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Life, death, and self: Fundamental questions of primitive cognition viewed through the lens of body plasticity and synthetic organisms

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ABSTRACT

Central to the study of cognition is being able to specify the Subject that is making decisions and owning memories and preferences. However, all real cognitive agents are made of parts (such as brains made of cells). The integration of many active subunits into a coherent Self appearing at a larger scale of organization is one of the fundamental questions of evolutionary cognitive science. Typical biological model systems, whether basal or advanced, have a static anatomical structure which obscures important aspects of the mind-body relationship. Recent advances in bioengineering now make it possible to assemble, disassemble, and recombine biological structures at the cell, organ, and whole organism levels. Regenerative biology and controlled chimerism reveal that studies of cognition in intact, "standard", evolved animal bodies are just a narrow slice of a much bigger and as-yet largely unexplored reality: the incredible plasticity of dynamic morphogenesis of biological forms that house and support diverse types of cognition. The ability to produce living organisms in novel configurations makes clear that traditional concepts, such as body, organism, genetic lineage, death, and memory are not as well-defined as commonly thought, and need considerable revision to account for the possible spectrum of living entities. Here, I review fascinating examples of experimental biology illustrating that the boundaries demarcating somatic and cognitive Selves are fluid, providing an opportunity to sharpen inquiries about how evolution exploits physical forces for multi-scale cognition. Developmental (pre-neural) bioelectricity contributes a novel perspective on how the dynamic control of growth and form of the body evolved into sophisticated cognitive capabilities. Most importantly, the development of functional biobots – synthetic living machines with behavioral capacity – provides a roadmap for greatly expanding our understanding of the origin and capacities of cognition in all of its possible material implementations, especially those that emerge de novo, with no lengthy evolutionary history of matching behavioral programs to bodyplan. Viewing fundamental questions through the lens of new, constructed living forms will have diverse impacts, not only in basic evolutionary biology and cognitive science, but also in regenerative medicine of the brain and in artificial intelligence.

1. Introduction

What is it like to be a caterpillar, changing into a butterfly [1]? We have some idea of what cognitive processes are possible for caterpillars, and for butterflies, but how does a single agent move gradually between those two Umwelts? How does a mind (whether simple or complex) transition bodies in a single lifetime, which does not afford evolutionary timescales in which to hone behavioral programs to a specific kind of anatomy? What (if any) cognition is possible in the transitional states? This is important for science and philosophy of mind because such transformations are far more common than most assume; indeed, given the coming advances of regenerative medicine of the brain, and the increasing sophistication of brain-machine interfaces, you (or your children) are likely to someday find out, first hand, what it's like to undergo a significant modification of the biological substrate underlying your mind. This is the province of a newly emerging, interdisciplinary subfield at the intersections of cognitive science, regenerative biology, synthetic bioengineering, and neuroscience beyond neurons.

Traditional cognitive science operates on a living Subject: we

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study the information it absorbs, computations it performs, memories it may have or form, behaviors it can deploy in different circumstances, goals it may pursue, etc. All those capacities are taken to be the properties of a fixed, embodied Agent; the fact that it is a collection of cells or subcellular fragments, which proliferate and actively interact to build its body, is relegated to developmental biologists. That phase of a subject's life is usually ignored as behind-the-scenes setup, after which real study can begin. Even organisms that undergo metamorphosis, with drastic changes of body, brain, and behavior, are usually studied in their separate life stages as "fixed", unchanging bodies (with important exceptions [2–4]). That is convenient, and it dovetails with the mainstream paradigm in which genomes code for specific bodyplans, and with a view of evolution as shaping behavioral repertoires in tight connection with the evolution of the anatomy. But, this paradigm is importantly incomplete; it is now essential to begin to unravel the plasticity of both, bodies and minds, within continuous life histories that highlight the fact that no agent is a monadic (indivisible) mind – all are made of parts, and those parts can rearrange. What happens to cognitive agents when their bodies are modified, at various spatial and temporal scales? Fortunately, recent advances in synthetic morphology are enabling experimental approaches to understand the formation of cognitive agents de novo in a myriad novel anatomical forms. To begin to appreciate the plasticity of life, and the implications for understanding mind in all its possible guises, we begin with a short fictional vignette that amplifies the key concepts across levels of biological organization.

1.1. A thought experiment

Imagine yourself on an interplanetary expedition, investigating an aqueous world that harbors life. There are multicellular creatures, and amoeba-like ones. Eventually you learn to sequence their hereditary information, and are stunned to find out that some of the single-cell life forms have precisely the same genomes as some of the complex vertebrate-like animals, which also matches that of a set of primitive multicellular forms with diverse blob-like anatomies. How can that be? Upon further study you discover an aquatic animal with a surprising life cycle (Fig. 1). They develop from an egg and undergo embryogenesis to become a complex multicellular body. They live a full life, moving and reproducing through their ecosphere. However, upon death, something remarkable happens: as the body falls apart, many of the individual cells disband, dispersing to move out into the environment to continue their life as amoebas. You find that these amoebas can merge together (having recombined with others they encounter, like slime molds do [5]) and form a new kind of primitive multicellular aggregate. At the same time, some others activate reprogramming factors to become oocytes, eventually becoming fertilized and initiating embryogenesis of the complex anatomical form.

It occurs to you that this lifestyle exploits an interesting way to cheat death, at one level of organization (and blurs definitions of "age"). While the larger organism dies, the individual cells live on – death at the larger scale is compatible with continued life on a smaller scale. While initially surprising, you realize that there is nothing inherently impossible about such a life history. Vertebrate bodies already contain a number of amoeba-like cells (immune cells for example), and one can easily imagine an evolutionary advantage to genomes that, although capable of cooperating in a multicellular form factor, continue their lineages as unicellular organisms when the body is no longer viable as a whole. The unicellulars in Fig. 1 exploit the kind of niches in which amoebas flourish on Earth, but can also reboot their multicellularity by aggregation into novel functional, anatomical forms. Basically, this is a symmetric reversal and alternative to traditional embryogenesis [6,7], in which distinct cells move, react, and deform their microenvironment working together in progressively-tighter swarm relationship to build and re-build complex bodies. Similarly, planarian flatworms are complex organisms that reproduce by fission (or being chopped up into pieces) and subsequent regeneration, muddying comfortable notions of death, aging, and evolutionary relationships between lineages of cells, organisms, and "Individuals" [8,9].

This raises a series of fundamental questions focused around somatic plasticity, and begins to crack the typical picture of a fixed body architecture, evolving with a matching cognitive program, both inevitable functions of a specific genomic lineage. What would be the evolutionary dynamics of such a life form, in terms of cooperation, competition, and kin selection at the level of the cells and the organisms they can form [10–12]? Genetic relatedness is clearly not the whole story with respect to multicellular forms. Individual cells from very different genetic lineages can cooperate as chimeras [13], and genetically-identical cells and tissues within one body compete for information and resources [14]. Why doesn't this routinely happen to aquatic organisms on Earth? Every part of this cycle has actually been seen on Earth. In fact, a similar life cycle, including "reverse development", takes place in the jellyfish Turritopsis dohrnii and other marine hydrozoa [6,7,15], and cancer cells have been suggested to be attempting to turn into embryonic blastomeres or oocytes [16]. Why hasn't evolution found the few tweaks that would enable, for example, some of a frog's cells to move out and continue to live as unicellular forms in the pond if the frog is killed? Clearly being a single cell in a pond is a viable niche, and cancer cells are perfectly able to revert to an ancient unicellular transcriptional program [17] and live forever (with the help of a human scientist as vector) in a Petri dish or in another body [18]. If somatic cells were brought together in new environments – liberated from their host bodies – would they build something else despite their wild-type genome? And if so, what?

You realize that this is an ideal model system in which to ask questions about the identity and coherence of large-scale Selves, and how they appear and disappear at a scale distinct from that of their subunits. Continuing your experiments, you discover that enabling those cells in to assemble in various combinations and in several different microenvironments, results in functional bodies of very diverse morphology and behavior. Apparently, the cells' drive toward multicellular cooperation, when possible, enables them to build novel forms with coherent structure and function – not a single genome-default anatomy. This seems to have major implications for cognitive science and the evolutionary trajectory of advanced capacities from humble unicellular homeostatic beginnings [19,20]. Every cognitive system is made of components. In the case of artificial, robotic agents those parts might be passive, but in biology, those parts are themselves highly active, competent agents [21,22]. How do those parts merge together into a unified cognitive agent, which has behavioral repertoires, goals, memories, and preferences belonging to the collective but not to any of the individual subunits? Traditional brain science has largely worked within two assumptions. First, the body structure is considered to be fixed – determined by the genome and thus a reliable, stable machine for which to evolve appropriate control policies (behaviors). Second, individual neurons somehow work together to implement a higher-order entity that has coherent memories, beliefs, and goals. Brains are thought of as a stable, fixed structure in which the individuality of the immobile cells is gone for good (despite the known turnover rate of neurons in adult human brains, which does not seem to impede continuity of memory or Selfhood [23]). But here you have a model system in which we can see larger selves appear and disappear before our eyes; what an opportunity to understand the boot-up and dissolution of minds, and the

