new set of specific pair interactions CW-CW, CCW-CCW, and CW-CCW. This leads to situations of segregation with particle clusters only composed, or dominantly composed, of particles of type either CW or CCW. The interaction of chiral particles with walls is also type-specific, which leads to edge currents with a parallel transport at the walls depending on the sign of the rotation. This surface flow can be used to sort particles depending on their sign of rotation. Surface flow is also observed at the free surface of chiral particle ensembles and the peculiar dynamics of interacting rotating particles leads to exotic phases with odd properties [6].
- **Non-polar activity**. Another illustration of novel type of individual motion is the volumetric oscillation of disk-like particles with T-shaped arms [7] (Fig. 14.1). In such systems, the activity of the individual elements has no action on their centre of mass. Collectively, however, the particles can influence each other and self-organize into static or dynamic clusters. In this situation, one of the new physical ingredients is the possibility to choose the relative phase of the oscillating particles.
- **Superstructures**. A last approach consists of embedding active granular particles into more complex structures to form compound objects with peculiar dynamical properties (Fig. 14.1). With active particles placed inside a flexible closed membrane [8], the coupling between the particles' motion and the membrane deformation leads to a cell-like dynamics of the membrane with locomotion, large deformation, and exploration of confined environments (see, e.g. **Section 4**). Active particles are also used to realize active elastic crystals and therefore explore the effect of activity on mode dynamics in periodic structures. Finally, it is possible to combine the approaches of activity beyond directional motion and superstructures

[9]: flapping particles composed of three articulated segments placed in a circular enclosure form an entity capable of diffusive motion under the collective contact interaction of the active flapping particles. If the activity is made dependent of a light intensity threshold, the superstructure demonstrates phototaxis, which is here a rectified motion towards a light source.

- **Inertial regimes**. Another question with active granular systems is the role of inertial regimes in the emergence of collective states. In the Vicsek model, the dynamics of the particles' orientation is of first order, which means that two particles close to each other will align in an overdamped regime. For experimental physical systems, this overdamped regime is valid for, e.g., microswimmers with relatively large viscous forces (see, e.g., **Section 2**). With dry granular elements, there are almost no viscous forces at play and the inertial regime dominates. Inertia can be responsible for non-aligning collisions of elongated particles, which prevents the formation of aligned phases in the absence of walls. Inertial regimes can also lead to unusual thermodynamics [10].
- **Control**. This challenge concerns the control of the trajectory, the different types of motion, and the configurational dynamics of the particles. So far only very few examples have been considered, and it is not clear how to optimize different collective behaviours by modifying a simple property whether for the trajectory or the configurational change. Further, as encapsulating particles into scaffolds opens new possibilities, the challenge is again how to optimize the behaviour and function of superstructures by designing intelligent scaffolds and new particles with well-adapted properties.
- **Energy**. Energy optimization was originally not an important consideration in active granular matter. The use of a vertical vibration is an efficient method to animate a set of identical granular particles, but it is not an efficient conversion mechanism regarding the energy transfer. In the perspective of using active granular matter approach for robotics application, it is necessary to address the question of energy optimization and develop driving mechanisms that do not waste a significant portion of the energy input in non-motile degrees of freedom (*e.g.,* vertical oscillation).
- **An out-of-equilibrium model system.** Active granular matter can be considered as a conceptual framework to study the statistical mechanics of out-of-equilibrium systems. Active particles are, by definition, non-Brownian particles, which means that equilibrium statistical mechanics does not apply. However, there is no comprehensive theory that quantifies how far from equilibrium an active granular system is. In dilute regimes, active granular particles essentially behave as a gas for which some analogous of temperature and pressure can be used with the active velocity in place of the thermal velocity in an equilibrium system. For denser regimes, the description of an active granular bath as a quasi-equilibrium system is usually not possible. This can manifest as large deviations in statistical quantities or the formation of dynamical phases that have no equilibrium counterparts.

Advances in Science and Technology to Meet Challenges

The field of active granular matter is going through a diversification phase with new types of assemblies performing new collective tasks. In Fig. 14.1, we have sketched an overview of recent strategies implemented in active granular matter. By modifying either the particles' activity properties or environment, new types of functions and collective phases can be observed. Required advances to push the field forward relate to:

- **Functionalization.** A direct challenge is not only how to implement different types of motions or configurational changes but how they can be optimized to generate a particular function or behaviour. The advent of 3D printing is certainly a step forward, however, optimization in view of a task or function is not straightforward and may need accompanying simulations and numerical work. Using enclosures can benefit from the advent of new materials with, for example, sensitivity to local stresses or forces so that one can generate more deformation or resist deformation depending on the forces acting on the enclosures; this may give rise to possible feedback loops between collective formation near the walls and the scaffold itself. Further, the use of active or intelligent scaffolds (see, e.g. **Section 15 and 16**) interacting with the granular assembly can give rise to new emergent behaviour allowing new functions. The technology for such materials is sufficiently advanced so an implementation can be carried out with minimal developments.

- **Complexity/minimality trade-off.** The essence of granular systems is the simple structure of their constitutive elements. This is both a strength and a limitation in the possible achievements of active granular systems with advances that primarily rely on curiosity-driven exploration. The recent results in the field of active granular matter have shown that it is possible to foresee active granular schemes as part of complex animate entities as it is for robotic systems (see, e.g. **Section 17**). In robotics, the design of a specific robot is usually via reverse engineering approaches in which the structure of the robot is designed from the task it is expected to perform. In the field of granular systems, the research approach is via exploration with usually no specifically targeted function. The challenge is to bridge the two approaches and be able to gauge when active granular elements are interesting compared to conventional approaches in robotics with higher levels of programming. Introducing some form of elementary communication between granular agents is a way to explore new collective properties: introducing some simple communication between agents in collision-dominated crowds can for example lead to collective learning schemes [11].

Concluding Remarks

Active granular matter is a surprisingly rich domain. Although granular particles are simple entities, making them active, using different schemes, reveals the complexity of granular interactions. This activity can consist of simple locomotion, rotation, or simply shape shifting. These different modes give rise to a multiplicity of behaviours. This complexity opens the way towards the emergence of functional entities capable of deformation, complex exploration, foraging, etc. Besides, a variety of collective dynamics emerge, going from cluster formation, to flocking, to interfacial flows. Finally, adding a layer of basic communication between agents can give rise to learning crowds and even enhanced functionalities: while improved phototaxis has been demonstrated, other tasks, e.g. cargo transport or searching, cleaning or depolluting still need testing with learning strategies. The timescale for achieving such tasks remains reasonable (i.e. within a few years) as most of the materials and the technology are either relatively mature at present or are on the verge of becoming so.

Acknowledgements

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15 – Active mechanical metamaterials

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Status

Animate materials interact with their environment in a dynamical and adaptive manner. This entails the combined ability to (1) change shape, (2) do work and (3) process information. In the last few years, mechanical metamaterials integrating flexible (rubber) and active (electromagnetic) elements—often fabricated through additive manufacturing—have started to appear that exhibit these three abilities. We consider each in turn.

First, a range of design methods have been developed for realizing metamaterials that morph between arbitrarily complex shapes [1]. These methods include spatially grading the material such that the local kinematics add up to a shape-change over many unit cells, using combinatorial techniques to control the local kinematics and texture, or exploiting geometrical frustration to obtain large out-of-plane deformations. Moreover, the building blocks of these metamaterials can be either monostable, leading to a single shape, or multi-stable, leading to the integration of many shapes and memory [2,3].

Second, while most active matter systems to date fall into the class of active fluids that lack a reference state (see also **Sections 2, 3, 4, 5, 14** and **17**), recently active solids have emerged where elastic restoring forces to a reference state compete with active forces [4,5,6], where in all cases active means that the system is driven out of equilibrium by consuming energy. These materials consist of discrete units – thus falling in the class of active metamaterials (see also **Section 13**)– and their response typically fundamentally differs from that of ordinary elastic solids, viz. whereas ordinary passive solids are described by symmetric dynamical matrices and elastic tensors, activity can turn dynamical matrices and elastic tensors asymmetric [4,5]. As a result, when the active driving components are sufficiently strong, geometric feedback between deformations and direction of forcing may lead to active waves, synchronized oscillations, and other complex spatiotemporal patterns [6]. These may allow the active metamaterial to do work on its environment and to locomote autonomously [4].

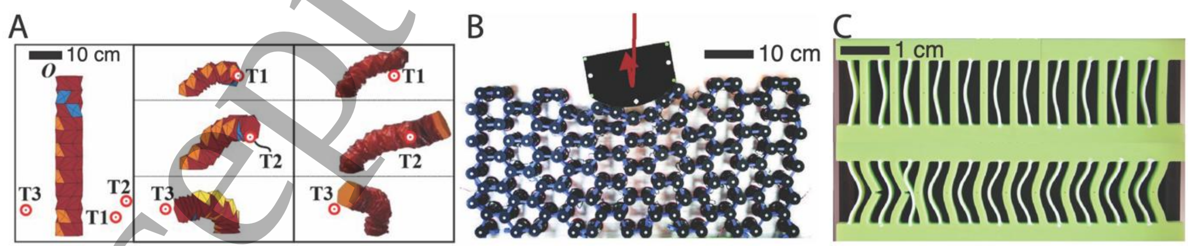

Figure 15.1 | Examples of active mechanical metamaterials. (**A**) Example of a shape-changing metamaterial made from an origami unit cell. The metamaterial consists of a pneumatically actuated origami, which is only actuated via a single pressure source. It can bend and twist such that the top of the column can reach points T1, T2 and T3 only by adjusting the history of the pressure loading. Left panel: metamaterial at rest; middle panel: simulations; right panel: experiments. Reproduced with permission from [11], Copyright © 2022, Wiley-VCH GmbH. (**B**) Example of an active metamaterial deflecting a projectile. The metamaterial consists of 120 robotic hexagons made from building blocks that break reciprocity. The metamaterial as a

whole is described by a generalization of elasticity called odd elasticity. Odd elasticity leads to non-reciprocal coupling between the two shear modes of the material when perturbed by the projectile and, in turn, to deflect the projectile [4]. (**C**) Example of a multistable metamaterial performing a counting task under cyclic compression. The metamaterial consists of a series of thin and thick beams. The thick beams are designed to be asymmetric: they buckle initially towards the left, but once nudged by the thin beams, they snap towards the right, in turn making the adjacent thin beam on their right snap. The metamaterial at the smallest (top panel) and largest (bottom panel) compression of cycle 2 [9].

