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# Materials Inspired by Living Functions

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**Engineering or mimicking living materials found in nature has the potential to transform the use of materials. Unlike classic synthetic materials which are typically optimized for static properties, economics, and recently also for sustainability, materials of life are dynamic, feedback-controlled, evolving, and adaptive. Although synthetic materials do not typically exhibit such complicated functionalities, researchers are increasingly challenging this viewpoint and expanding material concepts toward dynamic systems inspired by selected life-like functions. Herein, it is suggested that such materials can be approached from two perspectives: through engineering of biological organisms and their functions to provide the basis for new materials, or by producing synthetic materials with selected rudimentary life-inspired functions. Current advances are discussed from the perspectives of (i) new material features based on built-in memory and associative learning, (ii) emergent structures and self-regulated designs using non-equilibrium systems, and (iii) interfacing living and non-living systems in the form of cellular community control and growth to open new routes for material fabrication. Strategies combining (i)–(iii) provide materials with increasingly life-inspired responses and potential for applications in interactive autonomous devices, helping to realize next-generation sensors, autonomous and interactive soft robots, and external control over the bioproduction of self-organizing structural materials.**

## 1. Introduction

Over the recent years, increasingly advanced functionalities of soft matter have been in the focal point toward pursuing new material applications. Therein, stimulus-responsive and shape memory materials have attracted major efforts to allow materials properties that can be changed on demand by the imposed stimuli, such as temperature, pH, electric and magnetic fields, and mechanical stimulus.[1,2] Classically, such materials are in equilibrium or kinetically trapped states under the different exposed stimuli. Even if such materials have turned useful in a wealth of applications, in some cases the required stimuli can be unduly large because of large potential barriers between the states, for example when using electric or magnetic fields. Also, they are typically still limited to a fixed number of states, and thus show no evolution toward new properties. By contrast, it has been recently pointed out that driving systems dissipatively out of equilibrium by stimuli, the potential barriers between the different states can be crossed more easily.[3] This could promote dynamic properties, however, another challenge is to maintain and select the desired states, i.e., not to end to unwanted states. One suggestion is to incorporate also feedback loops, as in biological homeostatic systems.[4] On the other hand, bio-inspired materials have already amply been pursued, for example, for promoting mechanical properties to combine strength and toughness, superhydrophobicity, structural colors, and adhesion.[5–9] Also such bio-inspired materials

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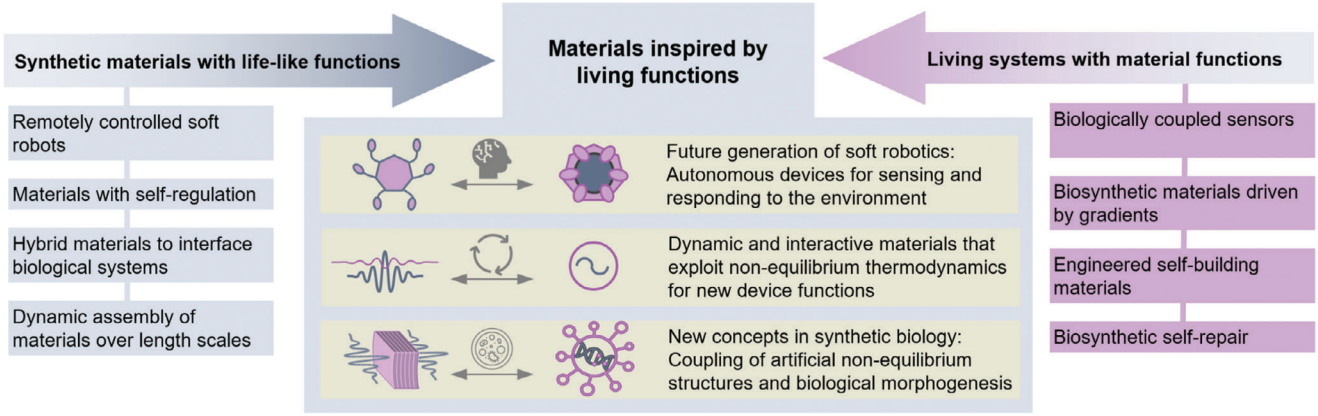


**Figure 1.** General concepts in approaching life-inspired materials from synthetic and biological perspectives. Key life-inspired functions that can (or could) be implemented in future materials.

have typically been in global or local equilibrium, and do not involve dynamism, adaptation, or evolution. Beyond them, biological systems could inspire a rich new platform of materials functions.

Combining the above considerations suggests that future development requires moving beyond the state-of-the-art stimulus responsive, shape memory, and bio-inspired materials toward dissipative dynamic, adapting, and evolving materials. Living systems are characteristically out-of-equilibrium, showing a rich palette of interesting functions involving utmost complexity: learning, homeostasis, evolution, different forms of adaptation, signaling, life cycles, and buildup of generations,[10] which cannot be fully engineered in synthetic materials. Still, the postulate herein is that some of the living functions could inspire the development of synthetic materials toward new engineered responses that could formally, i.e., "algorithmically" resemble those in the biological systems. In that way, such systems could utilize a wide selection of materials, responses, and stimuli, depending on desired functions and foreseen applications. We denote such materials "life-inspired".

Taken together, materials with life-inspired functions represent a new frontier in materials science and engineering[11] and can be broadly categorized as mimicking selected behaviors and functions of biological systems or interfaces and potentially acting together with them in concert.[12] Living organisms can also be harnessed for the production and assembly of such materials,[13] which are typically designed to incorporate selected life-like properties such as triggerable memory, sensing, self-repair, and adaptability.[14] Concretely, recent research has demonstrated that the incorporation of linked memory elements or feedback loops into synthetic materials provides a new level of dynamic functionality and performance not achieved using the traditional stimuli-responsive and shape-memory materials alone. This progress paves the way for a new class of artificial materials that are inspired by the adaptive principles of biological systems, or, from another perspective, can even incorporate increasing level of "physical intelligence", relevant for emerging autonomous devices.[15,16] The numerous implications of the quest for multifunctional and autonomous materials envision the next generation of functional materials and devices translating fundamental biological concepts into engineering design rules, e.g., in soft robotics[17,18] (**Figure 1**).