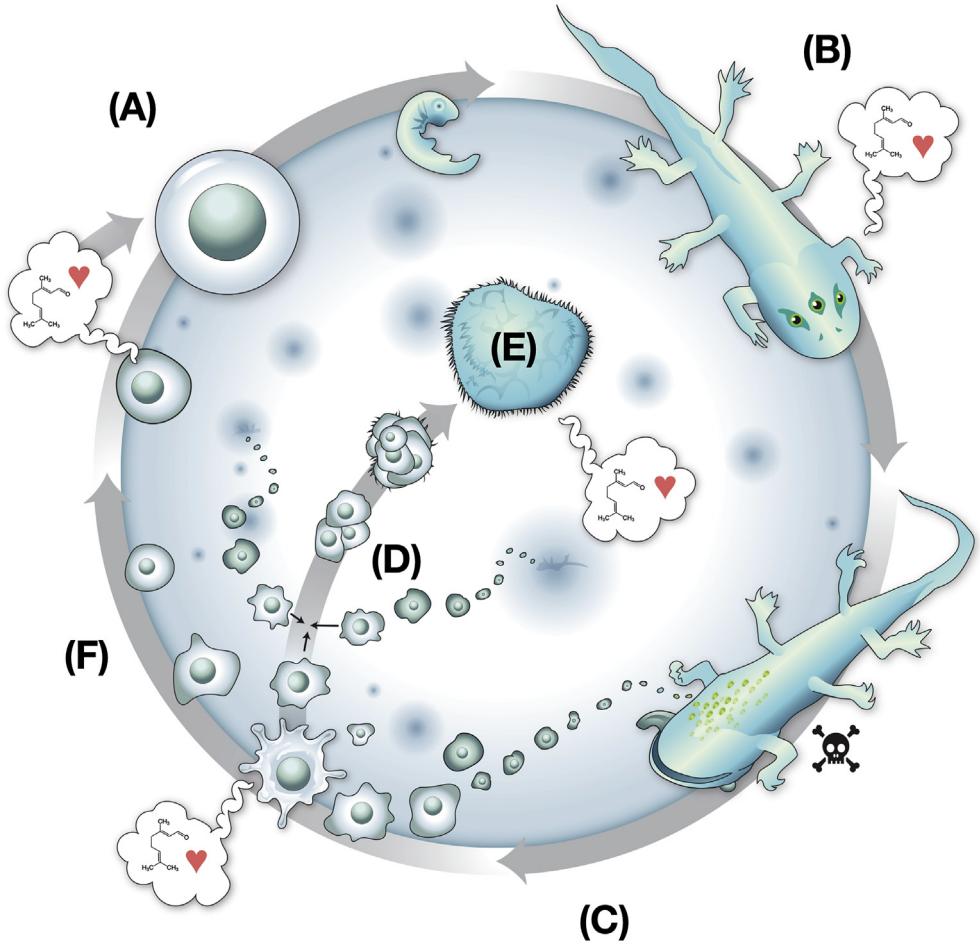

Fig. 1. A hypothetical multi-scale life cycle. This schematic represents a hypothetical creature with a life cycle that spans levels of organization. Every part of this cycle has been found on Earth. (**A**) Embryogenesis (cooperation of cellular progeny of an egg cell toward a specific anatomical structure) gives rise to a complex organism with memory (**B**). After death of the animal, some of the individual cells convert to a cancer-like unicellular mode and exit the body, existing as amoebas (**C**). Some of these can coalesce into multicellular organoids (**D**) which exist as simple multicellular forms (comprising cells possibly originating from different bodies), moving via ciliary motion (**E**). Other cells, in an iPS-like reprogramming event, become eggs and re-start embryogenesis (**F**). In each phase, memories (such as learned preference for a specific chemical – in this case, the citral molecule [102]) persist and are transferred from single cells to the behavioral program of the animal and vice versa).

relationship of minds to highly plastic bodies!

You decide to test these animals' cognitive capacities and notice that they can learn in associative and instrumental training assays. Using simple surgical transplants, and exploiting these animals Axolotl-like regenerative capacity, you then find that you can transfer their memories (e.g., association of specific colors with food) from a trained donor to a naïve host by transplanting brain tissue [24,25] or even extracts [26,27]. Likewise, you find that the individual amoebas can learn in simple assays, as has been shown for slime molds on Earth [28]. You wonder: would amoebas resulting from a trained body's death retain the information as individuals? Conversely, would an assemblage of such individually-trained amoebas result in an organism that remembered the information? Could learning be propagated between cells, and could the information transcend scales of organization – between single cells and a whole organism? Could a collective synthesize individual, simple memories of their cells into a compound, complex memory for the whole? Whose memories would they be? Should true memories of an associatively-trained animal be considered false memories in the host that inherits them via transplantation or aggregation, since that Subject has never actually experienced the association they now remember?

While this vignette sounds fanciful, every part of it is biologically plausible – not just as "life as it could be" [29] but as actual examples that have been studied here on Earth (reviewed in the next section). Crucially, this sort of scenario highlights two important things. First, that our comfortable "I know it when I see it" categories, such as "genetically-determined bodyplan", "organism", "death", and "memory" are actually quite fluid and in need of better definitions. Second, a critical aspect of studying cognition is understanding who its subject is – defining a system that is the owner of the cognitive processes. Memories, goals, preferences, cognitive abilities, etc. all have to belong to some specifiable system. Thus, understanding the mechanisms and evolutionary origin of cognition requires us to think deeply about the bodies which enable and constrain various cognitive functions, and their potential plasticity [30]. This is not simply the claim that all cognition is embodied and we should pay attention to the interaction of an agent with its environment [31–33], or the parallels between cognition in traditional embodiments (groups of cells making up an organism) and groups of animals making up a swarm [34–37]. The next level of advances in this field will be based on recognizing that the scale and definition of the biological agent, and the boundary between its own Self and its environment, are actually much more complex and malleable than has been appreciated. Living forms exhibit proto-cognitive autonomy at multiple scales, which enables

a spectrum of different minds [38] across very diverse body architectures (Figs. 2 and 3). This is as important for evolutionary, developmental, and cognitive biology as for the development of artificial intelligences [39] and regenerative medicine's efforts to control the results of cellular activity [40].

The imaginary scenario described above strains our everyday definitions of common terms, including memory, cognitive identity, evolution of body shapes, cooperation/competition, and death. Fortunately, we do not have to solve the problems of interplanetary travel to explore this new domain. An emerging technology which is already revolutionizing cognitive science is synthetic morphology [41–44]. Going beyond metabolic rewiring of individual cells, the guided self-assembly of multicellular artificial living machines is now enabling us to watch the appearance of primitive cognitive agents from scratch, and track (and edit) the memories and goals of living beings as they emerge de novo. Feynman's Rubicon – that we don't understand something until we can build it ourselves – can be crossed in the domain of cognitive science by a multi-disciplinary approach to the emerging field of biobots [45–49]. One of the fascinating things about this field is that it is, for the first time, enabling tractable experimental approaches to variants of thought experiments in the philosophy of mind (such as splitting brains/persons), which have long been used to sharpen questions about personal identity [50–52]. The remarkable thing about synthetic organisms is that they enable us to observe cognition in bodies that are created de novo for the first time on Earth, with no lengthy evolutionary back-story. What kinds of minds are immediately manifested in entirely new life forms?

I argue below that making progress on understanding cognition requires an even stronger emphasis on the biophysical and computational aspects of the structures that house and implement cognition. First, because the bodies in which cognition manifests are remarkably plastic, and the scale and boundaries between Self and world can shift during the lifetime of a biological system. As the substrate of memory and behavior changes, it's essential to understand what consequences this has for its cognitive apparatus. Second, because biological systems are fundamentally multi-scale – agent-like competency on many levels of organization is a key aspect of evolvability. The inter-penetrating, concurrent operation of numerous layers of cognition within the same living system expands this field way beyond familiar questions about the cognition of "an animal in its niche".

In the following sections, I first review some experiments that distort the familiar relationship between memories and their unambiguous owner, focusing on the cognitive implications of body/brain modification and memory transfer. I then describe biological case studies that illustrate the plasticity of bodies in which minds reside, paying attention to different scales of organization and the interplay between them. Synthesizing modern genetic, cell-biological, and evolutionary perspectives on body structure with advances in cognitive neuroscience is essential for a mature, sufficiently inclusive understanding of Mind in its many guises. I then discuss recent advances in biobots as a new model system for the future consilience of biology, cognitive science, and computer science.

1.2. Corner cases: expanding beyond our comfortable view of the subject of cognition

> "Treasure your exceptions! Keep them always uncovered and in sight. Exceptions are like the rough brickwork of a growing building which tells that there is more to come and shows where the next construction is to be."
>
> - W. Bateson

Numerous areas of bioscience proceed with an unspoken shared assumption that the genome encodes a specific body type which changes slowly (only on the evolutionary timescale), together with an associated cognitive apparatus that is tightly bound to an invariant brain and body structure. A number of cases at the boundaries between subfields reveal that the reality is much more interesting; the following are a brief survey of data (organized by the assumptions that each set of examples disrupts) revealing these assumptions to be incomplete in important ways, showing the incredible plasticity of minds and bodies beyond the mainstream examples of neuroplasticity.

Cognitive capacity is not hard-wired to a specific body architecture. It is often assumed that cognitive programs become tightly bound to the standard body of any given species, being shaped together over evolutionary time scales. Classic questions in cognitive science and philosophy of mind, such as "What is it like to be a bat?" [1] are often understood to assume that there is a discrete natural kind, for example a "bat". However, cognitive programs show incredible ability to adapt on the fly to novel body configurations. For example (Fig. 4A and B), when tadpoles are made with eyes only on their tails, they can perform very well in visual learning assays, showing that they can see Ref. [53]. These ectopic eyes connect to the spinal cord, not the brain, conferring vision – the brain has no trouble determining that this unusual tissue in the tail is providing visual data, and the information coming from the spinal cord should be processed in this way [54,55]. Thus, behavioral programs relying on vision, which evolved for millions of years to expect visual input from specific locations in the head, are immediately portable to a novel anatomical architecture that likely never existed in the biosphere before. This provides a tractable model in the broader field of "sensory substitution" and brain-sensor interfaces [56–59], research on which is limited for obvious ethical reasons in human patients. Indeed, even cultured neurons can be taught complex tasks, such as running a flight simulator [60], showing the wide range of "bodies" that can be managed by brains (dovetailing to the extensive literature on "brain in a vat" in philosophy of mind [61]).

(Basal) Cognition does not require a nervous system or brain. The realization that many organisms, including aneural ones [62], exhibit proto-cognitive functions such as memory, integrated decision-making, prediction, and ability to learn general rules from instances is very old [63,64]. The emerging field of Basal Cognition focuses on the phylogenetic origins of learning and goal-directed activity, drawing a continuum between the humble origins of information processing in the metabolic homeostatic mechanisms of ancient cells and more complex learning, representation, and goal-directed activity [65,66]. Taken together, work on behavioral capacities of non-neural systems, and recent results on the molecular genomics of pathways involved in learning and memory in brains, reveal a key insight necessary for broadening our understanding of substrates of cognition [20,67,68]. First, decision-making and scaling of integrated information processing is ancient and ubiquitous across the tree of life, spanning from bacteria [69] and bacterial biofilms [70,71] to protozoa [72] to plants [73,74] and even somatic cells of complex organisms [75]. Many aneural organisms show the ability to learn and behave adaptively in novel situations [76] (Fig. 4C–E). Second, as befits the underlying evolutionary origin of all life on Earth, the mechanisms used for cognition are highly conserved and predate multicellularity [21,77], working in similar ways in the control of morphogenetic behavior of single cells as in the control of animal behavior [40,78]. Indeed, various subsystems in animal bodies show evidence of learning and primitive cognition, including cardiac [79], bone [80], and pancreatic [81] tissues. In some cases, they are able to anticipate future