Finally, the geometric nonlinearities of mechanical metamaterials have recently been explored to realize mechanical logic, storage of information, and elementary information processing *in materia* [7,8,9,10]. Crucially, the input and output here are via specific physical channels, distinct from the symbolic, general-purpose functionality of silicon-based computing. The simplest form of information processing has no memory, but directly translates (a number of) inputs to one or more outputs, with Boolean logic the paradigmatic example; such logic gates have now been realized in metamaterials by using buckling and snapping in, e.g., origami and slender elements [7]. More advanced forms of information processing require memory, in which the output depends on both the current input and the internal state, and where the latter stores information on past input and computations. This requires developing strategies to write, erase, and read information, and to design multistable metamaterials [2,3,8,10].

Current and Future Challenges

Shape-changing, activity and computation have thus far been achieved in separate platforms. Yet, to achieve animacy, they would need to be integrated in a single metamaterial, while maintaining long-term reliability. We first discuss what we see as the key challenges in each field, and then present a future strategy – based on realizing non-reciprocal cycles in active, multistable metamaterials – to integrate these key elements of animacy.

- **Shape-changing metamaterials** (**Figure 15.1A**) with a single shape change are by now well established. The next challenges lie in the design of multiple on-demand shapes into a single metamaterial and in the controlled actuation of such metamaterials. There is an inherent trade-off between freedom in the shape-change and complexity of actuation: metamaterials with a single shape-change are easy to robustly actuate, but their single shape can be limiting, whereas metamaterials with many shape-changes can be more versatile but require more advanced actuation.
- **Active metamaterials** (**Figure 15.1B**) need to do useful work on their environment in an adaptive fashion: think of an active metamaterial that can autonomously roll or crawl depending on the terrain. We see several important requirements:
    - Efficient design methods for active metamaterials that combine the flexibility to efficiently do work on their environment with the rigidity to carry a load.
    - Robust and scalable approaches to embed activity within a flexible metamaterial. One strategy may be to leverage rapid advances in materials such as liquid crystal elastomers, graphene actuators or shape memory alloys, and use their responsiveness to continuously harvest energy from the environment and convert this energy into purposeful work.
    - Strategies to control the behaviour of active metamaterials as their dynamics are inherently far-from-equilibrium and nonlinear, they are hard to predict and to design.
- **Computing metamaterials** (**Figure 15.1C**) should be able to perform sequential computational tasks. Such materials materialize finite state machines, the paradigm of computing that describes finite sequential computations. Strategies that use a distribution of bistable or hysteretic material bits - realized by, e.g., buckling and snapping beams or bistable origami elements - form an attractive route towards controllable and scalable stability [8,9,10]. The first examples of metamaterials capable of sequential computations (specifically, counting

and recognizing a sequential sequence of inputs) are appearing [8,9,10]. The complexity of mechanical metamaterials also allows other forms of *in-materia* computing, inspired by artificial neural networks, reservoir computing and neuromorphic computing.

Advances in Science and Technology to Meet Challenges

Realizing the next generation of active metamaterials that integrate autonomous, life-like functions (such as shape changes, locomotion and intelligence) relies on fundamental breakthroughs in each of these fields, as well as integrative work.

- **Fundamental Science**. There is an opportunity for advanced design techniques for metamaterials, building on recent advances in our understanding of geometric nonlinearities, topology optimization, and combinatorial design as well as integrating recent advances in machine learning and AI (see **Section 18**). In addition, distributed control strategies for such advanced metamaterials need to be developed. This may require revising tools of continuum mechanics, dynamical systems and control theory so that they can be applied in active systems, i.e., when reciprocity is broken; alternatively, model-free methods such as physical reinforcement learning may be helpful once they are generalized for multi-agent schemes. Both design and control suffer from the combinatorial explosions of the design and action space; efficient computational and optimization techniques need to be developed to navigate these vastly under-sampled, rugged parameter spaces and discover the rare metamaterial designs that are functional.

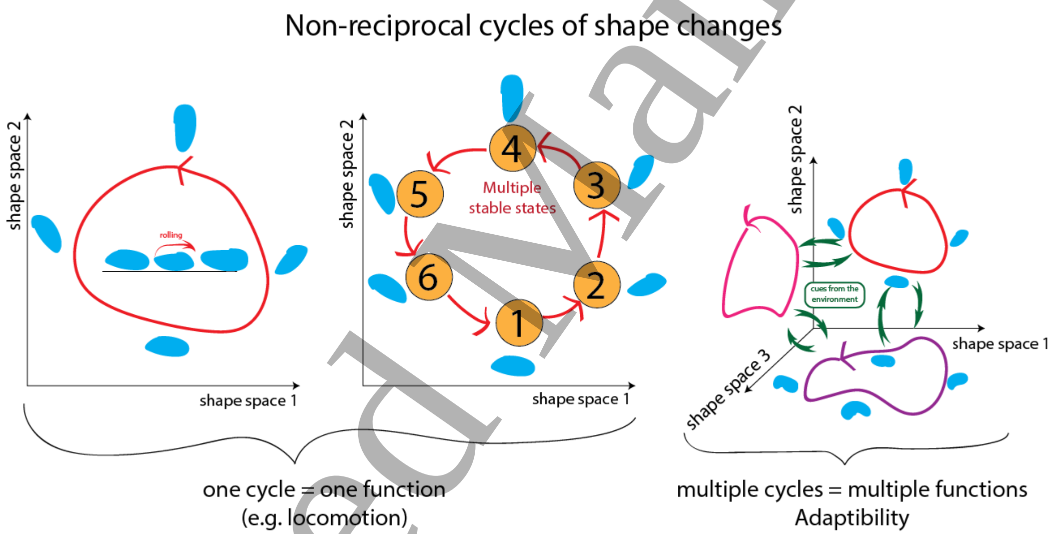

Figure 15.2 | The notion of non-reciprocal cycles of shape changes. Non-reciprocal cycles of shape changes through configuration or shape space break time-reversal symmetry and enable energy conversion into work (e.g., locomotion). (Left) In active metamaterials, limit cycles or travelling patterns are often emerging from a Hopf bifurcation. (Middle) Multistable metamaterials can feature periodic pathways through a sequence of metastable states. (Right) An important challenge is to embed multiple non-reciprocal cycles to integrate multiple functionalities (e.g., multiple modes of locomotion) and with adaptability between cycles (e.g., swap between rolling and crawling when the terrain demands it).

- **Technology**. We see great potential for improving the manufacturing of advanced active metamaterials. 3D printing techniques allow for an ever-increasing palette of materials as well as for increasingly fine resolutions, which ultimately may allow to move from the current macroscopic sample scales (order 10s of centimetres) to the millimetre and sub-millimetre regimes. However, these fall far short of the complexity seen in living systems, or more modestly, in most advanced metamaterial designs; we currently cannot (routinely) print complex metamaterials with 1000^3 voxels – which would not be unreasonable if one wants a linear dimension of at least 50-unit cells, and each unit cell with a reasonable resolution of 20^3

voxels. Another crucial challenge is to combine different materials classes, which is needed to combine multiple functions (e.g. combining passive elastomers for deformations and responsive materials for driving them). Finally, integrating chemical, electrical or electromagnetic sources of energy with sufficient power density and practical actuation mechanisms in metamaterials is a daunting challenge.

- **Conceptual Advances**. These are required to unify the three subfields of shape-changing, active and multistable metamaterials. We put forward the notion of non-reciprocal cycles: time-ordered cycles through configuration or shape space (**Figure 15.2**). In the context of active metamaterials, such cycles imply a sequence of shape changes that break time-reversal symmetry. These sequences are key to: (i) convert input energy into mechanical work for e.g. locomotion [4] or controlled gripping and release; (ii) perform advanced computation, store and process information in multistable metamaterials that sequentially hop between many stable states in sequence [8,9,11] (Fig. 15.1B), e.g. to achieve multiple shape-changes [3] yet using a single input [8,11] (Fig. 15.1A). Questions remain open: How do we embed such non-reciprocal cycles in a metamaterial? How do we efficiently couple these to large shape-changes to optimize their interaction with the environment? How do we embed multiple such cycles to achieve multiple functionalities (e.g., rolling, crawling and jumping)? How do we ensure that a target cycle is selected on the fly when the environment demands it?

Concluding Remarks

Animate matter should be able to perform purposeful actions in an autonomous and adaptable fashion. Mechanical metamaterials have been introduced over the past decade that display the individual functionalities of animacy: the ability to shape change, to do work and locomote and to perform *in-materia* information processing. Interweaving these functions via the notion of non-reciprocal cycles provides a unique opportunity to elevate metamaterials towards synthetic animate matter, to push forward the fields of rational and computational design, soft and active matter and alternative computing, and to reach impactful applications within the next decade. These applications may include intelligent soft robots (see also **Section 10**), non-invasive medical devices, autonomous infrastructure capable of self-adaptation to environmental fluctuations and climatic changes (see also **Section 20**), and efficient distributed information processing systems (see also **Section 18**).

Acknowledgements

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16 – Mechanically intelligent devices: Mechanical intelligence in animate systems

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Status

Animate matter is not merely active, it responds dynamically, adaptively, and intelligently to its environment. Environmentally adaptive systems, be they biological or robotic, are often described in terms of active sensing and neuronal/electronic computation. However, passive physical processes that occur downstream of sensing, computation and locomotor commands can profoundly impact the dynamics of animate systems, functioning as an auxiliary control system. When these passive mechanical processes are tuned such that they spontaneously facilitate environmentally adaptive responses, we call this system *mechanically* [1] or *physically* intelligent (**Figure 16.1**) [2]. Roboticists have begun to identify situations where mechanical intelligence can supplement and simplify computational control to improve locomotion (see also **Sections 10, 11** and **14**), and in biology the importance of passive mechanical processes in controlling adaptive responses has become increasingly clear. However, limited progress has been made in developing descriptions of mechanical intelligence that apply across different systems. Where computational intelligence is governed by the laws of logic and discrete mathematics, mechanical intelligence is governed by the dynamics of driven and damped mechanical systems. Hence, physics may provide a bridge between biological and engineered systems, by identifying fundamental principles that describe how mechanical and computational intelligence interact to produce behaviour across the diversity of animate systems. Identification of such principles will in turn contribute to the basic science of ethology and neurobiology while simultaneously enabling the creation of autonomous systems that can truly go anywhere, from microsurgical environments to search-and-rescue operations and interplanetary exploration.