Biological systems are driven from the global or local energy minima to non-equilibrium states using chemical fuels or applied external or internal fields, and the involved processes provide the basic mechanisms for adaptability and organized structure formation. Non-equilibrium states inaccessible through standard equilibrium assembly have also been rationally approached in dissipative and life-inspired materials.[19] These underlying principles can be captured in a wide set of systems by combining magnetic and electric fields, light, chemical reactions, etc. to achieve selected life-like functions, as exemplified by the dynamic organized structures and energy dissipation observed for non-equilibrium states. The underlying idea here is that structure paves the way to function, i.e., by controlling dynamic assembly, one gains advanced life-inspired functionalities. Furthermore, dissipative mechanisms enable the generation of adaptable responsive assemblies with advanced functionalities such as controlled self-regulated feedback. Homeostasis is a key life-like function that is characterized by the use of dissipative energy to maintain a system in a non-equilibrium state, allowing for constant interaction with the environment through feedback control,[20,21] and enabling robust adaptation. Such systems are inspired by biological signaling and responses, e.g., to membrane potential in cells, where the signals are transmitted by a stimulus disturbing the homeostatic state or setting it to a new level.[22]

Living organisms can be engineered to construct materials in a technically useful way,[23,24] as exemplified by the fabrication of autonomously structured 3D materials without external control. Moreover, living systems can be materials themselves or produce a major part of their cell mass as materials (even in the absence of specific stimuli), a notable example being the construction of protective shells. The interaction dynamics between living cellular systems and their surroundings can provide concepts for material biomanufacturing, as exemplified by the on-demand activation of dormant microbes for self-repair processes. Recent examples include control over the interaction between material surfaces to direct growth, organize populations, and activate functions in organisms.[25,26] More broadly, this approach

aims to build interfacing systems applicable to cellular and living systems.

Living organisms producing materials that are useful to humans (e.g., polyesters, protein-based structures such as silk,[27] and polymeric carbohydrate structures such as cellulose) can be genetically engineered to do this more efficiently. However, researchers currently aim to determine how to produce components such as silk or carbohydrates so that they are purposefully and functionally deposited in the desired settings by engineered microbes. A further foreseen development is the use of multicellularity to ensure the functional formation of shapes and structures, e.g., controlled morphogenesis exemplified by the programmed and interactive positioning of porous or dense structures within a material. In these systems the living cells become integral parts of the materials and we can describe these as living systems with material functions. Our discussion relates to the use of synthetic biology for the development of microbial cells as novel material platforms and their engineering for new functions, accounting for the often very complex natural forms and development of the cells.

This perspective suggests our viewpoint on life-inspired materials by presenting how they can (i) achieve autonomous and interactive properties, (ii) be driven to non-equilibrium states through energy input, and (iii) be produced and interfaced with biological organisms. Initially, we compare stimuli-responsive materials with multi- and algorithmically responsive systems and discuss non-equilibrium functions and mechanisms, highlighting field-driven systems and engineered biomolecular assemblies outside equilibrium. Finally, we assess the living-nonliving interface phenomena and the biological production of materials. Molecular computing, e.g., computing achieved using highly programmable DNA-based systems, is not covered, and readers interested in this topic are directed to recent comprehensive reviews.[28–31]

## 2. Autonomous and Interactive Materials

Next-generation autonomous soft robots capable of functioning without electrical wiring or pneumatic tubing require advanced materials that can perform complex and dynamic functions without external control. Such materials are envisioned to dynamically interact with the environment, collect information from multiple environmental cues, and autonomously act in response to the information received. These features are usually associated with living organisms and their unique ability to self-regulate their actions, heal upon injury, and learn from past experiences. The quest to bridge the gap between synthetic materials and living systems has brought about a paradigm shift toward autonomous, interactive materials and physical or embodied intelligence, raising several thought-provoking questions related to the ability of synthetic materials to show responses inspired by rudimentary forms of learning and evolve, make simple decisions, or communicate and collaborate without human intervention or computer programming. Herein, we discuss some key concepts central to autonomous and interactive materials, providing critical insights into how responsiveness to multiple stimuli and memory can endow material systems with response plasticity, ability to mimic simple forms of learning, and adaptivity.[32,33]

### 2.1. Stimuli Responsiveness

Stimulus responsive materials respond to changes in external conditions (temperature, light level, pH, humidity, and electric and/or magnetic fields) by changing their properties (color, dimensions, shape, mechanical, or electronic properties; **Figure 2a**). Despite their relative simplicity, such materials have numerous applications such as sensing,[34] tissue engineering,[35] and drug delivery/release.[36] For example, temperature-controlled protein-ligand binding affinity can be realized by conjugating a poly(*N*-isopropylacrylamide) polymer chain in close proximity to the binding site.[37] Specifically, aqueous solution heating induces a volumetric change in a collapsed polymer chain conformation that blocks the ligand-binding site. Stimuli-responsiveness can be extended to create more life-like functionalities using multiple orthogonal stimuli[38] (Figure 2b). Such multiresponsive materials can experience programmable structural changes in response to, e.g., light, humidity, and temperature to achieve actuators that crab, crawl, and twist.[39] The responsive states can be distinct and depend on the number of stimuli. Both single- and multiple- stimulus responsive processes can be designed to be reversible; however, they do not evolve upon subsequent stimulation. In other words, a fixed stimulus always yields the same response.