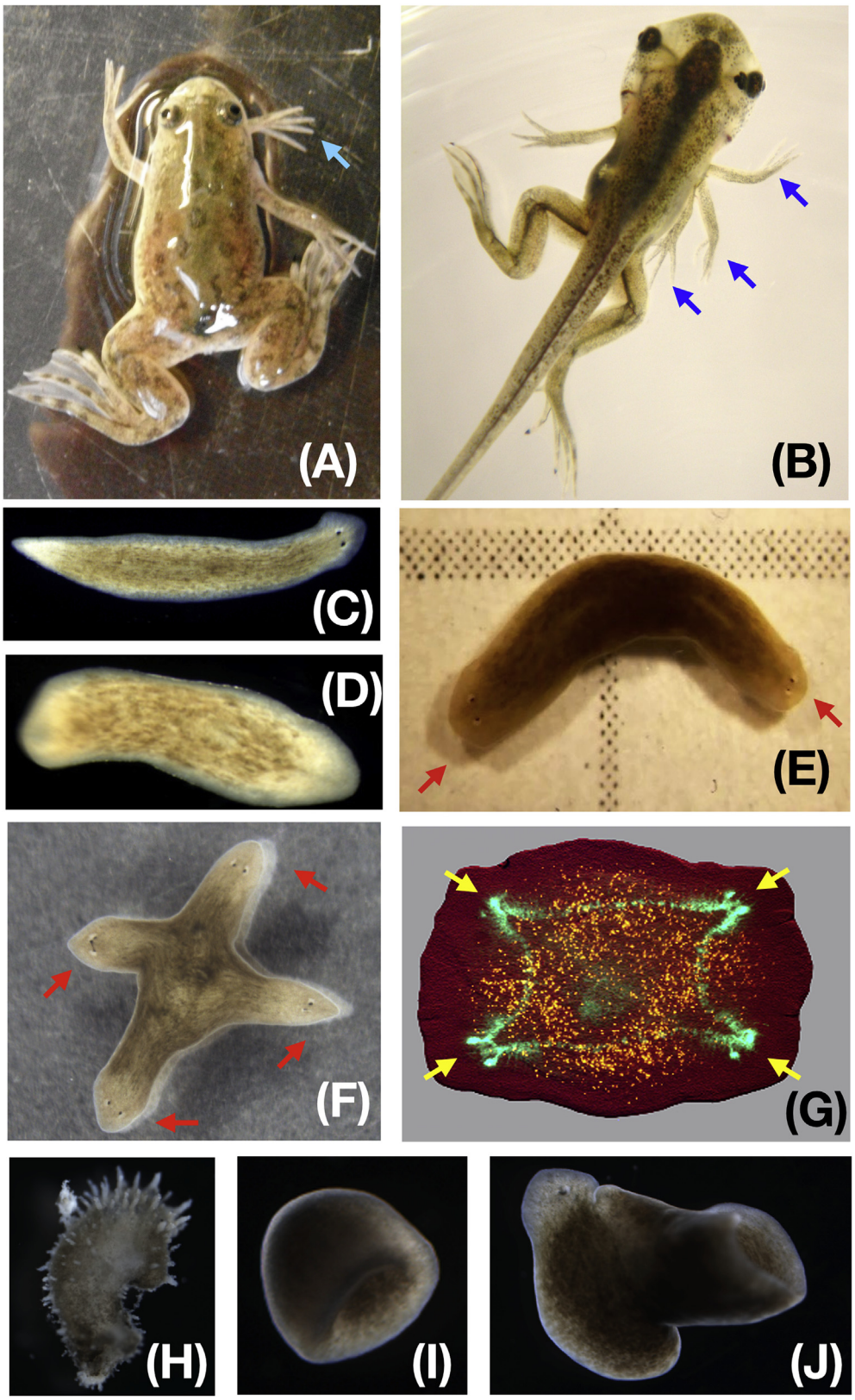

Fig. 2. Examples of alterations of bodyplans in standard model species. (A) A frog with an ectopic limb emerging from its mouth, produced by optogenetic stimulation (Gufa Lin and Levin lab, unpublished data). (B) Ectopic limbs in a froglet produced by ion channel misexpression (Sherry Aw and Levin lab, unpublished data). (C) Normal planarian flatworms, contrasted with headless worms (D) and two-headed animals (E, arrowheads indicate heads; Junji Morokuma, Levin lab). (F) Four-headed planaria produced by disruption of gap junctions and surgical cutting of the ventral nerve cords, with nervous system connection between the brains stained (G, green stain marks neurons, yellow stain marks stem cells, yellow arrows indicate brains; Nestor Oviedo and Junji Morokuma [178]). Additional forms of planaria induced by bioelectric and electromagnetic modulation include spiky forms (H), cylindrical forms (I), and ones in which normal flat planaria bodies are accompanied by growth into the third dimension (J).

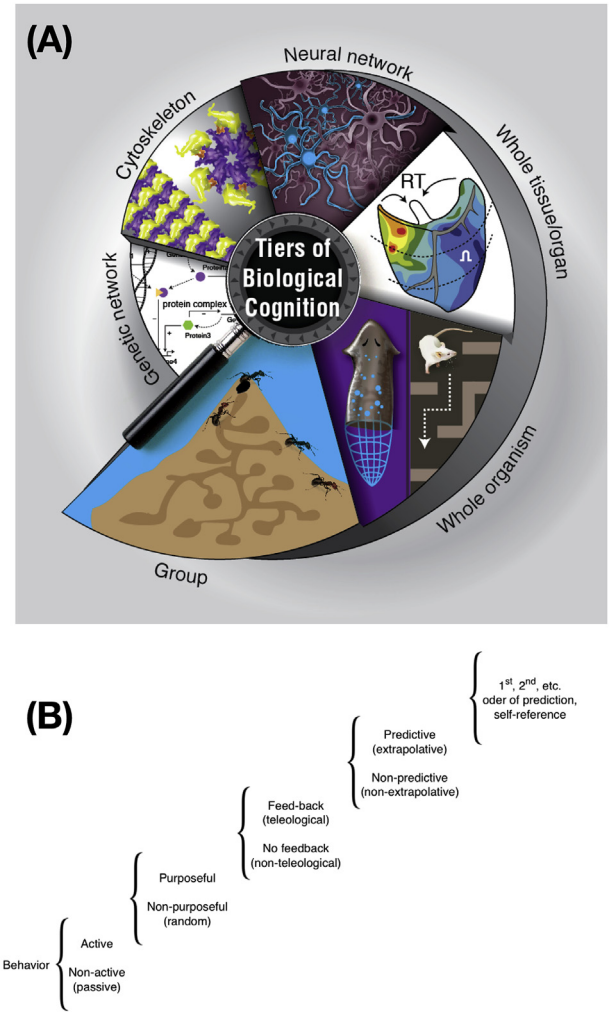

Fig. 3. Cognition is a multi-scale continuum of organizational levels and capabilities. (A) Cognitive capacities have been studied at multiple scales and material implementations, including chemical networks, subcellular cytoskeletal dynamics, neural networks, tissues and organs, whole organisms (both behavioral and morphogenetic aspects), and swarm cognition of groups of organisms. The schematization is of a cycle because each level contains computational units which comprise a group intelligence at the larger scale, such as that of cellular collectives functioning toward large-scale body-level anatomical goals. (B) Cognitive capacities of diverse body forms occupy a gradient of increasing agency and self-determination, starting from purely reactive processes to those which have feedback, learning, memory, anticipation, and the ability to modify their own goals and model themselves and counterfactual conditions within the external world. Panel A courtesy of Jeremy Guay of Peregrine Creative. Panel B modified after [252].

events based on prior experiences [28,82,83]. For example, planaria exposed to the non-selective potassium channel blocker Barium experience a rapid degeneration of their entire heads, but soon grow new heads that are completely insensitive to barium by regulating a small number of genes that enable cell physiology to proceed under these exotic, harsh conditions [84]. Other examples of adaptive decision-making in novel circumstances, occurring at the cellular/tissue-level (but would be called intelligent problem-solving behavior if it could be achieved by robotic agents) has been demonstrated in bacteria [85–87] and Drosophila embryo [88,89] biochemical networks. Thus, it is now clear that the generic mechanisms of memory, problem-solving, and decision-making can be supported by a wide range of biological architectures at various scales, requiring us to expand neurocentric connectionist models of cognition [90–93].

Not only somatic, basal cognition – but also advanced behavioral cognition – can exist in radically different neural structures. Remarkably, there are cases of human beings born with radically reduced brain mass who nevertheless show normal or above normal human cognition [94,95]. For example, one patient with an IQ of 126 and a mathematics degree had, instead of a normal 4.5 cm thickness of brain tissue between the ventricles and the cortical surface, just a thin layer of mantle measuring about 1 mm; his cranium was filled mainly with cerebrospinal fluid. This is often explained away as redundancy within the brain, but given the evolutionary pressure against increases in brain size (due to massive metabolic demands by the brain, and the risks of giving birth to mammals with large heads), it's more likely that there are additional architectures that provide the same level of performance but exist as a peak in the evolutionary landscape which is not easy to reach from the current architecture. On the other hand, there are human beings with multiple brains in the same body (certain kinds of conjoined twins), which raise fascinating questions about the degree of internal communication between the brains and the implications for cognition and its Subject of architectures with novel distributions of brain tissues [96,97].

Memory does not only exist at one level - that of neural networks – it can span levels of organization. In addition to learning in unicellular organisms [98–101], memories can jump levels of organization. For example, odorous compounds injected into the 1-cell egg will cause the resulting frog to seek out that compound for food [102]. This requires that information about this compound be transduced from the chemical mechanisms occurring inside of a single cell into tropisms belonging to a complex multicellular neural network guiding frog behavior. The parental inheritance of olfactory experiences has also been shown in mice [103], revealing the movement of specific memories between behavioral and developmental processes. Indeed, the paradigm of memories storied as finely-tuned weights of a neural network [104,105], the basis of the exceptionally popular modern connectionist machine learning paradigms [106], is clearly not the whole story either [107–109]. Memories survive radical brain remodeling and regeneration [110], which would not be true if the engrams or invariants representing information relied on memories being encoded as permanent sculpting of synaptic structures maintained. For example, moths retain information learned as caterpillars [111] (as do insects and amphibians [2,112–115]), despite the massive brain remodeling that occurs during metamorphosis.

Memories can be moved across tissues within a body. Memories not only survive in a remodeling brain, but they can move between tissues in a body. For example, planarian flatworms can be trained and form memories in a range of learning paradigms [3,116,117]. Remarkably (Fig. 4F and G), trained worms whose heads are amputated and allowed to regenerate show retention of the original learning [118–120], suggesting that information can be stored in the body outside of the head, but is imprinted on their newly-regenerating brain in order to then give rise to the correct behavior. While this has currently only been explored in planaria, which are a unique model in that it offers both, extensive regeneration and learning capacity, the efforts of regenerative medicine will likely eventually avail the community of new model species (e.g., vertebrates with augmented regenerative capacity, already available to some extent in Axolotl [25]), in which these questions can be asked. Indeed, one of the hopes of stem cell therapy is to eventually repopulate the brains of human patients, with decades of stored memories, with the progeny of naïve stem cells in cases of degenerative brain diseases. What will happen to the memory and personality of such patients? It is essential to begin to develop animal models of this phenomenon, to understand the cognitive implications ahead of the medical technology.