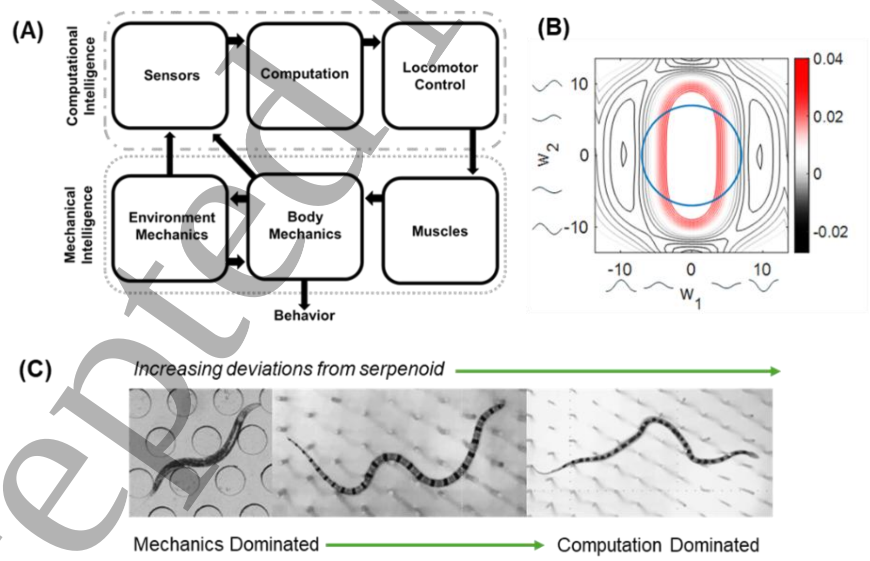

Figure 16.1 | Defining mechanical intelligence. (**A**) Schematic illustrating the interaction of computational and mechanical intelligence. Sensors take information from the environment in the form of mechanical, optical and other information. Algorithms perform computations based on those inputs to create commanded locomotor patterns, these then activate muscles or actuators, which filter the commands based on their dynamic properties. The forces generated by the muscles induce response forces in the passive material of the body and surrounding environment that feedback to modulate the final output behaviour. (**B**) A serpenoid curve (blue circle) in the shape space defined by the weights α_1 and α_2 which indicate the

amplitude of the shape basis functions. The height functions can be used to calculate speed in the lab frame. Curves which enclose more of the positive parts of the height function (red region) move faster. (**C**) Images of *C. elegans*, *C. occipitalis*, and *P. guttatus* in lattices.

One successful approach to discerning principles of mechanical intelligence in locomotion is the use of "robophysical" models [3]. These models are typically mesoscopic and macroscopic and rely on currently available materials (e.g. polymer such as thermoplastic polyurethane, TPU, and polylactic acid, PLA) and fabrication techniques (e.g. 3D printing, microelectronics). In this approach, robotic systems embodying drastically simplified models of organismal mechanics and 'neural' (electronic) feedback control are used to model the emergently simple, low-dimensional dynamics of organisms. This technique has its intellectual origins in the work of early cyberneticists, who first recognized that animals and machines could be described in a common language of feedback and control. Starting in the 1980s, robots as models were used to identify the role of mechanical control in legged locomotion, including hopping, bipedal and hexapodal legged locomotion, later in flapping flight and recently in limbless and myriapod locomotion. These models demonstrate how mechanical intelligence can simplify and augment active neural feedback control processes for diverse organismal morphologies. However, these approaches are often hard to generalize. Integrating robophysical models, which act as experimental tools, with theoretical tools taken from other branches of physics, offers an attractive path towards fundamental principles that describe how mechanical and physical intelligence interact to create behaviour across systems.

Current and Future Challenges

We can identify the following challenges for the development of mechanically intelligent devices:

- **Emergent simplicity in mechanical Intelligence.** Mechanically intelligent systems are complex, involving many degrees of freedom and multiple length scales. However, such systems typically display emergent simplicity. For example, longitudinal behaviour recordings of the nematode *C. elegans* have been described with data-driven dimensionality reduction techniques, such as PCA and other embedding schemes [4]. Subsequently, theoretical models of the transition probabilities between the low-dimensional behavioural states have invoked concepts like Markov models, and free energy landscapes – using ideas from non-equilibrium statistical physics and dynamics to rationalize behaviour in a generic way suggestive of principles [4]. Because these models focus on describing *kinematics,* they are fundamentally limited in their ability to discriminate between the computational and mechanical origins of animate behaviours.
- **Mechanics as a path to dimensionality reduction.** In contrast, mechanically oriented models offer an alternate path to dimensionality reduction that may point to principles of mechanical intelligence. Many organisms, including *C. elegans,* move in a regime where inertia is unimportant (e.g., viscous fluids), and consequently, body-environment interactions are analytically tractable. This facilitates the connection of *geometric phase* (initially developed within particle physics) to locomotion [5], which *mechanically* rationalizes the low-dimensional kinematics of undulatory gaits. This approach (referred to as "geometric mechanics") has helped to explain the gaits of worms, lizards and snakes [6], all which converge to a common gait template called a 'serpenoid curve' [7] – a sinusoidal traveling wave of curvature, which, when mapped into a two-dimensional 'shape space' creates a circular orbit that can be used to calculate the centre-of-mass motion using the enclosed area of a 'height function' (Fig. 16.1B). This technique describes the role of mechanics in creating motion *outside* the animate agent (in the environment) and does not capture the role of mechanical feedback in producing the serpenoid gait in the first place. To complete the rich

feedback system in Fig. 16.1A requires delving into the dynamic material properties of the body itself, and understanding how these properties control the mechanical coupling to the environment.

- **Mechanics to rationalize internal control schemes.** Internal mechanical control is especially important when encountering environmental heterogeneities, which produce large mechanical effects. *C. elegans* [8] and the sand-specialist snake *Chionactus occipitalis* [9] (Fig. 16.1C) display small deviations from serpenoid curves, thought to arise from mechanically controlled dynamic buckling. Alternatively, the corn snake *Pantherophis guttatus* displays large deviations from serpenoid behaviours suggestive of complex mechanosensory feedback [9] (Fig. 16.1C). Dissecting the relative roles of these modes of control in response to mechanical perturbations requires a new class of robophysical models and corresponding theory.
- **Interaction between Computational and Mechanical Control.** Understanding how computational intelligence interacts with particular mechanical control modes, both in biology and in synthetic mechanically intelligent systems will also be crucial to identifying principles and developing mechanically intelligent machines. Because mechanically intelligent actuators typically produce much more complex dynamics than simpler ones (e.g. servo motors), existing sensory modalities and control architectures may be less effective. The development of novel mechanically intelligent actuators therefore necessitates the development of complementary sensory modalities and potentially new theories of feedback control.

In summary, existing ways of describing emergently simple locomotor dynamics are either data-driven (ignoring mechanics), case specific, or rationalize behaviours by considering mechanics outside the body, taking kinematics as an input. To realize general mechanically intelligent machines requires:

- systematic mechanically parameterized dimensionality reduction schemes;
- comparative mechanical models that transcend system specificity; and
- models that rationalize both the internal (body) dynamics and the mechanical environmental responses simultaneously.

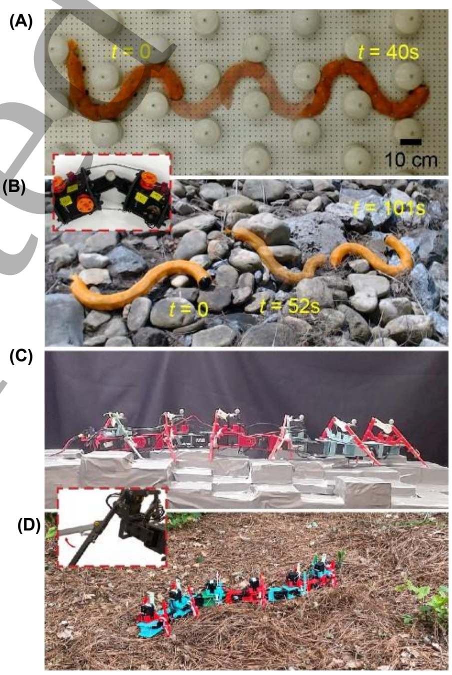

Figure 16.2 | Examples of mechanically intelligent devices. (**A**-**B**) A robophysical model of a bilaterally actuated undulating robot leverages the redundancy of its multi-joint architecture and the asymmetric compliance to confront (**A**) lab and (**B**) natural terrain through mechanical intelligence. From [9]. Reprinted with permission from AAAS. The inset shows a close-up on the multi-joint architecture. (**C**-**D**) A centipede robot similarly leverages both the redundancy of its legs and the asymmetric compliance its limb joints in (**C**) lab (from [10]; reprinted with permission from AAAS) and (**D**) natural settings. The inset shows a close-up on the limb joints. Reprinted with permission from [11], Copyright © 2020, IEEE.

Advances in Science and Technology to Meet Challenges

The following advances are required to meet the previous challenges:

- **Robophysical models of mechanical control in undulation.** To describe the role of mechanical feedback *within and outside of* the body, a recent robophysical model (**Figure 16.2A,B**) was developed to capture aspects of the bilateral muscle activation patterns of worms, snakes and other undulating organisms [8]. This model goes beyond previous work by revealing how mechanical feedback can *create* kinematics. An open-loop serpenoid gait (derived from the geometric phase approach) is commanded by the robophysical 'nervous system'. Downstream mechanical feedback mediated by collisions with environmental obstacles and the dynamic material properties of the body then conspire to modify the commanded gait kinematics to produce effective locomotion in highly complex terrain. Specifically, the dynamic, asymmetric compliance of the body, acts like a mechanical diode – would-be drag-inducing collisions spontaneously lead to body yielding and turning around the obstacle, while thrust-producing collisions, like hooking behaviours, result in body rigidity and forward movement. This example illustrates how external perturbations to optimal gaits derived from geometric mechanics can be mediated from mechanical feedback alone, demonstrating mechanical intelligence.
- **Robophysical models of mechanical control in multi-legged systems.** Beyond undulation, recent work on the limbed locomotion of centipedes has revealed another case where a combination of theory borrowed from fields outside biology, and robophysical models of mechanical control (**Figure 16.2C,D**) have shed light on mechanical intelligence. Centipedes exploit limb redundancy, as well as the asymmetric compliance of each leg to rectify perturbations to their commanded stepping gaits from obstacles in the environment. This effect was formally described using an analogy from Shannon's information theory [10], where discrete foot contact patterns were mapped onto binary bit sequences, and message transmission was analogized to the robot's self-transportation through the terrain.
- **Moving toward principles via experiment and theory.** Both cases illustrated above offer examples of how robophysical models of mechanical feedback, combined with theoretical models of computational control, can point to principles of mechanical intelligence that transcend morphology. In both cases asymmetric compliance (either of the limbs or the body) along with the redundancy (either of legs or body joints) helped to buffer the optimal, physics-derived gait commanded by the nervous system to unexpected environmental perturbations. Elevating these observations to the level of principles will require further experimental and theoretical development. On the experimental side, a proliferation of novel soft actuation schemes analogous to the ones above and testing in a greater variety of environmental regimes will produce a rich foundation of phenomenology which can be organized and explained with theory.