As another state-of-the-art material class, shape-memory materials,[2,40,41] rely on kinetically trapped states to change between different physical configurations in response to external stimuli. In a typical approach, the kinetically trapped states are realized by mechanical deformation under specific conditions dictated by, e.g., glass or other phase transitions, followed by shape fixation upon cooling. External stimuli can sequentially release the kinetically trapped states, restoring the system to an equilibrium state (original shape; Figure 2c). Shape-memory materials have been widely used in biomedical devices, e.g., as embolization plugs, in which case the shape-memory effect provides efficient deployment within aneurysms.[42] Stents are widely used in clinical settings, as the shape-memory effect minimizes the need for invasive surgery and enables the delivery of large devices in an initially compact state that can be preprogrammed to be activated with a certain stimulus, notable applications being expandable stents for supporting narrowed coronary arteries.[43] Shape memory materials can also provide electrode mounting.[44,45] Moving beyond traditional shape-memory materials, the two-way shape-memory effect may yield reversible bidirectional actuation.[2] However, as in the case of stimuli-responsive materials, the response is typically programmed to the material during fabrication and is always the same for a given stimulus. Transformative medical materials critically depend on the development of more advanced systems paving the way for example toward life-like implants[46] and neural iontronic interfaces.[47]

Clearly, both stimuli-responsive and shape-memory materials lack the dynamism and autonomy required for life-like functionality. To devise synthetic materials with increasing level of complexity,[16,48] one must realize responsiveness to multiple coupled stimuli. In natural systems, the sensing of multiple environmental cues and feedback controls between sensory and motor functions lead to remarkable adaptive behavior, as exemplified by the frequency-gated sensing and snap-closure function of the Venus flytrap[49] or camouflage effects used by many species, e.g.,

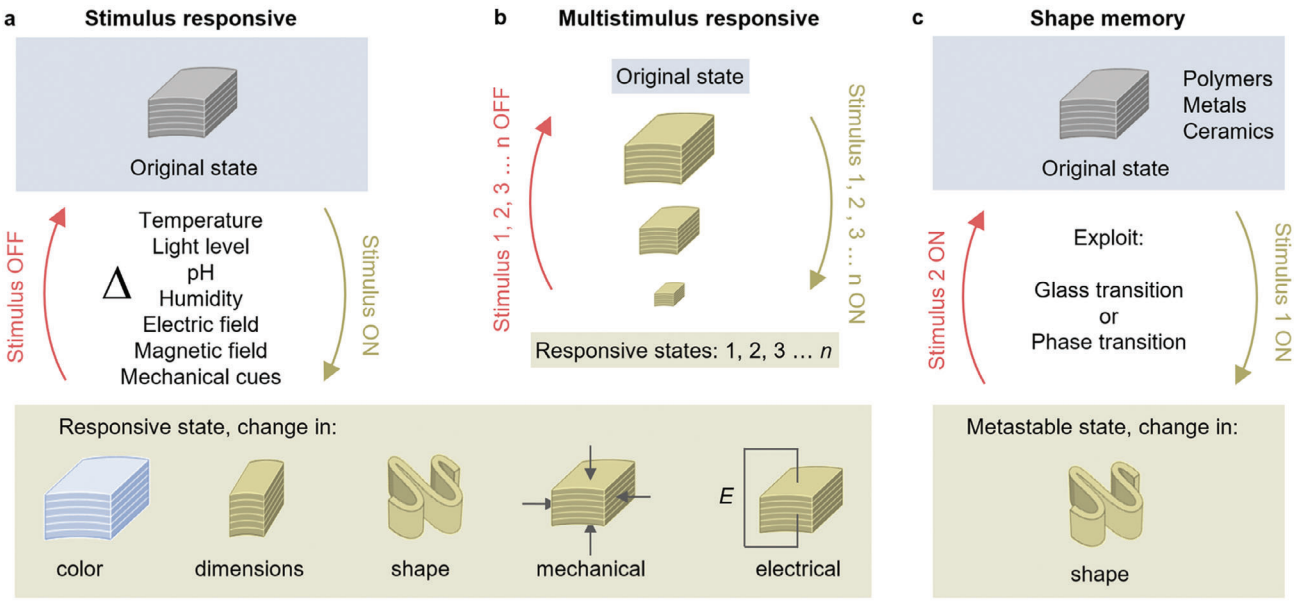


**Figure 2.** Comparison of different response types in materials. a) Stimulus responsive materials switch states in response to changes in a single stimulus such as temperature, electric field, or pH. b) Materials that respond to multiple stimuli can adopt various unique responsive states depending on the number of stimuli. c) Shape-memory materials switch to a metastable state in response to a given stimulus and revert back to their original state in response to an orthogonal stimulus.

to seek protection.[50] For synthetic materials, which are inherently highly simplistic compared to their natural counterparts, biological adaptation is beyond reach; however, multi-stimulus responses can still be designed in several ways.[12,51] In the case of coupled stimuli, the presence of one stimulus influences the response of the material to another. Such coupling enables materials with gated stimuli responses, where one (gating) signal can trigger a response to another signal[52] and thus paves the way for materials responding to different input patterns via different logic gate operations.[53,54] Another important concept enabled by responses to coupled stimuli is reconfigurability. Unlike stimuli-responsive materials, in which case fixed stimuli always yield identical responses, reconfigurable materials exploit an additional programming step that allows for distinct responses to a fixed stimulus, enabling reprogrammable shape morphing of polymeric actuators for light-driven soft robotic functions.[55–57]

Although materials with coupled stimulus responses display many advanced functionalities, those orthogonally responding to multiple stimuli may also exhibit life-inspired features unattainable in other classes of materials. Below, we outline how multiresponsive materials, when coupled to material memory, enable the simplistic mimicking of processes solely associated with the learning of living species.