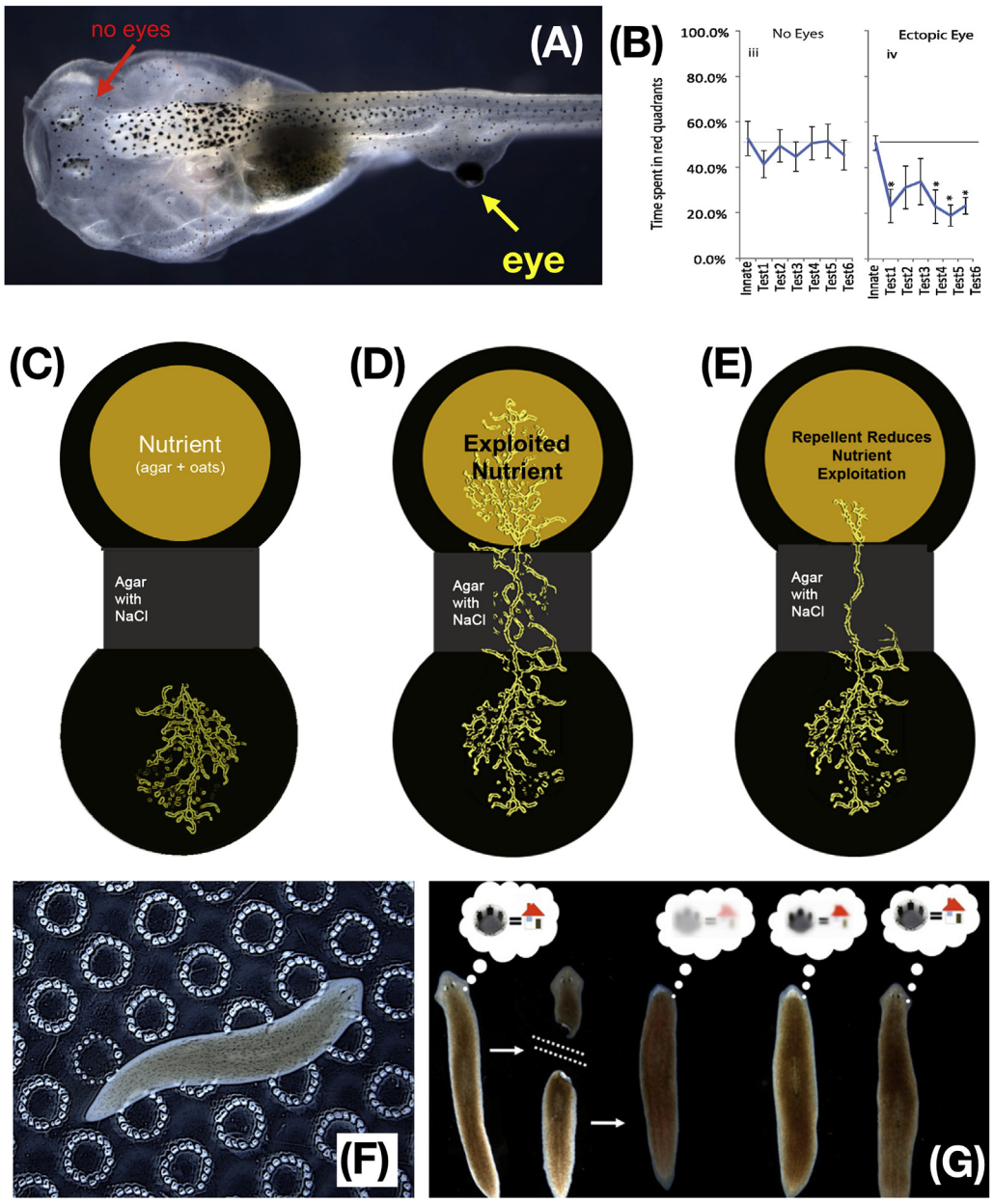

Fig. 4. Basal cognition and memory in deforming anatomies. (A) Tadpoles constructed to have no eyes in their head (red arrow) but to have an eye on their tails (yellow arrow) can learn efficiently in visual training assays, such as avoiding specific moving color patches (B), despite the abnormal anatomical layout, and the fact that the ectopic eye connects to the spinal cord, not the brain [53]. Slime molds exhibit behavior by deforming their body structure, and can store and pass on learned information throughout their unicellular network; for example, in an assay where its native preference to avoid extending across an agar bridge with salt (C), is modified after experiencing food on the other side (D) so that in future instances, it crosses the salt barriers (E). Panels C–E drawn by Nirosha Murugan, Levin lab, after data in Ref. [135,253]. Planaria which learn to feed on a specific texture of plastic (F) will continue to seek out those regions in a place preference learning assay, even after their heads are removed and an entirely new brain grows from a tail fragment (G). Panels F,G made by Tal Shomrat, Levin lab [110,120].

Memories not only move between tissues in the same body, they can apparently be moved across bodies. Transplantation studies have shown the transfer of (so far) simple memories by movement of material presumably containing engrams - cells, RNA, or protein extracts from one animal to another [26,121–129]. More modern approaches have successfully incepted false memories into mice using optogenetics to transfer bioelectric state information directly [130,131]. All of this raises important questions for defining memory as the product of experience, belonging to a specifiable mind as its owner [132]. This is especially true in the cases of transference of memory across slime molds, which are unicellular, large organisms that can be fragmented and recombined at will [98,133–135]. For the recipient of such transplants, these are in a sense false memories because the host did not participate in the experience that caused the memory; and yet the memory represents a real past event, which the host can access very much the way it accesses its own long-term memories of things that happened to its past self. Thus, for a given Self at any point in time, memories result from interpreted biophysical states of cell collectives (which may have gotten there via learning – true experience – or via the actions of neuroscientists who wrote to the memory medium directly). In this way, science has caught up to ancient philosophical (skeptical) worries about the inability to know whether our memories really represent past events or were written

into our minds recently and directly. The ability to transfer information via tissue's normal sensory stream (the "input layer" of the network) as experiences, or directly into the deeper layers, offers unprecedent opportunity to understand a diverse range of basal cognitive encodings. These approaches can be used to uncover how organisms read and interpret biochemical/bioelectrical traces of former experiences (memories) as a kind of stigmergic message from their past selves. Studying this in evolved and synthetic living model systems is an essential complement to fascinating clinical cases (such as split-brain patients, multiple personality disorders, confabulation, etc. [136]). Anterograde amnesia patients who, due to a broken internal scratchpad, often externalize the memory features of the mind [137] by writing their memories on paper to be read by their next day's future self, are in this way conceptually linked to bioengineering of brain-machine interfaces in which memory storage for living Selves might indeed be implemented on external chemical, cellular, or silicon media.

This brief survey illustrates two things. First, that cognitive abilities and the content of a mind are both tightly linked to the physical structure of the body, at multiple levels – from the anatomical arrangement of the sensor/effector organs to the molecular and bioelectric states that store its information. Second, that there is incredible plasticity in both structure and function – cognition continues to operate despite changes to the body/brain and despite modification of its information at the cellular, molecular, or bioelectric level.

Individual cells can learn, as can networks of cells and even molecular networks [138], and information can propagate across molecular, cellular, and whole body behavioral levels of organization [116,139–141]. What happens to the memories of a body if it is dissociated into individual cells? What happens if those cells are reassembled into a new body [142]? How memory relates to the structure of its substrate is the key to cracking the problem of what memories really are. Computer memories (and trained artificial neural networks) are very brittle, with their hard-won information disappearing if the medium is structurally altered; how can biological memories survive brain remodeling and regeneration? Moreover, how tightly are behavioral repertoires tied to the anatomical structure of the body – how do they adjust to new configurations arising during evolution and what consequences does plasticity and the ability to handle anatomical novelty (change) have for evolvability and fitness? In general, what is the relationship of specific cognitive capacities with the evolutionary process that shapes the body?

Numerous fascinating questions become tractable when we explore the capacity for making novel bodies, brains, and minds on both the evolutionary and ontogenic timescales. Understanding change to a body structure requires thinking about what encodes or determines the standard body specification (the large-scale anatomy toward which cells cooperate during embryonic and regenerative morphogenesis). Where is this information stored, and how much can it vary beyond the default anatomy we observe in each species? We next review some examples of the range of plasticity of bodies, which can be exploited to better understand the embodiments of mind.

"Organisms" are not well-defined structures with clear boundaries. It is now well-established that most organisms are a patchwork of genomes, containing microbiota in addition to their metazoan host, and numerous complex cases of colonial organisms exist that make it very hard to draw specific lines about what exactly an organism is [143]. Since microbes and parasites living on human and animal bodies contribute to personality traits and cognitive function [144,145], it is clear that the difficulties that evolutionary biologists have had in defining an "organism" extends to cognitive science, with aspects of basal cognition of an agent receiving contributions from multiple co-existing genomes [11,143]. In planaria, transplantation readily allows horizontal recombination of individuals; this alternative to straightforward vertical genetic lineage in which all cells in the body are clones and should be in perfect cooperation with their kin mirrors the endogenous situation in planaria, where their somatic inheritance of mutations (across reproduction by fission and regeneration) makes each animal a patchwork of genetic material [146] and raises important questions of what exactly demarcates a planarian individual, from the perspective of the genes, the cells, and the information present in each animal [8,9].

The unicellular/multicellular distinction is not absolute. While most organisms live their lives as single cells or multicellular organisms, it is important to consider examples in which this boundary is transgressed, and cognitive dynamics that might be invariant across changes in scale. Dictyostelium alternates between an amoeba phase, and a multicellular phase where the amoebas gather together into a body structure [147]. This continuous cycling is even more impressive than the one-way lifestyle described in the exobiological vignette above. Cells extracted from bodies can often only divide a certain number of times; however cancer cells are not thus limited, and even somatic cells can be induced into stem cells or gametes by relatively few tweaks of totipotency factors [148–150]. It's widely accepted that after death, our molecules continue their journey through the ecosystem. This can occur at other higher levels, such as cells and tissues. A cancer cell in the body could potentially leave the body at death and continue as a life form indefinitely, as observed in immortal cell lines from human tumors. Mammalian cells would require a supportive environment (such as the body of another creature, as occurs in transmissible cancers, for example among Tasmanian Devils [151,152]), but transformed amphibian cells could easily be envisioned to go on as amoebas after the death of a frog, since unicellular amoebas in ponds succeed in that ecological niche. One would expect evolutionary pressure to suppress such rugged independence in metazoan somatic cells, but there is no obvious reason evolution couldn't have found a way to turn on unicellular transcriptional programs, as occurs in cancers, at death occurring after reproductive years where the selection pressure to maintain a coherent body is thought to fall off rapidly. The existence of planaria, whose bodies contain ~30% highly plastic stem cells, are very resistant to cancer, and maintain a highly robust morphology that can re-form even from tiny fragments taken from an adult animal, shows that the pressure to avoid cancer is not an insurmountable force reducing cellular plasticity and proliferative potential in diverse circumstances.