Concluding Remarks

Developing principles of mechanical intelligence will lead to major changes in the way engineered animate systems are designed and controlled. While most of the systems we discussed here are macroscopic, the principles we hope to uncover should transcend scale to a degree. The emphasis on kinematics in the study of biological animate matter reflects a similar focus on body-shapes – and not body-environment physical dynamics – in the design of existing robotic systems. Focusing on connecting behaviour (defined as kinematics) to neurobiology (defined as neural activity) as the goal of neuro-ethology, while neglecting mechanical control, produces a fundamentally incomplete picture of animate behaviour in general. To develop engineered animate matter that can reckon with the full complexity of the external environment efficiently and robustly will require both mechanical and computational intelligence. However, the overwhelming paradigm of contemporary robotics is oriented towards computational solutions to often intrinsically mechanical problems. One of the main advantages of mechanically intelligent control systems relative to their computationally based counterparts is their robustness to sudden environmental changes. Their complex dynamics do not, in general, require prior knowledge of environmental conditions. Hence, they are likely to be an important part of the adaptation of animate systems to larger-scale ecological and climatic changes as well. Shape control either relies upon the environment being simple or requires high bandwidth sensing and computation. This approach limits animate matter in two ways: 1) at microscopic length-scales, the relative cost of computation may increase rapidly; 2) for macroscopic matter, at the scale of large swarms (see also **Section 17**), the cost of computation may too become prohibitively significant. Principles of mechanical intelligence could lead to a paradigm shift in the control of animate matter to overcome these challenges. Because mechanical intelligence studies have begun to proliferate for a diverse set of locomotion types, and also because the development of mechanical intelligence relies on novel deployments of currently available materials and fabrication techniques (e.g. 3D printing, microelectronics), practical technologies that exploit these control strategies will likely emerge within the next several decades.

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17 – Swarm robotics

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Status

Swarm robotics stands as a beacon of innovation in the realm of robotics, embodying the principles of collective intelligence, resilience, and scalability [1]. This emerging field harnesses the power of collective behaviour exhibited by groups of simple robotic agents (e.g., see a swarm of miniature robots in **Figure 17.1**), which resemble an animate material composed of many interacting, autonomous units like cells of an organism. More precisely, robot swarms take inspiration from collective animal behaviour, where animal societies display coherent, cognitive behaviour as a group, such as ant colonies or flocks of birds. Self-organisation imbues swarm systems with the ability to exhibit emergent behaviours, enabling adaptability to dynamic environments and robustness against failures. Unlike traditional robotics, where centralised control prevails, swarm robotics embraces decentralised control, where autonomous robots achieve common objectives only relying on fragmented knowledge and local coordination.

Figure 17.1 | A swarm of Kilobots, a *de facto* standard platform for swarm robotics research. This is a small robot of 3.3-cm diameter, designed to move on a flat surface and communicate efficiently with its immediate neighbours. Several design choices have been made to simplify the electromechanical components and experimental procedures like recharging and uploading control programs—which become cumbersome with large swarms—enabling experimentation with thousand robots lasting several hours [2].

Research has focused on two main problems. On the one hand, specialised robotic platforms (with sizes ranging from microns to meters) have been developed to enable coordination through communication and physical interactions [2]. For instance, self-assembly of autonomous swarms in large functional structures constitutes a distinctive paradigm of swarm robotics [3]. On the other hand, engineering methodologies have been proposed to address the design of the individual control rules that can lead to a desired swarm behaviour. Here, two distinct goals can be sought: (i) deliver a robotic system that efficiently solves some complex problem [1], and (ii) generate and test hypotheses about observed collective behaviours in nature, which hinge on the physical interactions and the communication abilities among individuals [4]. However, a general-purpose engineering methodology for swarm robotics is still missing.

The versatility of swarm robotics promises exploitation in numerous application domains, spanning from disaster response and environmental monitoring to precision agriculture and space exploration [1]. For instance, in disaster scenarios such as search-and-rescue operations, swarm robots could efficiently explore hazardous environments, locate survivors, and deliver essential supplies. Similarly, in agricultural settings, they could collaborate to perform tasks like crop monitoring and pest control, enhancing agricultural productivity and sustainability, especially with respect to the challenges imposed by climate change – an increasingly critical need. Moreover, swarm robotics could find applications in automated warehouses, infrastructure maintenance, surveillance, and many other fields, showcasing its potential to revolutionise diverse industries while meeting current and future sustainable development goals.

However, despite its promising applications, achieving the full potential of swarm robotics remains an ongoing challenge. There are still no commercial applications of swarm robotics. The main limitations to demonstrating robot swarms at scale are flexibility and adaptability to dynamic and uncertain environments, cost-effectiveness and security. Overcoming these limitations requires addressing various prospects and challenges in swarm robotics, including miniaturisation and control, heterogeneity, ensuring long-term autonomy, achieving scalability, and enhancing robustness.

Current and Future Challenges

In the future of swarm robotics, we can highlight the following challenges:

- **Miniaturisation**. Deploying and controlling large numbers of miniature robots represent critical aspects of swarm robotics, offering both opportunities and challenges [5]. Shrinking robotic components enables navigation of confined spaces and execution of precise tasks, e.g., in precision medicine. However, it also poses challenges like limited computational power, sensing, actuation and communication capabilities, which constrain the autonomy of the individual robots. While there are current attempts to develop robots at the micro- and nanoscale, full autonomy and interaction abilities likely require a few decades (see also **Sections 2, 3** and **4**). Novel concepts in hardware, energy efficiency and control algorithms are necessary to advance the field.
- **Novel materials**. Integrating soft robotics principles introduces deformable robots capable of seamless interaction with the environment [6], also enhancing adaptability and cooperation within swarms. Indeed, soft materials introduce novel possibilities for physical interaction within the swarm that challenge current ways of designing cooperation and control, and that are expected to become more and more relevant in the next decade with new soft materials getting integrated with autonomous robots. Hence, research should focus on robot interactions within soft-bodied aggregates where boundaries get blurred, making continuous structures adaptable to unpredictable situations, hence offering versatility in various applications (see also **Section 10**).
- **Scaling up complexity.** Achieving higher complexity of the tasks performed by robot swarms likely requires diversifying the functions and roles that robots can perform. This is a well-known challenge in swarm robotics, which received too little attention in the past and should be addressed in the years to come. Heterogeneity in swarm robotics, be it morphological or

behavioural, enhances adaptability and task performance, as specialised robots can provide different functions to fulfil task requirements at hand [7]. Integrating robots with different hardware and behaviours can lead to efficient resource allocation and adaptive responses to environmental changes. Further challenges derive from scalability of swarm systems, managing task execution effectiveness as swarm size increases. This is even more compelling in the case of heterogeneous swarms. Scalability limitations are well known and sometimes unavoidable [8]. A current challenge stands in guaranteeing effective scalability at least within the range of swarm sizes requested by the problem at hand.

- **Robustness beyond redundancy**. Enhancing **robustness** involves fault-tolerant mechanisms and resilience against adversarial conditions, ensuring mission success despite uncertainties and disruptions. While swarm robotics can exploit a high level of redundancy to tolerate failures in some of the robots composing the swarm, the system is not automatically protected from faults and from the injection of erroneous or misleading information. This is intimately related to safety in the deployed system, ensuring that it can sustain both internal failures and external attacks. Designing decentralised mechanisms to protect robot swarms remains an open challenge. Addressing such challenges together with ethical considerations is crucial for building trust and acceptance of swarm technologies, and ultimately for enabling real-world deployment within the next decades. This also intersects with the need to achieve long-term autonomy, so that functions can extend over long timeframes without the need for human intervention. This would unlock several application scenarios in remote environments, such as underwater or in space, where the possibility to rely on cooperation and collective intelligence would be a game changer.

Advances in Science and Technology to Meet Challenges

There are two main paths that need to be followed to meet the above challenges, one that is more science-oriented, and one that is rather technology-oriented. Clearly, these two paths should not develop in parallel but intersect and cross-fertilise.

The science-oriented path leads to the exploration of novel challenging directions for understanding swarm systems and enabling miniaturisation and control:

- **Improve models.** We need to produce better theoretical models that include spatial and topological dynamics, which can be used to explain collective behaviour and support design, especially tailored to predict and control heterogeneous swarm systems.
- **Exploit intrinsic stochasticity**. Further modelling efforts should also guide the development of novel mechanisms able to exploit internal variability and external perturbations. For instance, chirality of motion can derive from manufacturing variability, and could be exploited rather than counteracted (see also **Section 14**). Other sources of variability – e.g., malfunctioning or noise – could be seen as an asset rather than a hindrance, for example, to allow a collective system poised at a critical state to transit between different states, or to enable exploration and adaptation to environmental changes by exploiting stochastic fluctuations.
- **Move from bio-inspiration to biohybrid systems**. Bio-inspiration has been one of the main approaches to designing swarm systems but should be extended beyond the development of control systems to embrace also new materials and hardware concepts. Physical computing reduces requirements from control (as discussed in **Section 16**), especially if soft physical interactions are exploited. Bio-inspired morphologies can support collective behaviour, making robots more like living organisms that face similar energy constraints and operate in the same unpredictable world. Pushing this idea to the extreme, biohybrid systems (see **Section 11**) and organic swarm robots can be considered, possibly obtained through cybernetics, genetic engineering and controlled growth [9-10]. In this last effort, safety and

ethical consideration are of utmost importance, preventing unconstrained propagation and ensuring that the societal benefits largely overcome any potential harm, hence aligning with the most stringent standards.