### 2.2. Functions Enabled by Material Memory

To address the question of how to implement the simplest forms of learning in materials,[58] one must combine responsiveness to multiple stimuli with a memory element to preferably reversibly associate the stimuli with each other.[33,59] Although the biochemical basis for learning is tremendously complex, such built-in associative memory allows the mimicry of simplified learning processes, leading to dynamic systems that can evolve into new states and adapt. Arguably, the simplest form of associative learning is classic conditioning, in which case simultaneous exposure to two stimuli (one of which elicits a natural response, while the other yields no response) triggers a memory function that associates them, and the system learns to respond to the originally neutral stimulus (**Figure 3a**).[58] Although such behavior can be realized in biochemical network systems and utilizing electronic circuits,[60–63] examples of classically conditioned artificial materials are scarce,[64,65] one of them being the implementation of hydrogels using a photoacid-driven gold nanoparticle assembly. In this design, the system responds to heating and irradiation with light, which collectively trigger memory.[64] The irradiation of a photoacid with light triggers a pH change (neutral stimulus), which, together with a heating-induced sol-gel transition (unconditioned stimulus), leads to the formation of chain-like nanoparticle structures with a distinct optical absorbance (conditioned gel). Light irradiation alone is a neutral stimulus and does not lead to a sol-gel transition; however, the conditioned gel can respond by melting. Thus, this process resembles the associative learning and memory functions observed in biological systems. Importantly, the system can also "forget". As the above learning is related to the photoinduced pH reduction mediated by photoacids and the aggregation of plasmonic nanoparticles, forgetting can be implemented by programming a competitive pH increase to oppose the slow chemical reactions of enzymes.

Apart from classical conditioning, sensitization and habituation[58] are also elementary forms of learning, and the natural next step is to extend the material memory concept to these processes, which rely on multiple repetitions of a single stimulus to trigger memory (Figure 3b). Sensitization refers to the process in which the system's sensitivity and response to a stimulus increase in magnitude during repeated exposure,

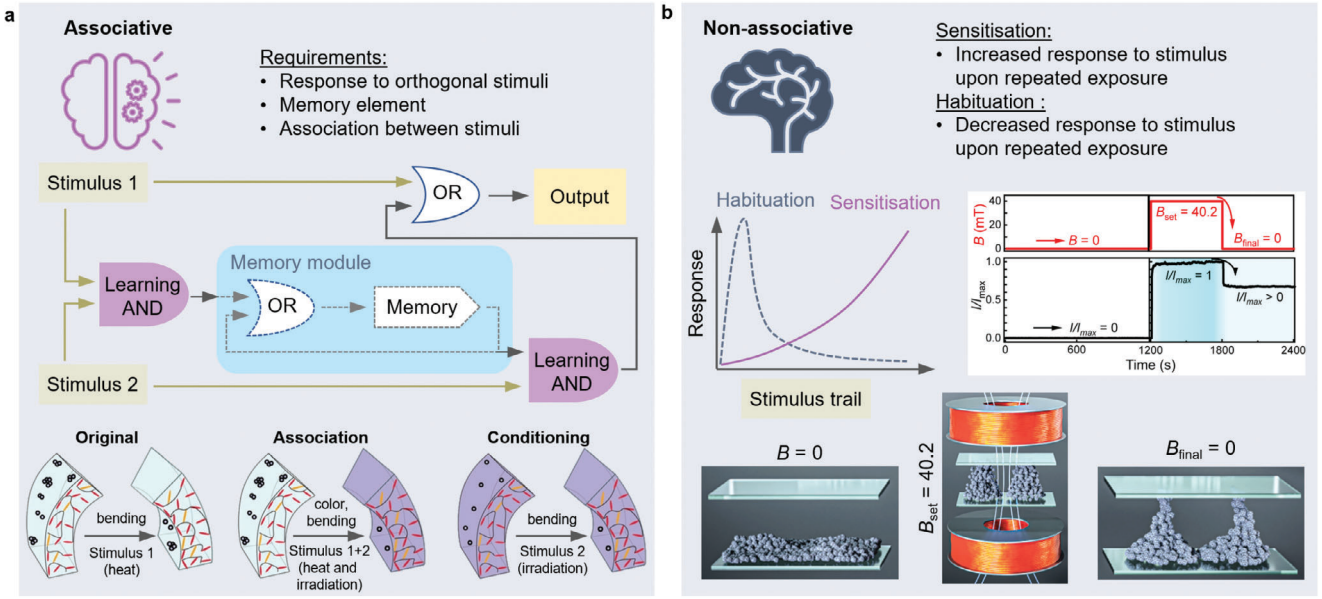


**Figure 3.** Mechanism and requirements for associative and non-associative learning in materials. a) Associative learning requires multiresponsiveness, a memory element, and association between stimuli. Figure adapted from refs. [64] and [65]. b) Promoted or depressed responses can be achieved by sensitization or habituation upon repeated stimulus in nonassociative learning or using bistable memories exemplified by electrically conducting soft ferromagnetic particle assemblies/disassemblies, which also can show plasticity in stimulus pulsing. Figure adapted and reprinted from ref. [66].

whereas habituation occurs when the responsiveness to a repeated stimulus decreases over time. Such plasticity has recently been achieved in magnetoresponsive clusters of colloidal nickel particles assembled into deformable micropillars between two electrodes.[66] The conduction between the electrodes can be controlled by the increase, decrease, and dynamics of the magnetic field and therefore exhibits hysteresis. Importantly, a constant field results in a static response, whereas pulsation enables frequency-dependent conductivity control. Consequently, this system is inspired by sensitization/habituation and mimics algorithmically synaptic plasticity in stimulus pulsation.

The above examples are still fundamentally different from living systems, as the latter function in non-equilibrium dissipative states, continuously consuming (chemical) energy to reduce the potential barriers between the different states, i.e., include more dynamism. Nature's dissipative systems are feedback-controlled, and the resulting homeostatic states are vital for essentially all functions of living organisms and present an inspiring avenue to pursue future research.

## 3. Non-Equilibrium Functions & Mechanisms

Given that structures and functions are interrelated, the ability to create structures inspired by those present in living systems can be considered a general approach to life-like functions in synthetic materials. In biological systems, these structures are based on non-equilibrium states achieved using chemical fuels such as ATP,[67] which has inspired the creation of non-equilibrium structures in synthetic materials with the help of other chemical fuels.[68,69] Although this approach requires the design of chemical reaction pathways that can rapidly become complex,[70] there is no fundamental reason why it will not eventually lead to the development of materials with functionalities and capabilities similar to those produced by nature or even beyond. For example, synthetic hydrogel-type polymer materials have been demonstrated for programmable complex multistep processes and transient characteristics rising from non-equilibrium conditions due to coupling in chemical reaction networks.[71] Life-like synthetic materials can of course rely also on other energy inputs, such as external fields and a variety of chemical reactions. For the latter, biomolecular condensates provide a promising platform for realizing the required non-equilibrium structures and functionalities.