Functional anatomy is both robust and plastic, using basal cognition of cell collectives to achieve specific anatomical goals [40,153]. When cells do cooperate toward large-scale anatomy, the result is robust – able to withstand massive insults during regulative embryogenesis (such as bisection, which leads to normal monozygotic twins) and regeneration (such as the ability to regrow limbs, eyes, jaws, portions of the brain, etc. in animals such as axolotls) [154]. At the same time, the process reveals important plasticity - the ability to achieve the correct functional anatomy in novel ways that use mechanisms, or traverses configurations, very different from the normal course of events [155,156]. For example, when the craniofacial structures of a frog embryo are experimentally scrambled in their relative positions, they take novel paths to rearrange themselves into normal frog faces [157,158]. Thus, the genetics specifies not a set of hardwired standard movements for each, but instead a problem-solving machine whose primitive test-operate-exit loop is able to recognize an incorrect starting configuration, undertake novel responses to reduce the error with respect to a specific target morphology, and cease the remodeling when a

correct frog facial pattern is achieved (anatomical homeostasis, as seen in regeneration also). The same scheme of exploiting novel mechanisms to achieve the same goal is seen in polyploid newts. In normal animals, small cells use cell-cell coordination mechanisms to arrange into kidney tubules; but when polyploid animals with huge cells are artificially created, individual cells wrap around themselves (a cytoskeletal, unicellular behavior) to create tubules of the same shape and diameter [159]. The matching of growth and morphogenesis to physiological needs is also seen in mammals: for example, hepatocytes implanted into swine lymph nodes form ectopic livers whose size is proportional to the degree of liver injury [160]. This flexible problem-solving is also deployed at the behavioral level (functional homeostasis): tadpoles made to have eyes on their tails instead of in the head nevertheless exhibit normal visual learning: this abnormal anatomical layout does not require evolutionary timescales to become functional – the optic nerves find and synapse onto the spinal cord, which is apparently enough for the brain to recognize the signal of a weird patch of tissue on their backs as visual data and behave correctly [53,54]. A classic case of this was Slijper's goat, which achieved the anatomical changes needed for bipedal locomotion within a single lifetime, due to a birth defect that deleted the forelegs [161]. Another relevant concept illustrating developmental plasticity is "nerve addiction": normal salamanders require nerves in order to be able to regenerate their limbs, but this is a learned dependency by the tissue – animals that develop without nerves can regenerate their limbs without the benefit of nerves as adults [162]. Taken together, these examples illustrate how genomes specify cellular hardware that can adapt to a wide range of non-standard configurations and behavioral repertoires [43,163].

The shape of bodies is not controlled entirely by their genome. The genome produces cells that, generally, work toward the same default species-specific anatomical outcome. However, other biophysical memory media besides DNA, such as cytoskeletal structures and physiological networks, can store information that alters the body structure [164–166]. Even commensal microbiota living within a metazoan body have an input into the anatomical form of their host, able to for example induce extra heads and changes of visual system structure in regenerating planaria [167] and regulating stem cell behavior in embryogenesis [168,169]. The influence of commensal organisms (with their own genomes) living within a complex body extends not only to their anatomy but also to complex aspects of cognition, as seen in the phenomenon of host-altered-behavior in zombie ant fungus [170–172] and the alteration of risk-taking and other complex behaviors in mammals by toxoplasma infections [173]. These facts make it clear that both body structure and behavior receive inputs from multiple genomes within the same "organism".

Non-genetic alterations to body structure and function are heritable. In considering the relationship between cognition and the evolutionary forces that shape behavior and enable its plasticity, it's important to note that DNA is not the only medium of hereditary body-shape information. A classic example of epigenetics is the determination of protozoan anatomy and functional behavior by the cytoskeleton [174], and the inheritance of changes made to the cortex structure during the life of the animal which persist in all of its offspring [175]. Recent data showed that this can also occur in complex bilaterian organisms, via bioelectrically-mediated pattern memory [176]. Planaria whose bioelectric circuits are altered briefly to specify a 2-headed prepattern result in 2-headed animals which, when fissioned, continue to regenerate the abnormal 2-headed anatomy (and their unusual behavior) in perpetuity [177,178]. Indeed, this primitive pattern memory system can store at least 2 different types of representations of what a correct planarian looks like (information used to guide morphogenesis by cells during regeneration of worm fragments), including the storage of 2-headed bodyplan information in the tissues of a 1-headed (normal anatomy) animal (Fig. 5). This illustrates the ability of a primitive somatic cognition system to represent counterfactuals – storing information about a bodyplan which is not reflecting the current anatomy, but rather what the cells will build if called upon to do so in the future [179].

Metazoan body cells are not obligate cooperators. The cells within a body do cooperate toward the same goal, but this process of coordination is not absolute, despite their evolutionary journey toward multicellularity. Cancer is a rapid breakdown of this cooperative activity, in which cells roll back toward an ancient, unicellular transcriptional program [180,181] and more generally reduce the scale of the goals toward which they work from tissue- or organ-level to that of single cells [66]. Thus, even "tame" metazoan cells are perfectly capable of abandoning multicellularity and treating the rest of the body as external environment [182,183]. Conversely, manipulation of bioelectrical connectivity (a mechanism that normally helps cells integrate their activity toward anatomical body-shape goals) and actively patterning microenvironments both have been shown to normalize cancer cells [184–187], demonstrating a bi-directional path between cooperative subunits of a complex whole, and unicellular lifestyles. The process of carcinogenic conversion and normalization are an ideal context within which to track the scaling up and down of the boundaries of an integrated, proto-cognitive Self as a swarm intelligence consisting of molecular networks, cells, organs, or whole organisms [35,47,188].

Genetic relatedness is not the only determinant of cooperation between cells and tissues within organisms. Coordination during embryogenesis is in part accomplished by competition of cells and tissues for informational and metabolic resources (reviewed in Ref. [14]). Indeed, this "struggle of the parts" [189] is a consequence of the multi-scale competency of biological structures, which enables not only cells to continue to live outside the body (as routinely occurs in cell culture) but in fact whole organs to survive and exhibit distinct behaviors when liberated from the body [190]. Importantly, brains too achieve their optimal structure and behavior in part because of the dynamics of a competitive architecture among sub-modules [191,192]. Conversely, numerous viable chimeras can be made by mixing or joining genes, cells, organs, or whole organisms from diverse species [193,194]. For example, Drosophila neurons can live in vertebrate (even rodent) brains [13,195]. The cognitive capacity of hybrid animals is a fascinating complement to studies in traditional model species for the same reason that experimental shuffling of genes, cells, and tissues has advanced developmental biology: combining elements at different levels of organization into one functional body offers the possibility to understand the modularity, flexibility, interoperability, and internal structure of cognition, as well as its mapping onto specific biological embodiments at multiple scales.

Death is relative to the scale of organization. Many kinds of death at the organism level occur despite health of most of the organs or cells in the body (as exploited during organ harvesting from cadavers for transplantations). HeLa cells are an immortal continuation of one human – Henrietta Lacks, who died decades ago but her body lives on in a spatially-distributed form all across the Earth as thousands of scientists propagate this popular cell line [196]. A transient, cognitive version of this spatial dissociation is routinely observed during general anesthesia in human patients, where the use of gap junction-blocking reagents (which break the electrical connectivity between cells [197,198]) result in the temporary dissolution of the cognitive narrator despite the fact that all of the brain cells are as alive as ever. Remarkably, when the anesthetic is removed, electrical connectivity of the network returns to

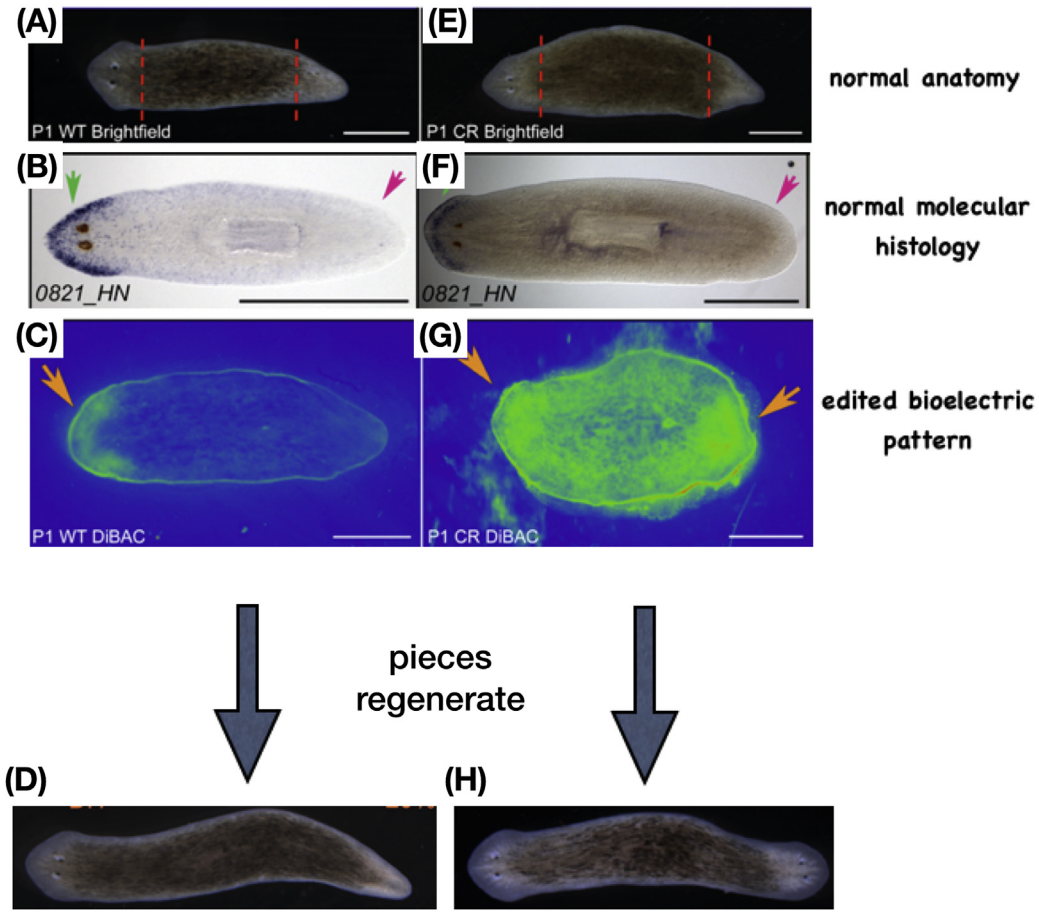

Fig. 5. Bioelectrical pattern memory in planaria can encode counterfactual anatomical states. Normal, 1-headed planaria (**A**), with correct anterior marker gene expression (**B**, pink arrow indicates posterior region with no expression signal, green arrow indicates anterior marker expression in the head) and bioelectric prepattern indicating the number and location of heads (**C**, orange arrow indicates green signal, which is depolarization revealed by voltage-sensitive reporting dye) give rise to normal 1-headed planaria (**D**) when cut into pieces. However, normal 1-headed bodies (**E**), with normal molecular marker expression (**F,** pink arrow indicates posterior region with no expression signal), but experimentally-induced duplication of depolarization pattern (**G**) can give rise to fragments which regenerate as 2-headed worms (**H**). This reveals that the bioelectric pattern is instructive for the number and distribution of heads, that an anatomically- and molecularly-normal body can store (at least) two possible pattern memories of what a correct planarian needs to look like, and that the bioelectric pattern is not a readout of the current anatomy but can diverge from it and store a counterfactual representation of what it would build if it got injured in the future.

enable the same cognitive Self – the patient maintains memories, goals, and personality traits (although not always, as seen in cases of psychosis and large-scale delusions induced by general anesthesia [199]). At the bench, "disassembly" assays highlight the need to understand and define the large-scale (cognitive) system which may be gone or modified even if the underlying subunits are alive and healthy. Examples include and organ/cell culture where an embryo (such as a frog tadpole or a Hydra) can be chopped into pieces, and cultured separately or recombined into new living organisms by transplantation. When a planarian is cut into (even as many as 250) pieces, the original worm is gone, but each piece will go on to make a perfect little copy [8]. The disappearance and reaggregation of minds in these cases, as well as the provenance of memories and behavioral traits during disassembly and reassembly of tissues, represents an important area for future study.