The technology-oriented path leads to the implementation of swarm robotics principles for real-world applications:

- **Provide energy autonomy for long-term deployment**. Real-world applications should not be limited to battery lifetime. While material science contributes with novel designs for solar cells and ultra-low-power sensors, swarm robotics research needs to focus on energy-awareness, harmonising swarm functionalities with sustainable usage of resources. Hence, minimalist approaches that achieve coordination and control with little or no computation should be considered, which also fit well with miniaturised hardware [11]. Orchestration of swarm activities and heterogeneity can enable managing continuous operations as well as collective energy management.
- **Exploit blockchain within swarms**. Recent research has shown that the integration of blockchain technology is a promising solution to address several of the outstanding critical problems for real-world deployment including security, resilience, accountability, and data integrity [12].
- **Increase social awareness of swarms.** Human swarm interaction needs to be considered, as swarm robots do not operate in isolation but must blend within our societies and enable efficient user control, with guarantees of no harm and unintended emergent effects [13].

Concluding Remarks

Swarm robotics promises to effectively produce a new form of animate material, a kind of artificial super-organisms that displays adaptive and resilient behaviour in the face of dynamic task requirements. While such large-scale robotics systems can have a disruptive impact on our society and industries, current research has shown that controlling a large number of autonomous robots—which influence non-linearly each other's behaviour—is a particularly challenging problem. We envision substantial progress can be achieved thanks to an interdisciplinary scientific effort, as the deployment of swarm robotics requires addressing challenges in several fields other than robotics, including material science, microelectronics, computer science, biology, and nonlinear dynamics. Once swarm robotics starts being employed in real-world applications, addressing ethical, political and economic concerns also becomes critical.

Acknowledgements

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18 – Machine Intelligence: Integrating Artificial Intelligence and Animate Matter

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Status

The integration of Artificial Intelligence (AI) into the development of bio-inspired synthetic systems heralds a new era with materials and agents that are self-sufficient and capable of complex behaviours mirroring the complexities of living systems. Historically, the field of AI has evolved from rudimentary algorithms simulating basic cognitive functions to sophisticated neural networks capable of learning and making decisions with minimal human oversight [1]. **Figure 18.1** presents an overview of current AI techniques. This progression has paralleled advancements in soft and active matter physics and chemistry, where the focus has increasingly shifted towards systems that can dynamically respond to their environment [2].

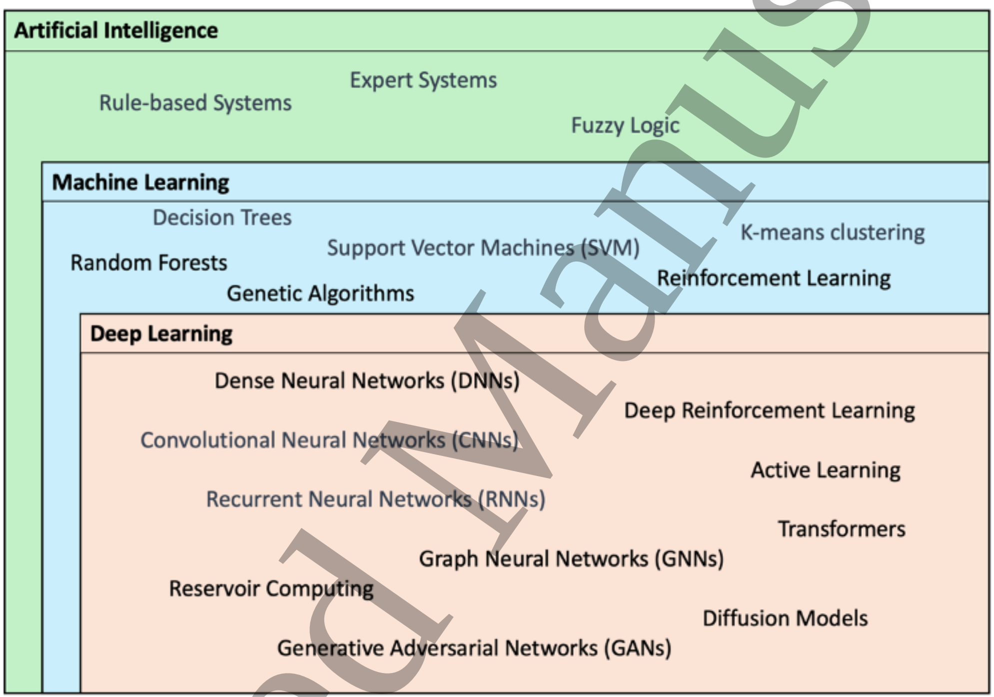

Figure 18.1 | Overview of AI techniques. Hierarchy within artificial intelligence (AI), breaking down AI into its core components: Machine Learning (ML) as a subset of AI that focuses on the ability of machines to learn from data, and Deep Learning (DL) as a further specialization of ML employing neural networks with multiple layers. Key techniques under each category are highlighted, showcasing the progression from general AI principles to specific computational models and algorithms in ML and DL.

By utilizing AI, researchers can endow synthetic materials and agents with the ability to adapt, evolve, and perform tasks autonomously. Such capabilities are inspired by living systems, where active matter constantly adjusts to stimuli through an interplay of mechanical, chemical, and biological processes. Current AI techniques facilitate this by enabling the design and control of agents and materials at an unprecedented level of precision and functionality. Machine learning algorithms, for instance, can predict these system's behaviours under various conditions, optimize their performance, and even discover new agents and materials with desired properties [2].

By using emerging AI methodologies—such as generative adversarial networks (GANs) and deep reinforcement learning—researchers can rapidly prototype novel materials and agent architectures by simulating diverse environmental conditions and molecular arrangements across multiple length and time scales. For example, GANs can generate thousands of candidate structures based on a small set of experimentally validated data, expediting the discovery of materials with specific mechanical or chemical traits. Deep reinforcement learning can be used to autonomously refine design parameters to meet targeted functionalities, such as enhanced responsiveness or minimized energy consumption—while accounting for molecular processes that occur in nanoseconds as well as morphological changes unfolding over hours or days. This iterative feedback process significantly accelerates innovation and helps bridge short- and long-term behaviour, while reducing trial-and-error in laboratory experiments. Other examples are shown in **Figure 18.2**.

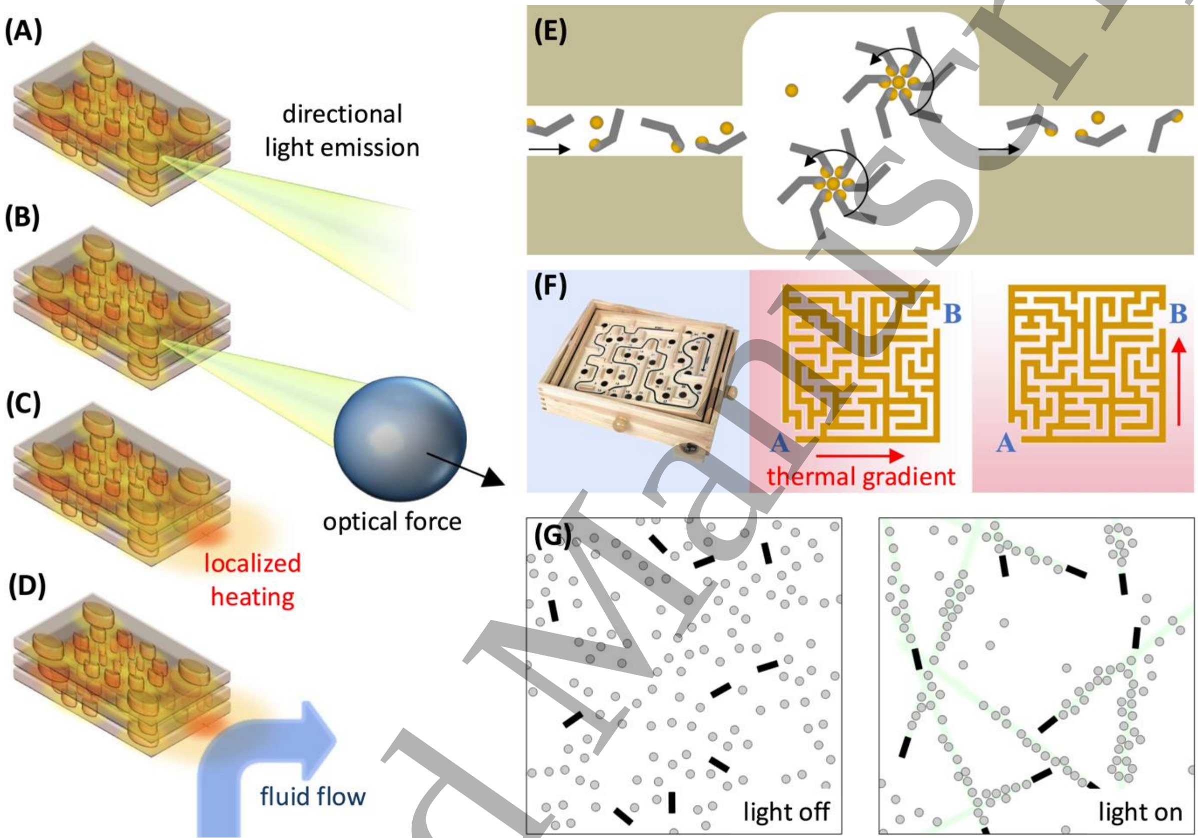

Figure 18.2 | Examples of potential use of AI techniques in animate matter. (**A**-**D**) AI-enhanced design can produce multimaterial microscopic particles capable to (**A**) control the scattered light direction (see also **Section 5**), (**B**) influence the motion of nearby particles through optical forces, (**C**) generate localized heating, or (**D**) drive fluid flows by generating localized heating. (**E**) AI-enhanced design can be employed to develop microbots that can be assembled in situ to perform a certain task (see also **Sections 3 and 4**). For example: their parts can be delivered to a cavity through a channel; the composite microbot is assembled in situ within the cavity and performs its task (e.g., to steer the solution); finally, the microbot is disassembled and removed. (**F**) In the labyrinth game, one tilts the playfield to guide the marble to the end of the labyrinth, without letting it fall into any of the holes. AI could permit to implement a microscopic version of this game, using an environment with a complex topography (the labyrinth) and thermal gradients introducing thermophoretic forces (the tilting). These gradients can be applied along different directions, as indicated by the shading and arrows for two possible directions. Since it is not enough to just apply a gradient from A to B and one needs to account for the presence of noise, one need to answer the non-trivial question: which is the best strategy to get the particle to go from A to B while avoiding the pitfalls by using a sequence of thermal gradients along different directions? (**G**) AI can be employed to build microscope animate particles capable of shining light along one direction that can organize a solution of colloidal particles into a network by taking advantage of optical (short-ranged) and thermophoretic (long-ranged) forces.