### 3.1. Field-Driven Systems

An approach to the formation of non-equilibrium structures is the input of energy using external fields (**Figure 4**a). For example, structure formation can occur even in simple fluids subjected to external fields.[72] Unlike for chemical-fuel-driven systems, molecular-level details and interactions are not important for field-driven systems, and matter can be considered a continuum. This implies that molecular-level details are often decoupled from the length scales and symmetries of the resulting structures. Perhaps the most well-known example is the convective cells arising in a horizontal liquid film heated from below (Rayleigh-Benard convection) and controlled using a temperature gradient. Analogous effects occur in fluids under shear fields (i.e., Taylor vortices).[72]

In the context of materials science, fields other than temperature and fluid shear are likely to be more useful for driving the formation of non-equilibrium structures. In particular, electric fields are promising because of the simplicity of their generation, as demonstrated by electronic devices. In addition, electrically powered devices are increasingly routinely used to interface and

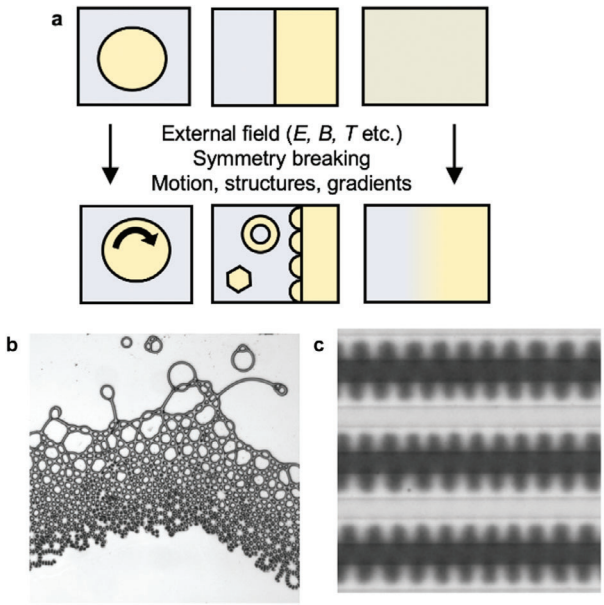


**Figure 4.** Out-of-equilibrium functionalities driven by electric fields. a) Examples of symmetry breaking under external fields leading to the emergence of motion, structures, and material gradients.[74] b) Microscopy image of the formation of diverse electrohydrodynamically driven structures in a two-fluid system. Figure adapted and reprinted from ref. [75] c) Microscopy image of nanoparticle gradients in a liquid driven by electrophoresis and further sculpted by a magnetic field. Figure adapted and reprinted from ref. [78].

manipulate living systems.[73] Recently, electric fields have been shown to drive life-like functions at various length scales. For example, behaviors analogous to biological microswimmers (including collective states) were achieved in electrohydrodynamically driven colloidal systems.[74] Advanced responses can be realized using two immiscible fluids instead of colloidal particles, allowing the dynamic generation of rolling droplets and a plethora of other non-equilibrium structures such as filaments, lattices, and polygonal droplets (Figure 4b).[75]

In another example, behavior analogous to biomolecular gradients inside living cells[76,77] was achieved via the electrophoretic driving of nanoparticles in a liquid to non-equilibrium gradients (Figure 4c).[78] In the case of magnetic nanoparticles, this allows for voltage control over magnetic responses, as responsivity is colloid-concentration-controlled. Generalization to other functionalities is expected, as magnetic nanoparticles can be replaced by other species with different material properties.

The above examples suggest that electric fields are useful for driving non-equilibrium structure formation for life-inspired functionalities at large length scales, from biomolecular gradients to the collective motion of living species. Progress relies on the identification and creative application of suitable electrokinetic phenomena[79] to suitable systems, potentially using multiple mechanisms simultaneously.

### 3.2. Self-Regulated Feedback-Control

Homeostasis is characterized by dissipative energy feedback to remain in a desired nonequilibrium state. This allows a constant interaction with the environment by feedback control and enables robust adaptation. In biological systems the dynamic states are controlled typically using several feedback loops, involving negative and positive feedbacks, which characteristically lead to biochemical oscillators.[20] Homeostatic autonomous synthetic materials are still relatively scarce, however, drawing inspiration from biological systems has provided new engineering designs. An early example deals with surfaces where bendable pillars are connected with stimuli-responsive gel.[80] The pillar ends are equipped with catalyst which activate chemical reactions selectively on chemical layers depending on the extent of bending, thus leading to feedback-controlled oscillations of pillar bending and reactions. Another example deals thermoresponsive poly(*N*-isopropylacrylamide) hydrogel connected with another hydrogel containing plasmonic gold nanoparticles.[81] A light beam is directed through the first gel via a mirror to the second gel, leading to its photothermal heating. This heats the first gel, which becomes opaque due to the phase transition, thus blocking the incident light. As a result, the gel cools and becomes transparent again and the oscillatory cycle starts again. The oscillation is robust against disturbances, thus warranting to be denoted as homeostatic. The temperature dynamics can be harnessed to drive the shape morphing of liquid crystal elastomer actuations, inspired by biological signal transduction. These examples encourage to identify mechanisms for different novel feedback loops.

### 3.3. Biomolecular Non-Equilibrium Assemblies

Liquid-liquid phase separation (LLPS) in biological systems, i.e., the spontaneous separation of biomolecular solutions into liquid regions differing in composition, allows the control of local composition, compartmentalisation, and inward and outward molecular flows,[82] thus holding great promise as a platform for designing materials with life-like functions.[83–87] In a biomolecular context, LLPS corresponds to the formation of condensate droplets. Condensates are membraneless assemblies enriched in biomolecules of interest, often proteins or nucleic acids.