The remarkable plasticity of biology and the body-mind interface is clearly telling us that our existing simple categories of both structural and informational definition of a given Self are insufficient. We need to understand how multiple competent subunits, such as cells, give rise to Selves that arise, die, and achieve an integrated internal cognitive perspective with coherent memories and goals that are more than the linear sum of the subunits' local computations. This is as critical for philosophy of mind and evolutionary neuroscience as for regenerative biomedicine and robotics/AI. Fortunately, advances in bioengineering are helping us to examine how functional (and possibly cognitive) wholes can be created out of a variety of diverse parts in a myriad of novel combinations and configurations. What kinds of minds would such artificial bodies have? Unlike in traditional AI, where a mind is built from dumb parts, artificial biological Selves are composed of subunits (cells and molecular networks) with rich competency in navigating their own relevant state space, enabling us to for the first time probe the scaling of tiny minds into bigger ones.

1.3. Biobots: a new model system for cognition research

The biological cases described above illustrate the complex relationship between dynamically changing minds, bodies, and evolutionary dynamics at multiple scales. One of the most important lessons learned from these examples is that cognitive capacity is not something that must be evolved in tight integration with a dependable body anatomy – it applies "on the fly" to adjust to changes in body structure. This is a concept that has been exploited for "morphological computation" in soft body and evolutionary robotics [200–204]. However, exciting recent progress has availed biologists of a model system in which the origin of bodies, and the

de novo emergence of cognitive programs and primitive minds, can be observed and manipulated at will: biobots [48,49]. Bioengineering of organoids in vitro is now enabling the creation of entirely novel small living bodies from cells, raising the question of what (if any) basal cognition and behavioral capacity they will display.

Several groups have made synthetic living machines which use muscle contraction to deform an inorganic scaffold and thus achieve locomotion on surfaces or through liquid volume [205,206].

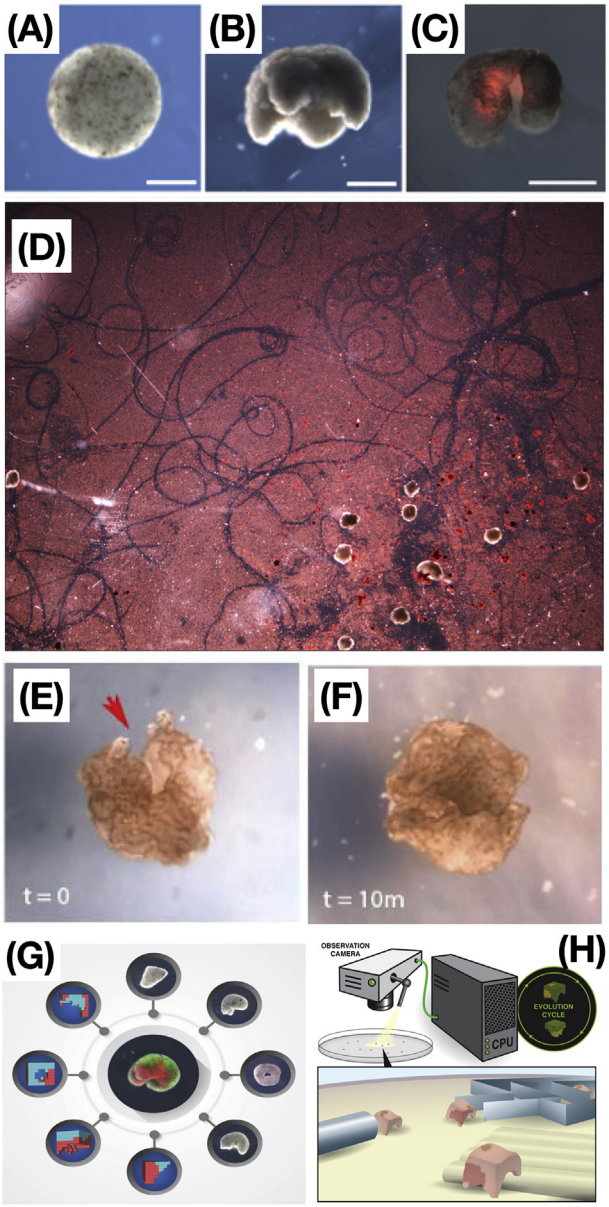

Fig. 6. Xenobots – synthetic bodies with functional behavior made from frog cells. Skin and muscle cells extracted from *Xenopus laevis* frog embryos and dissociated coalesce spontaneously into a novel form (**A**) which can be sculpted (**B**) and reveal emergent patterning of internal structure (**C**, red fluorescence indicates muscle cells). Spontaneous activity of these Xenobots enables them to move around their environment, leaving tracks in carmine powder (red, paths seen in black) which reveal their collective motion paths (**D**). If wounded (**E**, red arrowhead indicates cut), Xenobots heal to their new shape (**F**). A computer algorithm models this self-organization process enabling production of Xenobots in numerous different body forms (**G**), enabling tracking and automated analysis of their individual and group behaviors in diverse environments (**H**). Images by Sam Kriegman, Bongard lab, and Douglas Blackiston, Levin lab, from Ref. [207].

These have to be paced by external influences (optogenetic or electrical stimulation). However, it was recently shown (Fig. 6) that skin and muscle cells taken from a frog embryo will self-assemble into constructs (Xenobots, named after their amphibian of origin: *Xenopus laevis*) which move on their own, exhibiting a range of motile behaviors by which they interact with objects the environment and each other [207]. This is just the first foray into the field of synthetic morphology and it's clear that combinations of nanomaterials, diverse species as cell sources, synthetic biology circuits (transcriptional and bioelectric), and the propensity for cells to cooperate to build a coherent organism will result in a huge morphospace of novel living machines. Efforts to program their self-assembly [44,208] and behavior [46,47] are under way, but one of the most exciting aspects is their native functionality and cognitive capacities. The skin cells of which they consist have receptors for a plethora of sensory modalities (light, pressure, temperature, chemicals, etc.) and remains to be seen whether Xenobots for example have preferences or can be trained in simple assays.

Several interesting aspects are revealed by the Xenobot platform. First, this is the only known life form which does not have a long evolutionary past that specifically selected for their body shape and behavior. The cells evolved in the biosphere, but they were selected for sitting quietly on the surface of a frog to keep out the pathogens. The actual evolution of these novel forms took place in a virtual world inside a computer that predicted the necessary experimental manipulations and their resulting behavior. Nevertheless, these novel body forms exhibit coherent behavioral programs that did not require eons of selection but work "on the fly" to operate this new body by taking advantage of meso-scale biogeneric aspects of physics [209]. This strategy has already been demonstrated [210] in robots that build a self-model about their own structure in order to discover behavioral programs for their initial, and subsequently altered, bodies akin to the active inference model that has been proposed for neuroscience [211,212] and body morphogenesis [213,214]. Second, these cells have a completely wild-type genome – no genomic editing or transgenes were necessary to coax them to build a body and behavioral repertoire totally different from frog or tadpole. And, genetic sequencing of the material would reveal nothing but 100% pure *Xenopus laevis*, completely misleading the molecular biologist about the body shape and function they really had. It is a further testament to cellular plasticity that, when liberated from the constraints of a default body, the cells are willing to cooperate to build a completely different form. Finally, they repurpose their genomically-encoded hardware (specific cytoskeletal structures) toward a different functionality in a new environment – this is precisely the kind of problem-solving, basic intelligence that state-of-the-art robotics is still striving to achieve.

Xenobots have no nervous system – without a brain or neurons, these organisms move in coherent ways, signal damage to each other, and accomplish a variety of characteristic manipulations of loose debris in their environment. Their skin cells exhibit the same kinds of calcium flashing one sees in primitive nervous systems, and we are just beginning to use the same techniques used for neural decoding to try to understand its information content. However, future biobots will surely contain neural tissue or even entire brains taken from various animal sources. Using bioengineering in vitro and chimeric grafting in vivo, it is now possible to generate a dense spectrum of living beings ranging all the way from non-neural or primitive neural organoids to full human brains, and every combination (amalgam of human and non-human brain cells) inbetween, raising a set of ethical concerns and questions in the philosophy of mind. Experiments to track the primitive cognition (e.g., simple learning capacity) of such organoids have already begun [215,216]. Instrumentizing brains or other biological systems

to control virtual environments (such as a flight simulator [60]) or real-world vehicle robot [217,218] provides rich opportunities to explore diverse, non-standard cognitive architectures, in addition to the alternative living bodies produced by synthetic bioengineering.

1.4. Bioelectricity and pre-neural minds

The characterization of the cognitive worlds of novel bodies is a challenging task. One inroad that will facilitate it is the increasing information on the phylogenetic history of conventional minds [20,68,69,219,220]. Brains, and neurons, did not appear spontaneously – they evolved slowly from other cell types [221]. It is now known that all of the machinery which is used by brains - neurotransmitters, ion channels, synaptic proteins, etc. long predate the origin of nervous systems and indeed were present in our unicellular ancestors. This explains many interesting puzzles, such as for example why organisms, so distant that they acquired multicellularity separately from animals (e.g., fungi), just happen to possess biochemicals that have very subtle effects on complex, mammalian brains' cognition (hallucinogens). What were ion channels and neurotransmitters used for before the control of behavior at the organism level? It is likely that the origin of neural controls of body-level decision-making and problem solving lay in the control of cellular behavior and the coordination of the cellular swarm toward anatomical goals. Neural electrical dynamics were used by cells to configure bodies in virtual morphospaces (during regeneration, embryogenesis, and cancer suppression) long before their slow, analog bioelectric circuits [78] were speed-optimized to apply the same strategies to moving bodies in 3-dimensional space [68]. This is clearly illustrated in the ability of simple voltage states to drive modular changes in body form, inducing whole eyes in gut tissues [222] (Fig. 7A), and ectopic hearts, brains, and limbs [223]. Advances in molecular bioelectricity are now using conceptual [224] tools and experimental methods (such as optogenetics [225,226]) taken from neurobiology, in effect extending the deep principles of neuroscience beyond neurons (Fig. 7B and C).

It is now seen that all cells, not just neurons, form bioelectric networks that regulate cell behavior via neurotransmitter signaling [227–230], to coordinate morphogenesis across distance and store re-writable pattern memories that guide anatomy. For example, in planaria, the number of heads can be specified by transiently manipulating the endogenous bioelectric circuit that stores the anatomy toward which cells work: once set to a different layout, this "pattern memory" is stored by the tissue and used to guide the location of heads in cut fragments. Not only head number, but also head shape can be controlled [231]: brief interruption of bioelectrical communication among cells in a planarian fragment results in the regeneration of heads (and brain shapes) appropriate to other species of planaria, in the absence of genetic change (but in a stochastic manner with ratios proportional to evolutionary distance between the species). This has been modeled via dynamical systems concepts as the cellular network being pushed out of its usual, default attractor state (by the injury), and sometimes settling down into the wrong attractor if the normal cell:cell communication is inhibited [166]. The remarkable fact is that the reagent used to achieve this is a gap junction blocker, which breaks the bioelectric gestalt between the cells [232,233] in precisely the same way as general anesthetics interfere with gap junctions in the brain to cause a loss of high-level integration (consciousness). Much as patients coming out of general anesthesia that often have brief but significant hallucinations (visit incorrect regions of the brain state space), planaria exposed to an uncoupler of electrical synapses inhabit an incorrect region of morphospace for about 3 weeks, but then remodel back to the much deeper default attractor [231].