The importance of AI combined with animate matter extends beyond the laboratory into practical applications promising revolutionary advances. In healthcare, the integration of AI with bio-inspired systems could enhance the development of responsive and adaptive drug delivery systems, for example, by using geometric deep learning to identify spatiotemporal fingerprints of microscopic motion of drug carriers engineering their diffusion properties and automatically tailoring their diffusion profiles to specific tissue conditions [1]. Similarly, there is a huge potential to advance diagnostics and patient care through improved imaging techniques relying on deep learning to improve robustness against noise [4] or to decrease the need for training data [5]. In environmental sustainability, AI has been shown to contribute to the understanding of microplankton life histories [6], which could inform the design of materials for cleaning pollutants or converting waste into energy. Moreover, AI-driven biohybrid systems could monitor and respond to environmental changes in real time, adjusting behaviours such as pollutant uptake or energy generation pathways to optimize performance under fluctuating conditions. Finally, AI can be used to create biohybrid microrobots using biological cells to create microscopic active agents [7] (see also **Section 11**).

The ongoing advancements in AI promise to further bridge the gap between synthetic materials and living systems. As AI algorithms become more sophisticated, their integration with bio-inspired materials will likely yield systems with levels of autonomy and adaptability that closely mimic, or even surpass, those of natural organisms. The potential gains from further advances in this interdisciplinary field include more efficient energy use, enhanced resilience and durability of materials, the ability to tailor or even "evolve" material properties in situ, and the creation of entirely new functionalities that today remain unimaginable.

Current and Future Challenges

The ambitious vision of creating bio-inspired synthetic systems and materials that are active, adaptive, and autonomous through the integration of AI presents significant challenges. These challenges span technical, ethical, and scalability issues, as detailed below.

- **Complexity of integration.** One of the foremost challenges lies in the complexity of integrating AI with the inherently unpredictable and dynamic nature of bio-inspired systems. The stochastic behaviours observed in living systems, influenced by countless variables, present a significant hurdle for AI models that thrive on predictability and quantifiable data. Developing algorithms capable of accommodating, predicting, and effectively responding to the dynamics of these systems remains a critical task—especially algorithms that can be trained with small amounts of data.
- **Data limitations.** The scarcity of high-quality, comprehensive datasets that accurately represent the complexities biological and bio-inspired materials limits the ability of AI to learn and make reliable predictions. A parallel challenge concerns the need for standardization and accessibility to these data.
- **Model accuracy.** The AI models must balance accuracy and generalizability, ensuring that they are robust enough to handle real-world variability without being overly specialized to specific datasets.
- **Ethical and societal implications.** As these materials gain autonomy, ethical considerations come to the forefront. Questions regarding the decision-making processes of AI-driven systems, their impact on privacy, safety, and the environment, and the potential for unforeseen consequences of autonomous action pose significant challenges. Addressing these concerns requires a multidisciplinary approach, involving ethicists, policymakers, and the public in the development process [8].
- **Scalability and deployment.** Transitioning from laboratory prototypes to widely deployed, scalable solutions are another challenge. Issues related to manufacturing, energy consumption, longevity, and maintenance of AI-integrated bio-inspired systems must be

addressed. Furthermore, ensuring these materials can be produced and operate sustainably and economically on a large scale is essential for their widespread adoption.

- **Interdisciplinary collaboration:** The cross-disciplinary nature of this field demands unprecedented levels of collaboration between material scientists, biologists, AI researchers, and engineers. Bridging the knowledge gaps and fostering effective communication among these diverse groups are crucial for tackling the complex problems at the intersection of AI and bio-inspired materials.

Advances in Science and Technology to Meet Challenges

Addressing the challenges of integrating Artificial Intelligence (AI) with bio-inspired synthetic systems requires significant scientific and technological advancements, matched with the challenges described above.

- **Enhanced machine learning models.** Progress in machine learning algorithms is vital to handle the unpredictable nature of bio-inspired systems, while exploiting the intrinsic symmetries and properties of these systems to enhance the model performance also with minimal amounts of training data. Physics-inspired deep learning, deep reinforcement learning, and unsupervised learning offer promising pathways to develop models that can learn complex patterns, adapt to new environments, and make decisions in real-time. Advances in these areas will enable more accurate predictions and control of material behaviours, leading to systems that can autonomously adapt to their surroundings.
- **Synthetic data generation and simulation technologies.** To circumvent the limitations of scarce or incomplete datasets, advances in synthetic data generation and simulation technologies are essential—as already successfully done in the field of microscopy [9-11]. These technologies can create high-fidelity, diverse datasets that simulate the vast range of conditions that bio-inspired materials and agents might encounter. This approach improves the training of AI models, while facilitating the testing of materials and agents under virtual conditions that are difficult or impossible to replicate in the lab.
- **Ethical AI frameworks.** Developing frameworks for ethical AI is critical to ensure that autonomous systems operate within predefined ethical boundaries, for example, in biomedical and ecological applications. These frameworks should include guidelines for transparency, accountability, and privacy protection, incorporating feedback from diverse stakeholders. Furthermore, research into explainable AI will enhance our understanding of AI decision-making processes, making them more interpretable to humans.
- **Scalable manufacturing and integration techniques.** Technological advances in scalable manufacturing processes and integration techniques are required to transition bio-inspired materials from prototype to production. Innovations in 3D printing, bioprinting, and nanofabrication will facilitate the creation of complex, multi-functional materials. Additionally, the development of energy-efficient, durable systems that can self-repair or degrade safely after their lifecycle is crucial for sustainable deployment.
- **Interdisciplinary collaboration platforms.** Finally, the establishment of platforms and frameworks that promote interdisciplinary collaboration is essential. These platforms should facilitate knowledge sharing and joint research efforts, leveraging cutting-edge tools in data sharing, computational resources, and collaborative software. By breaking down the barriers between disciplines, these platforms will accelerate the pace of innovation and the application of AI in developing adaptive, autonomous materials. An effective way to enhance these interdisciplinary collaborations is through open challenges.
- **Infrastructure for AI Integration.** The development of suitable infrastructure is vital for real-time AI-driven feedback, particularly in complex bio-inspired systems. This infrastructure

should include robust sensor networks capable of collecting high-quality data—ranging from physical (e.g., temperature, pH, mechanical stress) to biological (e.g., cell viability, metabolic markers) signals. In parallel, reliable data communication systems (e.g., Wi-Fi, optical fiber, or emerging 5G/6G solutions) ensure low-latency and high-bandwidth transmission, facilitating immediate analysis and decision-making. To standardize and streamline this process, data protocols and interfaces must be agreed upon by the research community, supporting data interoperability and format consistency across devices and platforms.

- **Data management guidelines.** Guidelines for data preparation, labeling, and standardization are equally important to ensure reproducibility and robust AI model performance. Metadata standards—covering sampling rates, sensor calibration details, and experimental conditions—should be enforced, while consistent labeling (with clear annotation rules) helps maintain clarity and reduces risk of bias. Preprocessing steps, including normalization, noise filtering, and outlier removal, should follow well-documented protocols that allow for reproducible experiments. Collectively, these measures foster an ecosystem where sensors, communication systems, and data-driven models work seamlessly together, accelerating the pace of innovation in AI-integrated animate matter.

Concluding Remarks

The integration of AI with bio-inspired synthetic systems represents a frontier in materials science that promises to redefine our interaction with technology. By drawing inspiration from the adaptability, autonomy, and complexity of living systems, and harnessing the analytical and predictive power of AI, we stand on the cusp of creating materials and devices that can dynamically respond to environmental stimuli, self-organize, and even mimic biological processes. The timescales for the use of AI in animate matter are spread out over years to decades as the simplest implementations are already doable with current technology, but the most advanced/visionary ones will require breakthroughs and substantial technological advances. The challenges in this interdisciplinary endeavour are substantial, spanning technical, ethical, and scalability concerns. However, the ongoing advancements in AI and materials science, coupled with a growing emphasis on interdisciplinary collaboration, provide a solid foundation for overcoming these obstacles. As we navigate these challenges, we must recognize the ethical implications of autonomous systems and strive for sustainable, beneficial applications. The journey towards fully realizing the potential of AI-driven animate matter is complex and fraught with unknowns, but it is a journey that holds unparalleled promise for the future of technology, robotics (see also **Sections 16** and **17**), built environment (see also **Section 20**), medicine, and environmental sustainability.

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19 – Architectural Probiotic Materials

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Status

Architectural probiotic materials are a class of biologically active materials for the built environment containing benign microbes that are harmless to humans, but that are beneficial for health through their ability to shape the indoor microbiome and the microbiomes of building occupants towards a healthy state [1].

Recognition of the importance for limiting harmful microbial transmissions in buildings in relation to human health is long standing, and over the last 100 years, material strategies in buildings have broadly operated under the assumption that healthy buildings should contain fewer microbes. Materials in buildings serve as a significant source of microbial transmission indoors where they act as 'fomites', defined as surfaces or other inanimate objects onto which a microorganisms can deposit and from which they can be transferred to a host. Early material strategies of whitewashing and glazing were partly concerned with limiting the presence of germs, but since the development of antibiotics in the mid-20th Century, the use of antimicrobial materials and antibiotic chemicals has become commonplace across a range of building typologies. Their use rose drastically during the COVID-19 pandemic and is predicted to continue to increase in the coming years.