In contrast to equilibrium conditions, under which condensate droplets tend to grow (Ostwald ripening), those found in cells and biological processes allow condensates to maintain their size, differentiate into anisotropic structures, and divide. These properties also give rise to materials with life-like functions, as exemplified b***y*** the assembly of supramolecular structures with tuneable lifetimes[88] *or* feedback loops in properties as well as assembly control.[19,20] The key to this is the ongoing non-equilibrium processes in condensates.[89] For example, reactions or molecular flows with differing forward and backward rates lead to temporally evolving compositions and instabilities associated with structural differentiation and splitting[89] (**Figure 5**). Thus, by controlling the involved non-equilibrium processes, one can achieve, e.g., loading and release functions, active responsive assembly, and the reorganization of emergent structures[82,88,90] – all material functionalities known from biological and living systems but currently largely unavailable in synthetic materials.

The major question is how to achieve a sufficient command of non-equilibrium responses to gain these functionalities. Condensate growth control is driven by, e.g., chemical reactions.[82,91]

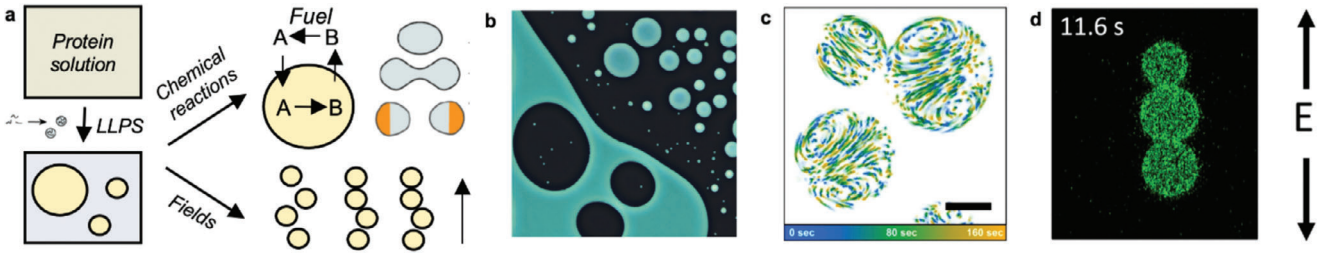


**Figure 5.** Biomolecular condensates driven out of equilibrium. a) Simplified concept of biomolecular condensate droplet formation via liquid-liquid phase separation (LLPS) and the driving of droplets to controlled growth, splitting, compositional polarization, and assembly organization. b) Biomolecular condensate droplets formed by a spidroin-like protein. Microscopy image by Teemu Välisalmi.[101] c) Experimental realization of molecular flows in condensates by enzyme-driven chemical reactions resulting in pH fields that drive surface tension gradients and flows. Figure adapted and reprinted from ref. [93]. d) Example of external electric field–driven structure formation in condensate systems. Reprinted (adapted) with permission from *J. Am. Chem. Soc.* 2021, 143, 17, 6434–6446, Copyright 2021 American Chemical Society.[102]

Biochemical processes such as phosphorylation[92] provide an in vivo option for controlling condensation. Internal fields such as enzymatically driven chemical reactions that drive pH fields driving surface tension gradients and flows can be used to propel droplets,[93] with yet another handle provided by temperature.[94] The interfacial tension between the condensate droplets and the surrounding liquid phase as well as that between the compartments in condensates lead to capillary forces capable of influencing the surrounding environment.[95] The internal structure and its control have interesting prospects for condensate assembly programming.[96] Condensate formation and assembly structure control are often considered in terms of sticker-like adhesion sites between molecular components separated by spacer domains.[96] This sticker–spacer framework provides a conceptual view for understanding how, e.g., assembly conditions and compositions[97,98] or biomolecular architecture such as length[99] control the condensate structure. As a result, complex internal structures such as bicontinuous networks may arise.[99–101] The manipulation of droplets by electric fields[102] or light[103,104] offers interesting options in terms of remote control. Kinetics offers yet another handle on life-like functionalities; for example, the dynamic arrest of condensate formation allows for structural control and multiscale compartmentalization in condensate droplets.[105,106] Examples of condensate control via non-equilibrium processes are provided in Figure 5.

## 4. Hybrid Living Materials

Given the abundance of materials with technologically relevant properties (wood, nacre, leather, etc.) produced by living organisms, the idea that even relatively complex materials can be produced in bioreactors using engineered cells has drawn much recent attention.[107] In such a living material production, engineered cells can spatially and temporally deposit and produce the required components (**Figure 6**). A further step is to maintain at least some part of the cells alive or in a dormant state during the use of these materials, which opens routes for establishing life-like functions such as repair and adaptability during subsequent use.[108] A widely explored example of living production is the formation of cellulose by bacteria such as members of the