Electric networks are ideal for computation and memory – a fact that we heavily exploit in our technology, but was discovered by evolution very early. These kinds of control systems can be traced all the way back to bacterial biofilms (Fig. 8) – proto-bodies just learning to scale single-cell homeostatic loops into group-level goals [70,71,234,235], and are now being implemented from scratch in synthetic excitable tissues made from non-neural cells that drive predictable bioelectric signaling dynamics [236–238]. Numerous parallels exist between cognitive concepts (e.g., bistable perceptual illusions, memory, predictive encoding, etc.) in single animals and animal swarms, and developmental controls of body form [36,37,40,153,213,239,240], differing only in characteristic timescales and levels of organization. Thus, it is likely that cross-pollination between computational efforts to understand the bioelectric encodings of anatomical homeostatic goal states during regeneration, and attempts to model basal cognition implemented in simple electrical circuits in novel body forms, will produce an extremely deep and fruitful synthesis.

2. Conclusion

The "dark matter" of cognitive science is to understand how parts integrate into coherent Selves, whatever their level of sophistication, and how this process plays out within the plasticity of the body substrate over evolutionary and developmental timescales. Rapid accommodation of behavior to novel body forms, whether in biobots, chimeras, or animals whose anatomy was re-specified by manipulation of endogenous bioelectric prepattern, is revealing that the old "brain in a vat" thought experiment is not an unlikely aberration but is in fact ubiquitous. All minds emerge to find themselves in, to them, a novel "world" and must adapt to the structure of the body and its external environment – whether it's a Petri dish of neurons driving a simulated airplane's six control variables to keep it from crashing in a virtual world [60] or a pancreas whose goals (in the cybernetic sense) involve keeping different sets of parameters in correct ranges [81]. The plasticity is readily observed in experiments on sensory augmentation and brain control of assistive devices [241–243], as well as the "Rubber hand illusion" [244–246], where on a scale of minutes or hours, the brain is willing to modify its internal map of a body whose basic layout has been reliably constant for hundreds of millions of years.

This dynamic embodiment works not only in "standard" evolved species but in a wide range of implementations, the limits of which we can't even begin to guess yet as we merge computer technology with biological tissues via bioelectric interfaces [247]. It is the mission of next-generation cognitive science, to move beyond traditional brains and work to understand plasticity of cognition in unconventional substrates. This task goes beyond real-time control and performance. Memory and anticipation are capacities that require us to investigate the encoding of memories, plans, and goal states. Brains have to be able to interpret the informational content of cellular, tissue, or molecular implants, in the same way they will have to interpret and decode their own memory engrams at future times, and in the same way that parts of a brain have to interpret the information coming from other pieces of the same brain. It is a grand challenge in this field to understand the encoding, storage, and decoding in its most fundamental aspect, not limited to familiar neural paradigms.

All cognitive Selves are made of parts. In the case of living beings, those parts are cells, which are themselves competent agents with the ability to lead their own independent lives (e.g., amoebas). Some of the biggest philosophical questions, still unresolved, include: 1) How do higher-order Selves come into being from collections of subunits, and how do they disappear at "death"? For that matter, what exactly is death of a multicellular creature, when most

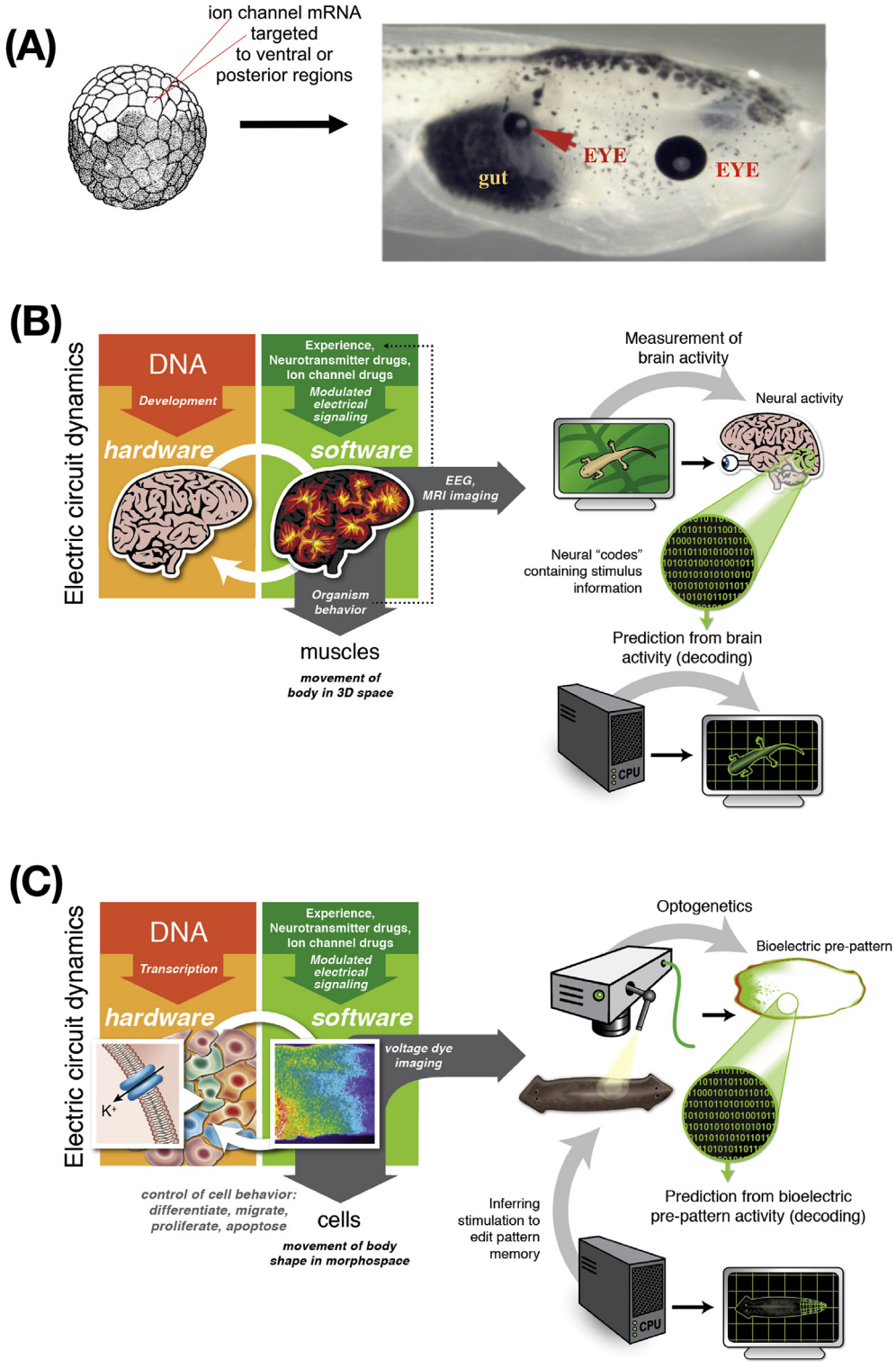

Fig. 7. Developmental bioelectricity as precursor of cognition. (A) Bioelectric prepatterns indicate the goals toward which cells will build, as for example induction of specific voltage states (via injection of ion channel mRNA into cells) can induce the modular building of an eye in the gut of a tadpole (red arrowhead) [222]. The relationship between the bioelectric patterns in neural networks which encode cognitive and semantic states and guide muscle motion to move in 3D space (B) are isomorphic to the bioelectric patterns in networks of non-neural cells which encode setpoints for anatomical homeostasis and guide cell behavior toward specific morphogenetic goal states in regeneration and development (C). Panels B and C were provided by Jeremy Guay of Peregrine Creative.

or all of its individual cells are still alive? 2) How do complex Selves store and interpret distributed memories – the results of learning from experience – across their internal collective? How do we recognize the "owner" of a specific memory residing in a complex brain or body? How can memories be moved between such collectives? All of these are profound questions affecting not only the