While there is a clear need to target sterile surfaces in certain buildings such as hospitals, antimicrobial materials and chemicals have various limitations that are problematic for human health. As well as being harmful for human exposure, chemical disinfectants are time-dependant and are subsequently ineffective against recolonisation [2] — a key factor in building acquired infection. More worryingly, their overuse appears to be creating conditions of stress which are actively selecting for antimicrobial resistance in buildings [3]. As well as removing harmful microbes, they also remove other benign microbiodiversity which act as a kind of shield against pathogens through principles of microbial competition. In line with the emerging understanding of microbiome health, this lack of microbial diversity in buildings is also being associated with the observed rise in immunoregulatory illnesses described as diseases of missing microbes [4].

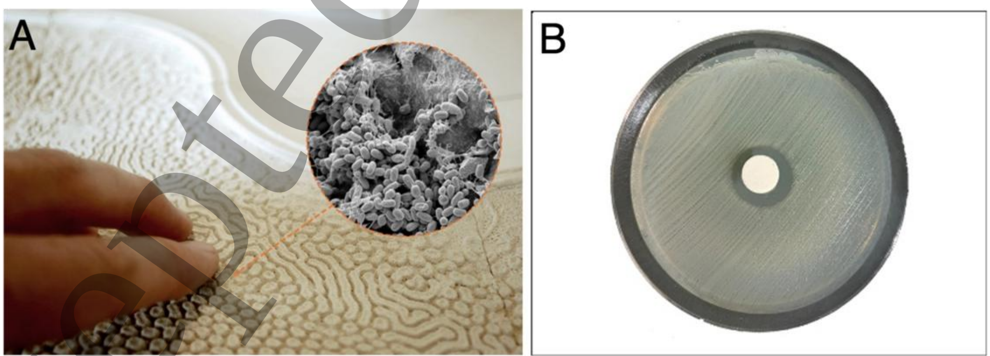

Figure 19.1 | Examples of probiotic surface tiles. (**A**) Photograph of probiotic surface tiles embedded with *B. subtilis*; inset with SEM image of bacterial cells within the material matrix. (**B**) Growth inhibition of Methicillin-resistant *Staphylococcus aureus* (MRSA) by a probiotic disc. The creamy yellow/white background on the plate is MRSA and the zone of clearing around the disc shows inhibition of MRSA.

These positions suggest that healthy materials could be ones that support and maintain a degree of benign microbial diversity. This can serve to outcompete pathogens and potentially support healthy immune function through their impact on the human microbiome. This animacy of competitive exclusion, and the need to implement strategies to restore microbial diversity in certain built environments forms the basis for Probiotic Materials. These approaches align with the emergence of other 'probiotic' strategies for the built environment including cleaning products [5] and efforts to create microbiome inspired landscape designs [6], but with a specific focus on architectural applications for walls and surfaces in buildings (see also **Section 20**). Work by the authors to date has developed methodologies for the creation of probiotic ceramics, concretes and plastics, and is exploring their use towards the engineering of surface tiles (**Figure 19.1**), furniture, or even entire structures (**Figure 19.2**) out of microbially-active materials [7]. This envisages buildings that are healthy today, but that also offer resilience to future challenges including pandemics and biodiversity loss.

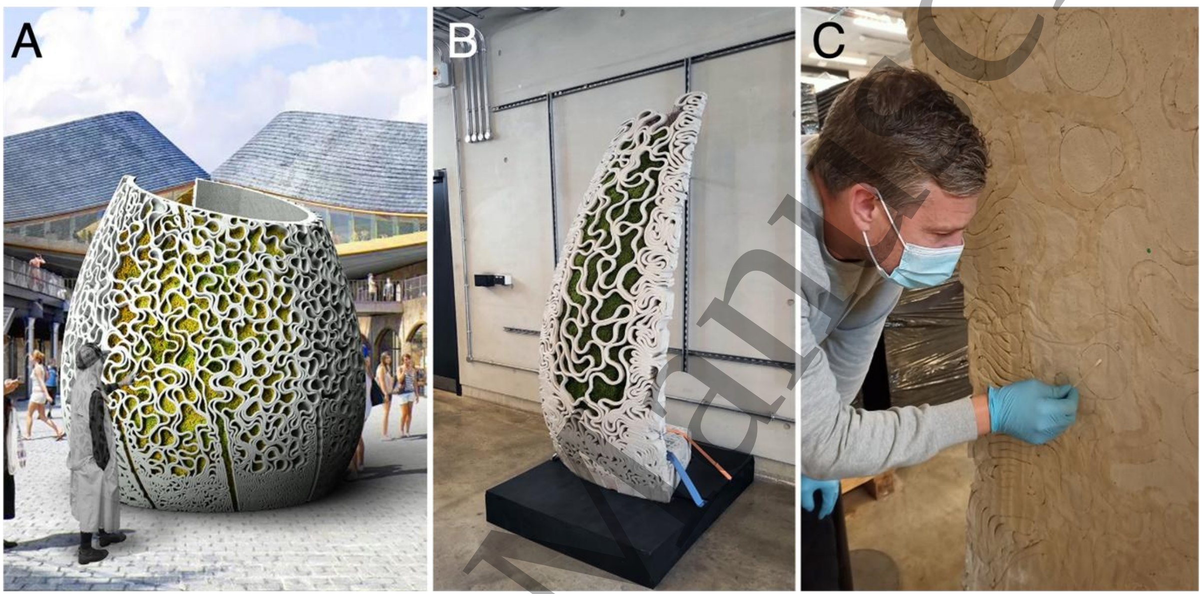

Figure 19.2 | Probiotic building protypes. (**A**) Rendering of an imagined probiotic pavilion structure. (**B**) 1:1 scale 3D printed, microbially active building prototype, embedded with bryophytes (outer facing) and soil microbes (inner facing). (**C**) Photograph of prototype undergoing a microbiome monitoring study using 16S DNA sequencing.

Current and Future Challenges

Architectural probiotic materials have emerged to include the microbial scale as a design parameter in shaping materials for buildings that are sustainable, healthy and resilient. Such approaches involve the intentional integration of living organisms, typically microorganisms or microbial communities, into the design and function of materials, that utilise the beneficial biological agencies of the respective organisms (see also **Sections 8, 12** and **20**). Within this hybrid condition, more research is needed to understand how the physical and chemical properties of the material substrate can augment the beneficial biological mechanisms of benign microbes. Important properties might facilitate adhesion of microbes to the material surface, modulate biochemical pathways and ensure their ability to survive and remain viable indoors over time. Building materials have been described as microbial wastelands, due to the typically dry and nutrient poor nature of contemporary indoor environments [8]. Materials might provide nutrient sources for specific strains or facilitate spore formation to offer long term survival with limited maintenance.

Spore of *Bacillus* spps have been directly integrated into hydrogel materials [9], yet such materials are unlikely to be able to survive the rigours of daily building life. The use of harder materials for buildings (ceramics, concretes, hard plastics, etc.) is preferable. Methods of manufacture will be important to reliably produce material properties such as porosity, pH and hydrophobicity so they can serve as a resilient source of beneficial microbes, but also perform as part of the building fabric.

Probiotic materials can be fundamental in shaping what we envisage as healthy beneficial human-microbe interactions in buildings. In line with this, we highlight two key outstanding challenges:

- **Probiotic materials to limit AMR**. Biologically active materials and surfaces could be applied in buildings to limit the emergence and spread of AMR in the built environment. Researchers recently developed novel porous ceramic materials, inoculated with strains of the *Bacillus subtilis* bacterium, a Gram-positive soil microbe which exhibits known antimicrobial mechanisms. The study demonstrated the efficacy of these probiotic material to inhibit the presence and persistence of the AMR superbug Methicillin-resistant *Staphylococcus aureus* (MRSA) and were shown to remain viable over time under normal building conditions without the need for nutrient or water supply [1]. These hybrid materials can reduce adverse selection pressures and offer potential for application across a range of building types including hospitals, homes and other public buildings. New networks of materials scientists, architects and microbiologists will be required to make this happen.
- **Probiotic materials to promote immunoregulation**. The hypothesis that probiotic materials could modulate or inform the microbiome of the built environment (MoBE) towards a condition that is directly beneficial for the human microbiome is an attractive yet currently understudied. Probiotic materials can serve as a source of a diverse range of immunoregulatory relevant microbiota for both the building and the human microbiome. Such approaches have been explored for biodiverse outdoor landscaping materials that aim to enhance the immunoregulation of children in urban daycare centres [10]. Similar material strategies for the indoor condition will require new collaborations between immunologists, material scientists, architects and engineers. These might inform new planning policies to promote microbial diversity in buildings in dense urban areas where the surrounding environmental microbiome is likely to be low.

Advances in Science and Technology to Meet Challenges
A series of key advances are needed moving forward:

- **Probiotic Mechanistic Interactions**. Research focus into the mechanistic interactions between probiotic microbes and pathogens that influence competition outcomes will be important in the coming years. This will require the development of Metabolic and Gene Expression Models and will require longitudinal competition studies using multi-omics methodologies to generate gene expression and metabolite data. Advances in this knowledge may then permit the possibility to genetically modify specific probiotic strains, to engineer traits to improve their persistence and competitive activity on specific materials.
- **Microbiome**. To engineer probiotic materials that can provide human health benefits through their impact on the human microbiome, scientific advances are needed to better understand exactly what constitutes a healthy microbe, a healthy human microbiome or indeed what a healthy indoor microbiome might constitute. A research focus on real-world intervention trials will be required to identify and determine the effectiveness of probiotic materials in buildings. These will need to take into account many of the complexities relating to different populations, geographical regions and building uses etc.
- **Understanding data**. The field of the MoBE has been informed through the sciences and technologies of metagenomics, and to date, its characterisation has been led through the field

of the building sciences. While further advancements relating to the sciences of the microbiome are required to address the challenges described above, the clear role that architectural design plays in shaping the indoor microbiome, highlights the need for interdisciplinary knowledge and workflows that can span the fields of science and design. Key to this is the development of computational technologies and software's that will enable architects and designers to understand and engage with the complex data sets that emerge from metagenomic studies and use them as a tool to inform, test and iterate design strategies.

- **Broader challenges**. Finally, the further development of probiotic materials also faces broader cultural and societal challenges related to people's perception of such materials. Their use in hospitals may be particularly controversial and would require significant shifts in existing cleaning practices to avoid inhibiting probiotic agency. There is also likely to be challenges in relation to regulatory oversight for how to govern probiotic microorganisms in building materials. Their long-term use is likely to result in other unknowns or knock-on effects which will need to be monitored.