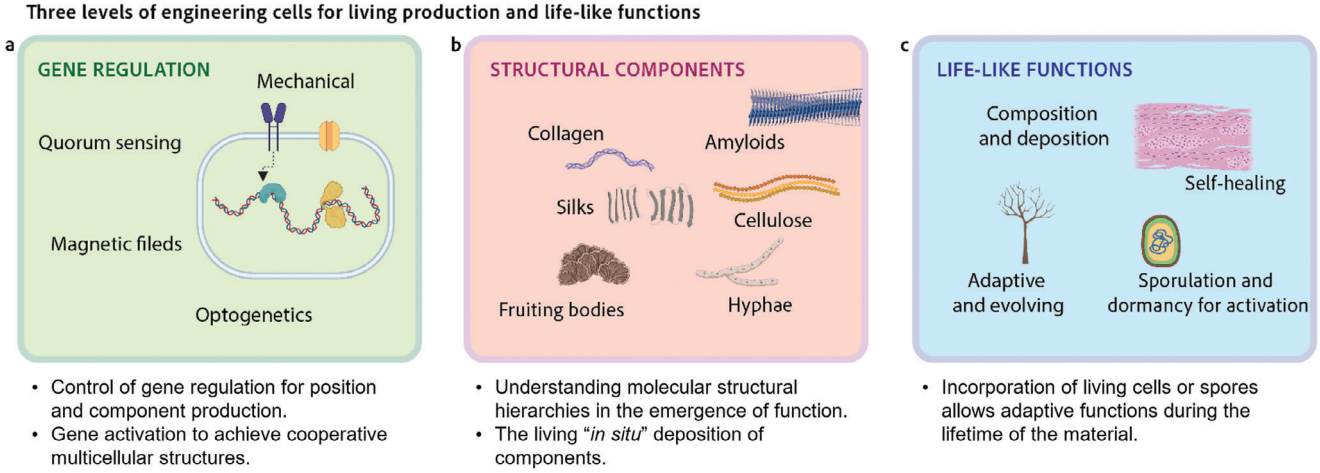


**Figure 6.** Living–non-living interactions. The use of living cells to produce materials involves the production and placement of components in time and space. The control of cells and their communities opens new routes for material fabrication. a) Mechanoregulation, chemical signals, magnetic fields, or light can be used to control component production. b) The use of structural elements requires an understanding of molecular assembly and the emergence of material properties from their interplay. c) The incorporation of living cells or dormant states into materials allows for adaptive functions such as localized strengthening or repair. Created with BioRender.com.

genus *Komagataeibacter*,[109] in which case cellulose mats were deposited at the air-water interface as viscoelastic gels. However, ways to form specific shapes and produce other material components that function together with cellulose (e.g., composites) are needed.[110,111]

### 4.1. In Situ Production and Deposition

A pioneering example is the tough mineralized structures prepared by combining cultures of polyglutamic acid-producing bacteria and bacterially produced cellulose by sequential deposition.[112] In such materials, cellulose acts as a reinforcement for mineralized components. For a more programmable approach, it is desirable to engineer the behavior of organisms that function together with cellulose-producing organisms. Components are not added sequentially, but are grown in an integrative manner. One approach is to take inspiration from a natural system in which cellulose-producing bacteria live in symbiosis with yeasts, the so-called symbiotic culture of bacteria and yeast (SCOBY).[113] By engineering yeast strains, researchers prepared synthetic SCOBYs in which functional components were produced by the yeast within the cellulose matrix.[114] However, this promising approach is hampered by the lack of control over the amounts and placement of components in relation to each other. New solutions are likely to originate from synthetic biology, where the co-dependence of different engineered species is a much-explored topic for combined cultivations.[115–117] In addition, a single organism can be tailored to produce the desired material components in a controlled manner. Here, one can apply similar synthetic biology circuitries designed for the regulated expression of monomers to build co-polymers inside cells[118] (Figure 6a). Living cells produce classes of materials that are typically obtained from fossil resources, such as polyesters and polyamides, and can also produce various monomers that can be polymerized into homo- and co-polymers.[119,120] Filamentous fungi have been widely studied as alternatives to living scaffolds for materials. A promising form is fungal leather, namely a leather-like material obtained by processing mycelial mats of filamentous fungi and having properties similar to those of animal skin.[121] Another example corresponds to amyloid proteins, which are promising building blocks for various materials and are found in bacterial biofilms, which have inspired the production of biofilm-based living materials.[26]

Proteins, especially those with advanced functions, are the key components of biomaterials, with widely studied examples including silk, collagen, and adhesive proteins from marine organisms[27,122] (Figure 6b). Proteins can form biocomposite structures or function as materials without other components. Large strides have been made toward using structurally engineered versions of fiber materials together with other elements in composites. In the future, textiles and structural materials made of engineered proteins may play a significant role in sustainable manufacturing. In particular, the construction of newly engineered proteins and their tailoring to particular tasks is a powerful approach. One advantage of engineered versions is that they can be optimized for compatibility with industrially feasible production hosts and processes.[123] As an example of the versatility of proteins, we can make a comparison with supramolecular chemistry, in which click reactions have been very helpful for engineered macromolecule construction. In bioengineering, the family of SpyCatcher-tag proteins has been designed to self-catalyse click reactions.[124] In these Catcher-Tag pairs, an amide bond is formed between two complementary protein sequences, which makes covalent bond formation within materials possible through the suitable insertion of the above pairs without the need for any prior activation or use of reagents.[125] However, a clear bottleneck in the production of protein-based materials is the frequent need for intermediate harvesting and purification steps.

The application of engineered proteins to the living production of materials is highly desirable and would simplify manufacturing, as exemplified by the sequential deposition of components in nacre or the deposition of collagen in leather. The switch from using purified proteins as components to using in situ production with component deposition at the required location and sufficiently high concentrations poses many challenges. The functional deposition and release of protein components by protein secretion result in levels much lower than those needed in materials.[114] Here, we need to carefully consider the differences between animal cells that naturally produce the materials we aim to mimic and the microbes typically used in synthetic biology.[126] Bacteria are typically poor secretors of proteins and may have difficulty adapting to living materials.[127] However, alternative approaches may allow for their use. A step toward this goal was to find that silk proteins can be produced in *E. coli* at high concentrations and in a manner that leads to pre-assembly by LLPS within the cells, which might open paths for the functional deposition of materials.[128] A general path toward the use of animal cells for material production can take inspiration from the intensively studied cultured meat production using vat-grown muscle cells.[129] A possible development is to use such animal cell cultivations also for making materials — for example leather-like materials.[130] However, yeast and filamentous fungi may be more attractive because of their typically high protein secretion levels and technically feasible production.[131]

Considering technology transfer aspects, for example the artificial leather market was valued at 33.7 billion USD in 2021 and is expected to expand at a compound annual growth rate (CAGR) of 8% by 2030. Concurrently, there have been developments toward the increased production of biosynthesized bioplastics such as polyesters, with the related CAGR lying close to 12%. The smart polymer market was valued at 5.48 billion USD in 2021 and is expected to reach 19.21 billion USD by 2029, featuring a projected CAGR of 17.05%. Biomanufacturing, either through the cell-based deposition of material components or more traditional production by microbes in bioreactors, is supported by many national and EU-level strategies, the most significant being a recent US initiative "Bold goals for US biotechnology and Biomanufacturing".