Concluding Remarks

Architectural probiotic materials offer a new line of investigation for designing healthy buildings which can radically transform how we engineer building materials, construct buildings and maintain our built environments in relation to microbes (see also **Section 20**). Although the field is relatively new and studies in practice are limited, the potential for applying probiotic materials in hospitals, and other buildings such as homes, schools and workplaces in which people spend most of their day is fascinating, necessary, but at least a decade away.

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20 – Towards living architectures

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Status

Living architecture operates at the intersection of life and technology to offer a vision for next-generation sustainable buildings by applying 'living technology' to the practice of the built environment (see also **Section 19**). As an emerging field, approaches are diverse and integrate living organisms, such as plants, microorganisms, and fungi, into built environments to go beyond net-zero targets which cut carbon emissions down to a small amount of residual emissions that can be absorbed and durably stored by nature and other carbon dioxide removal measures. Instead, it aims to further enhance the potential of sustainability to regenerate our environment by for example, improving air quality, and promoting ecological resilience by drawing on the properties of life which make use of carbon in a circular, sustainable manner. Spanning all scales from architectural details to construction materials, to building services, and urban systems, the animate character of 'living' architecture confers our homes and cities with life-like properties to achieve its ambitious aims. Living architecture also emphasises the careful selection of materials and innovative fabrication methods by integrating digital fabrication techniques, the use of renewable energy sources, and local materials, aiming to distribute environmental impacts rather than centralise them. The use of digital fabrication, electrically-powered robots, cutting-edge software, and using materials from locally available sources, ensures that the benefits of these innovations are distributed more evenly, reducing the strain on centralised utilities, and promoting flexibility, customisability and sustainability at a local level. The practical ambitions of 'living' materials and building services are aligned with the European Union's Green Deal (2050 targets), the EU Mision for Climate-Neutral and Smart Cities (2030 targets), and the New European Bauhaus, a creative and interdisciplinary initiative that connects the European Green Deal to our living spaces and experiences. Since these emerging solutions are animate, they demand ethical consideration, inviting our care and consideration to ensure the innovations continue to generate life-promoting impacts throughout their implementation.

Figure 20.1 | Future Venice. Rendering by Christian Kerrigan, concept by Rachel Armstrong, 2009. Conceptual illustration: Here, buildings along the Venetian waterways have been fortified by applications of an animate, protocell-mediated mineralization process that also potentiates biomineralization in the native lagoon ecosystem. Collectively, the organisms and protocell technology form a protective reef-like structure around foundations, reinforcing damaged brickwork, and sealing woodpiles to prevent rotting, providing a sustainable solution for Venice's challenges with rising waters.

The pioneering project "Future Venice" held significant implications for the field of living architecture. Based on laboratory experiments, it proposed the growth of an artificial reef beneath Venice through a chemically mediated biomineralization process, catalysed by dynamic droplets [1]. Designed to protect the wooden piles of the city from rotting, it demonstrated that human-designed dynamic material transformations could positively impact the overall ecosystem in innovative ways to address the environmental challenges associated with construction, maintenance, and the end-of-life phases of buildings. Although the 'living technology' was at the earliest stage of commercial readiness, it pioneered the concept that an animate platform could uniquely counter the negative environmental impacts of the building industry that globally accounts for 40% of total carbon emissions. **Figure 20.1** shows a computer rendering of the concept.

Current and Future Challenges

Living architecture's visionary approach paves the way for next-generation sustainable solutions in reducing the environmental footprint of buildings, while incorporating the advantages of digital systems, to reduce and even reverse the construction sector's current huge environmental impact. While it faces various challenges, such as scalability and regulation, pathways to overcoming these hurdles are promised through rapidly developing advances in 'living technology,' which are summarised below:

- **Embodied Energy Reduction**. The construction industry faces significant environmental impacts due to high carbon emissions from embodied energy (used to mine and manufacture building materials) and operational energy (used to run, maintain, and manage buildings). Developing sustainable materials that reduce embodied energy remains a critical challenge.
- **Operational Energy Reduction**. Reducing emissions from building operations is an even greater challenge than addressing embodied energy owing to their dependency on fossil fuels. Scaling up living technologies, such as microbial fuel cells (MFCs), to meet household energy demands is still in its early stages but can form part of a green energy ecosystem.
- **Material Innovation**. While materials like mycelium biocomposites [2, 3] biomineralized sandstone [4] and bioconcrete [5] show promise (see also **Section 19**), their widespread adoption and scalability in the construction industry remain limited. Ensuring the durability, performance, and cost-effectiveness of these materials is an ongoing challenge.
- **Energy Output Limitations**. Current MFC systems, such as the Microbial Hydroponics (Mi-Hy) project, produce low power outputs (e.g., 6.5 mW) [6,7], making them suitable only for low-powered electronic applications. Increasing the energy output and efficiency of MFCs for broader applications is a key challenge.
- **Microbial Gardening and Biofilm Engineering**. Managing and scaling microbial ecosystems for large-scale applications, such as bioreceptive surfaces [8] and probiotic panels [9], requires advanced scientific and technological breakthroughs. Balancing complex microbial interactions to maintain functional ecosystems in built environments is a significant hurdle.
- **Integration of Living Materials**. Combining heterogeneous living materials (e.g., mycelium, bacteria, and agricultural waste) to create multifunctional building components is still in the experimental phase. Ensuring these materials can dynamically respond to environmental cues (e.g., self-healing, toxin metabolization, glowing on command) [10] requires further research.
- **Unconventional Computing and Machine Learning**. Harnessing microbial intelligence (e.g., slime moulds, mycelium networks) for urban planning and sustainable design is in its infancy [11]. Integrating machine learning (see also **Section 18**) with microbial systems to solve

complex urban challenges requires significant advancements in biofilm engineering and metabolic engineering.

- **Cyber-Physical Systems (CPS)**. Developing CPS that integrate biological processes with engineered systems for real-time monitoring and control is a complex challenge. Ensuring the reliability, scalability, and safety of these hybrid systems in real-world applications remains a critical area of research.

Advances in Science and Technology to Meet Challenges

Advances in science and technology are driving transformative solutions to meet the challenges of sustainable construction and urban development. Innovations in living architecture are leveraging the unique properties of microorganisms and biological processes to create materials and systems that reduce environmental impact and enhance functionality. Some of the most important advances are listed below:

- **Mycelium Biocomposites**: SMEs like Ecovative, MOGU, and Grown.bio are producing mycelium-based materials for packaging, insulation, soundproofing, and interior design [3], offering sustainable alternatives to traditional materials. These materials can exhibit excellent thermal and acoustic insulating properties.
- **Biomineralization and Bioconcrete**: Microbes like *Sporosarcina pasteurii* are used to create sandstone analogue materials and bioconcrete, reducing embodied carbon emissions in brick and concrete production [4]. Bioconcrete self-heals microfractures through biomineralization, extending its lifespan [5].
- **Microbial Fuel Cells (MFCs)**: MFCs, such as PeePower® urinals, convert urine into electricity, clean water, and biomass, providing sustainable energy solutions in refugee camps, schools, and festivals [6]. Projects like Mi-Hy integrate MFCs with hydroponics and biosynthesis to turn household liquid waste into energy and biomolecules [7].
- **Bioreceptive Surfaces and Probiotic Panels**: Bioreceptive surfaces enable complex microbial interactions, creating balanced ecosystems that benefit urban environments [8]. Probiotic panels colonized by *Bacillus subtilis* bacteria are being prototyped to combat antibiotic-resistant strains in homes and hospitals (see also **Section 19**) [9].
- **Living Material Combinations**: Companies like BioMason and Ecovative are collaborating to grow new materials from agricultural waste, mushrooms, bacteria, and sand, enabling multifunctional building components [10]. Some of the materials that retain their living properties when they are not 'cured,' can dynamically respond to environmental cues, such as self-healing, toxin metabolization, and even glowing on command.
- **Unconventional Computing**: Microbial systems, such as slime moulds and mycelium networks, are being used as unconventional computers to solve urban planning challenges, such as optimizing blue-green path systems [11]. Advances in biofilm engineering and machine learning are enabling the integration of microbial intelligence with neural networks for sustainable design (see also **Section 18**).
- **Cyber-Physical Systems (CPS)**: CPS are being developed to integrate biological processes with engineered systems, enabling real-time monitoring and control of bioreactors and biohybrid robots. These systems have potential applications in healthcare, agriculture, environmental monitoring, and addressing grand challenges across various domains.
- **Emergent Material Behaviours**: Research into the computational abilities of animate materials is unlocking new possibilities for smart construction materials that respond to

environmental changes such as bioconcrete's biomineralizing bacterial spores that heal microcracks in the structure.

- **Empathetic Design and Green Digital Revolution**: Software that transforms microbial data into relatable animations fosters empathetic connections between homeowners and living technologies, encouraging sustainable practices [7] (**Figure 20.2**). This approach lays the foundation for a bioremediating Green Digital Revolution.

Figure 20.2 | Living Architecture with Augmented Reality microbial animations. Courtesy of the Active Living Infrastructure: Controlled Environment (ALICE) demonstrator, 2020. Here, the Living Architecture series of bioreactors: photobioreactor with algae, microbial fuel cells with anaerobic biofilms and a synthetic bioreactor with modified organisms are generating a circular system of metabolic exchange that transforms household grey water into valorised substances that can be re-used within the home: bioelectricity, cleaned water, nutrient-rich biomass, and high-value biomolecules. The bioelectricity generated by the platform directly correlates with the metabolisms of the biofilm activity, giving an overall reading of the health and performance of the platform, where action spikes can be considered as 'data' that is then transformed by software to generate readable animations. The augmented reality image poetically shows the animate nature of the system generated by microbes via its real time metabolic activity.

Concluding Remarks

There is still some way to go before 'living architecture' solutions can be integrated in a single 'living' house or building within the next 10 to 20 years. Around 2035, we may start to see more 'living' features incorporated into new construction projects, such as green roofs, bioreactors for wastewater treatment, and bio-based building materials. By 2040 or beyond, the vision of coming home to a fully integrated 'living' residence equipped with digital interfaces for personalized comfort and sustainability could become a reality for many households. Advances in artificial intelligence, sensor technology, and smart building systems will play a crucial role in realizing this vision, enhancing the design, functionality and efficiency of 'living' spaces. By 2070, we will come home to a 'living' residence of our own that will greet us through digital signals, to make sure that our living space is *just the way we like it*.

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