### 4.2. Triggered & Feedback-Driven Production

Further life-like functions could involve morphogenesis with gradients of properties from stiff to soft and self-shaping into complex forms[132,133] (Figure 6c). In the case of plants, we increasingly acknowledge the importance of mechanical feedback for

shape forming.[134] Currently, we are in the process of understanding how the mechanical feedback and mechanical environment exert a wide effect on gene regulation, and how genes can be switched on and off in response to mechanical feedback. The direct mechanical link between gene expression and mechanical stimuli can be a mechanism that fulfils one of the basic ideas behind living materials and provides a route to mechanical adaptation, as exemplified by the mechanically induced local strengthening of structures.[104] Looking at externally controllable approaches, drivers such as electrical or magnetic fields can be used to induce shape formation in a manufacturing environment. Although such mechanisms are probably not used to shape materials in natural systems, evolution has come up with something similar for motility. Magnetotaxis is a well-known mechanism by which organisms, from microbes to birds, orient themselves in the Earth's magnetic field, and relies on the alignment of small magnetic particles.[135]

Cell activation during the material lifetime is an attractive property of living materials. This concept has already been explored for concrete containing embedded spores that were activated upon exposure to water to induce crack-sealing mineralization.[136] In a truly living system, force-sensing mechanisms can activate gene regulation for the deposition of reinforcing structures. In this way, not only self-repair, but also adaptivity to external conditions can be achieved. Optical methods provide extremely versatile and useful approaches for interfacing biology and probing biological systems. An example is the enormous impact of fluorescent proteins derived from green fluorescent proteins on bioscience.[137] Light also functions as a signal for a wide range of molecular switches and regulators in biological systems, particularly at the gene regulation level. In particular, light affects the circadian clock even in fungi, and the related mechanisms can be traced to regulatory protein complexes. Optogenetics is a well-established research field dealing with the use of external light to turn genes on and off.[138] Much pioneering work in neurobiology has been conducted using light to trigger neurons. However, the mechanisms for the light-directed control of cells involve membrane pumps and ion channels.[139] This type of time and space regulation opens possibilities for a new type of additive manufacturing using living systems.

## 5. Conclusions

Man-made artificial functional materials are profoundly different from living materials. Classic human-made materials have been pursued owing to their simplicity, durability, and cost-effective production, with sustainability becoming a major driving force only recently. In contrast, living materials can be considered dynamic multicomponent systems with feedback controls used to maintain key properties, allowing adaptation, evolution, replication, and learning toward new properties. Although such responsivities are typically slow, high efficiency is achieved through response parallelism. Future research should aim to bridge these two entirely different approaches to ultimately enable the interfacing of man-made and living matter for conceptually new functions.

Opportunities related to new functionalities such as adaptability, self-repair, and additive manufacturing are strong driving forces for the development of life-like materials. New concepts such as responding, adapting, and learning functions and their combination with mechanical changes may enable advanced materials to ultimately sense their environment, process the information received and become autonomously interactive. Such a paradigm change toward materials with embodied intelligence is expected to revolutionize the field of soft robotics, yielding functions such as "find, sense, and report." Additional functions can be learned for selective gripping and memorization, leading to new sensory interfaces. Soft robotic functions can be used, for example, in autonomous exploration to monitor parameters or manipulate materials in inaccessible environments as well as release active substances in a feedback-controlled manner.

The development of non-equilibrium systems, which can provide a wide range of emergent and complex structural states, adapt to dynamic conditions, and robustly respond using feedback control, is expected to bring further progress. As non-equilibrium systems are not limited by equilibrium energetics, dramatic changes can occur, and functions can be engineered to be highly selective and sensitive. For example, future developments may include new types of sensors that, similar to living sensors, are robust and allow a wide range of readout mechanisms. Properties such as adaptive structural coloring and magnetism can be realized in voltage-driven dissipative devices. Biological mechanisms can be linked to technically feasible fields (electric and magnetic) to create hybrid approaches for biomaterial assembly.

The pharmaceutical industry is transforming through drug delivery improvement, and the next steps will involve personalized or adaptive strategies based on the ability of delivery devices to "learn" the patients' needs and personal requirements. Homeostatic or life-like properties of materials, as described above, are essential and can provide better targeting and optimized dosage. The market for drug delivery was valued at 1500 billion USD in 2021 and is expected to grow at a CAGR of 3.7% from 2021 to 2030. Given the large size of this market and the need to develop biologicals for which delivery strategies are even more important, we expect many outcomes of life-like functions in materials to be observed here.

Materials with life-like properties have attractive functionalities, but the driving forces related to sustainability and raw material usage may be even stronger societal factors that push the development of biological manufacturing. The larger the expected overall material production volume, the more important are the independence of raw materials and production processes from fossil carbon and their generally high carbon and energy efficiency. The first wave of new bio-based materials relied on the use of plant biomass such as starch or (wood) cellulose. The latter renewed current forest-based industries and created new start-ups with sustainable packaging and textile material applications, also involving circular economy.

Living organisms invariably comprise multiple components with numerous signaling pathways and feedback loops. Therefore, they must be approached at the system level to understand how components influence each other within the whole. Living organisms offer a large variety of functionalities that can be engineered to create materials using synthetic biology. With such biomanufacturing, the use of organisms for structure formation, in situ metabolite production, and autonomous self-repair has become increasingly important. This combination is needed for

progress and will expand the concepts of materials and synthetic biology. Therefore, the increasing impact of biology on material development is a worldwide trend. The global research and technology development efforts to integrate life-inspired functions will be among the most significant in the field over the coming decade.

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## Conflict of Interest

The authors declare no conflict of interest.

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biological production, feedback loop, homeostasis, living materials, memory, non-equilibrium, stimuli-responsive

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