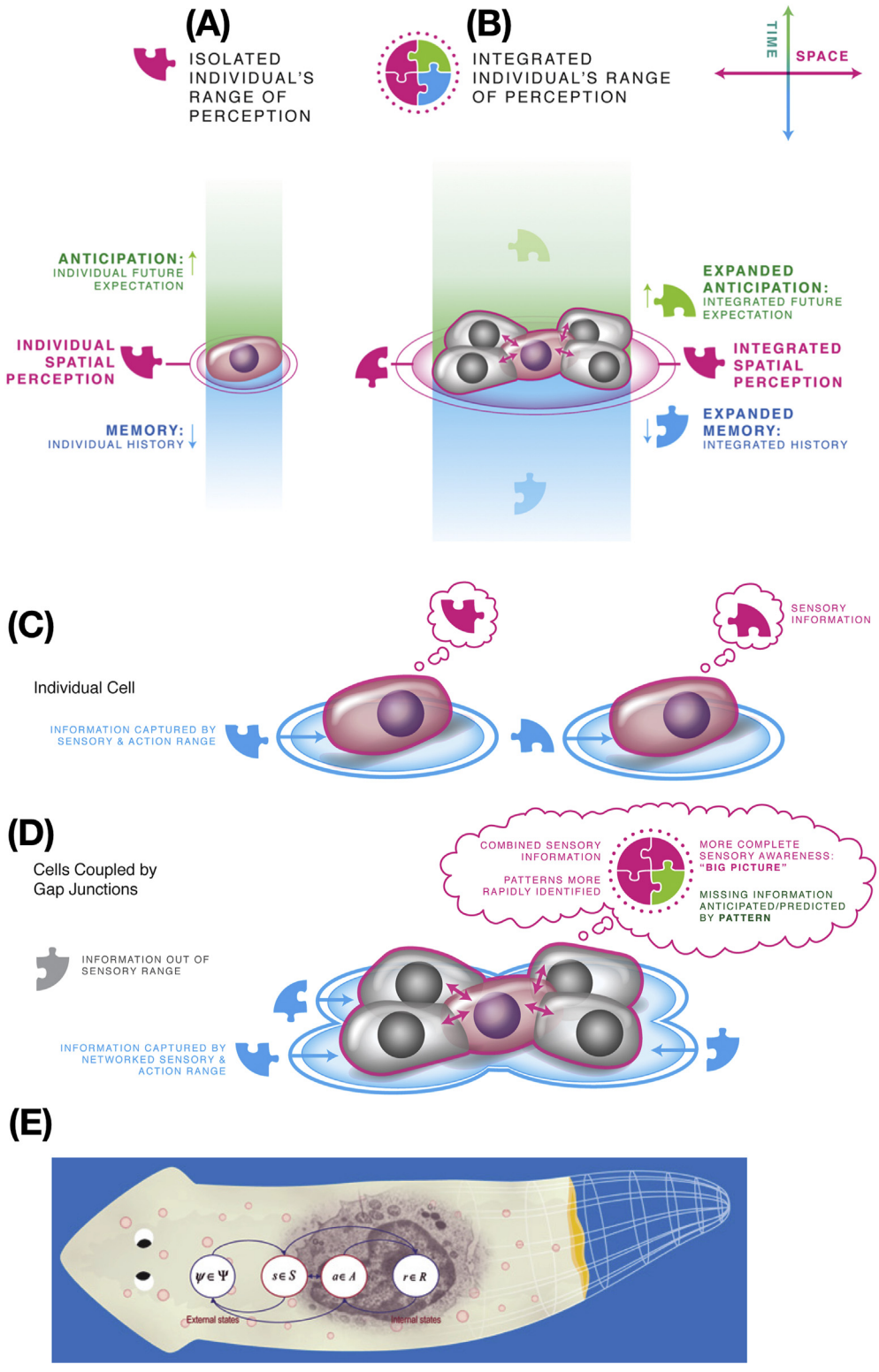

Fig. 8. Scaling of cognition. (A) Individual cells have a limited horizon of homeostatic goals, defined by the extent of their spatial perception, and memory/anticipation (temporal extent). (B) When joining into networks via electrical synapses, they link into a larger unified network with larger spatio-temporal horizons, thus able to pursue bigger (anatomical-level) goals such as regulative morphogenesis. The sharing of internal milieu through gap junctions inhibits the ability of cells to bind information or resources to their small Selves (C), increasing functional cooperativity at the tissue level and enabling evolutionary dynamics to result in large-scale cooperative systems where the selfish agent expands its boundary of Self [66]. This in effect creates a new group intelligence with distinct (and likely larger) processing power, IQ, and perceptual/modeling capacity (D). Such agents are able to perform cognitive tasks such as surprise minimization, active inference, and flexible pursuit of represented goal states, both in behavior and in the control of their own anatomical configuration (E, drawn by Allegra Westfal after [254,255]).

understanding of personal identity and cognitive science, but also of evolution of multicellularity and death. The answers will be as relevant to the regenerative medicine of brain disease and aging as to the computer science of engineering artificial intelligent agents and swarm robotics. Fig. 1 illustrates some of the challenges that possible biological phenomena raise for traditional concepts of life, death, Self, and memory. Importantly however, we do not need to wait for advances in Exobiology to confront these facts: the examples reviewed above show that many of these phenomena are already present here in our biosphere. However, this departure from the traditional study of cognition in fixed, evolved embodiments will be massively amplified by on-going advances in bioengineering. Synthetic biobots and exotic body layouts produced by bioelectric and other means will enable the community in this novel emerging field to address truly vast questions of personal identity, evolution, and cognition that have heretofore largely been the province of philosophy.

There are immense opportunities for future work. Synthetic transitions can be created as needed [248] – no longer must we wait for evolution to produce model systems exhibiting new aspects of form and function. Two- or four-headed planaria are readily produced, as are brain grafts in tadpoles, facilitating the study of body control and cognition in bodies with more than one central neural processor. Bodies, especially in amphibian models, are also readily constructed with novel effectors (additional limbs or eyes), and new sensory apparatus can be easily added. For example, model animals can be made with numerous additional receptors or bioelectrical transducers of any kind of data from electronic devices (for example, one could make an animal that felt the magnetic output of the sun, or variabilities of the stock market, directly in its skin). Much as cancer cells sometimes regain a primitive multicellularity as tumor organs [249], the cooperative capacity of metazoan cells can be harnessed for biobots whose cognitive capacities have not yet been tested. Beyond pure biological plasticity, chimeric organisms where cells are interfaced with smart nanomaterials, computational electronic components, and information interfaces (from specific devices to the entire Internet) open an ocean of possible bodies that could house minds with vast spatial awareness and causal reach.

Such work provides excellent fodder for exobiologists, who think about how to recognize and gauge cognitive capacity in entirely alien forms that could be encountered. However, it's important to realize that the implications strongly influence current, terrestrial questions of how we understand ourSelves and the other life forms with which we interact. Many human beings are already subjects for whom these issues are directly relevant - including genetic chimeras [250] and microchimeras due to normal pregnancy [251], participants in brain-machine interfacing (whether to correct disease or the transhumanist efforts to expand normal human sensory-motor capacity), cyborgs incorporating digital technologies such as machine-learning-driven pacemakers and insulin pumps, patients of impending brain regenerative therapies, conjoined twins, etc. More broadly, all of us – even those in traditional bodies - need to prepare for the ethical and social consequences of being surrounded by the impending deluge of highly diverse, dynamically changing bodies and minds of various scales of cognitive capacity, which will arise from the disciplines of swarm robotics, synthetic bioengineering, and their integration toward consumer products (e.g., Internet of Things and home robotics), food production, the pet industry, etc. Indeed, this field will have implications far beyond biomedicine and bio-philosophy, impacting also the field of machine learning. The lessons we learn about how biology implements creative, robust problem-solving in behavioral and structural spaces via multi-scale autonomy have clear applications to the design of novel artificial intelligences not restricted to neuromorphic architecture.

Crucially, bioengineering has now leaped ahead of philosophy in terms of the exotic configurations of beings that can now be entertained. Philosophy of mind has toyed with thought experiments about split and combined human persons, but the real, now empirically-tractable at the bench, scenarios are much stranger. We are witnessing the birth of a new field, at the intersection of computer science, cognitive science, evolutionary developmental biology, and engineering. As the field of Artificial Life explores "Life as it could be" [29], with the computer as their key tool, Unconventional Cognition will thrive by extending current tools and concepts to understand "Mind as it could be".

Conflicts of interest

I declare there is no conflict of interest.

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References

[1] T. Nagel, What is it like to be a bat? Phil. Rev. 83 (1974) 435–450.
[2] I.M. Sheiman, K.L. Tiras, Memory and morphogenesis in planaria and beetle, in: C.I. Abramson, Z.P. Shuranova, Y.M. Burmistrov (Eds.), Russian Contributions to Invertebrate Behavior, Praeger, Westport, CT, 1996, pp. 43–76.
[3] J.V. McConnell, A.L. Jacobson, D.P. Kimble, The effects of regeneration upon retention of a conditioned response in the planarian, J. Compar. Physiol. Psychol. 52 (1959) 1–5.
[4] T.M. Alloway, Retention of learning through metamorphosis in grain beetle, Tenebrio-Molitor, Am. Zool. 11 (1971) 639.
[5] M. Meima, P. Schaap, Dictyostelium development-socializing through cAMP, Semin. Cell Dev. Biol. 10 (1999) 567–576, https://doi.org/10.1006/scdb.1999.0340.
[6] J. Schmich, Y. Kraus, D. De Vito, D. Graziussi, F. Boero, S. Piraino, Induction of reverse development in two marine Hydrozoans, Int. J. Dev. Biol. 51 (2007) 45–56, https://doi.org/10.1387/ijdb.062152js.
[7] Y. Matsumoto, S. Piraino, M.P. Miglietta, Transcriptome characterization of reverse development in Turritopsis dohrnii (Hydrozoa, Cnidaria), G3 (Bethesda) 9 (2019) 4127–4138, https://doi.org/10.1534/g3.119.400487.
[8] M. Neuhof, M. Levin, O. Rechavi, Vertically- and horizontally-transmitted memories - the fading boundaries between regeneration and inheritance in planaria, Biol. Open 5 (2016) 1177–1188, https://doi.org/10.1242/bio.020149.
[9] C. Fields, M. Levin, Are planaria individuals? what regenerative biology is telling us about the nature of multicellularity, Evol. Biol. (2018), https://doi.org/10.1007/s11692-018-9448-9.
[10] R.E. Michod, Evolution of individuality during the transition from unicellular to multicellular life, Proc. Natl. Acad. Sci. U. S. A. 104 (Suppl 1) (2007) 8613–8618, https://doi.org/10.1073/pnas.0701489104.
[11] D.C. Queller, J.E. Strassmann, Beyond society: the evolution of organismality, Philos. Trans. R. Soc. Lond. B Biol. Sci. 364 (2009) 3143–3155, https://doi.org/10.1098/rstb.2009.0095.
[12] P.B. Rainey, S.D. Monte, Resolving conflicts during the evolutionary transition to multicellular life, Annu. Rev. Ecol. Evol. Syst. 45 (2014) 599–620, https://doi.org/10.1146/annurev-ecolsys-120213-091740.
[13] S.V. Saveliev, V.V. Lebedev, M.B. Evgeniev, L.I. Korochkin, Chimeric brain: theoretical and clinical aspects, Int. J. Dev. Biol. 41 (1997) 801–808.
[14] R. Gawne, K.Z. McKenna, M. Levin, Competitive and coordinative interactions between body parts produce adaptive developmental outcomes, Bioessays 42 (2020), e1900245, https://doi.org/10.1002/bies.201900245.
[15] P.J. Bryant, T.E. Arehart, Diversity and life-cycle analysis of Pacific Ocean zooplankton by videomicroscopy and DNA barcoding: Hydrozoa, PLoS One 14 (2019), e0218848, https://doi.org/10.1371/journal.pone.0218848.
[16] A. Salem, K. Pinto, M. Koch, J. Liu, E.G. Silva, Are polyploid giant cancer cells in high grade serous carcinoma of the ovary blastomere-like cancer stem cells? Ann. Diagn. Pathol. 46 (2020) 151505, https://doi.org/10.1016/j.anndiagpath.2020.151505.
[17] K.J. Bussey, L.H. Cisneros, C.H. Lineweaver, P.C.W. Davies, Ancestral gene regulatory networks drive cancer, Proc. Natl. Acad. Sci. U.S.A. 114 (2017)

6160–6162, https://doi.org/10.1073/pnas.1706990114.
[18] M. Bleijs, M. van de Wetering, H. Clevers, J. Drost, Xenograft and organoid model systems in cancer research, EMBO J. 38 (2019), e101654, https://doi.org/10.15252/embj.2019101654.
[19] N.D. Cook, G.B. Carvalho, A. Damasio, From membrane excitability to metazoan psychology, Trends Neurosci. 37 (2014) 698–705, https://doi.org/10.1016/j.tins.2014.07.011.
[20] P. Lyon, The biogenic approach to cognition, Cognit. Process. 7 (2006) 11–29, https://doi.org/10.1007/s10339-005-0016-8.
[21] F. Baluška, M. Levin, On having No head: cognition throughout biological systems, Front. Psychol. 7 (2016) 902, https://doi.org/10.3389/fpsyg.2016.00902.
[22] B.J. Ford, Cellular intelligence: microphenomenology and the realities of being, Prog. Biophys. Mol. Biol. (2017), https://doi.org/10.1016/j.pbiomolbio.2017.08.012.
[23] K.L. Spalding, O. Bergmann, K. Alkass, S. Bernard, M. Salehpour, H.B. Huttner, E. Bostrom, I. Westerlund, C. Vial, B.A. Buchholz, G. Possnert, D.C. Mash, H. Druid, J. Frisen, Dynamics of hippocampal neurogenesis in adult humans, Cell 153 (2013) 1219–1227, https://doi.org/10.1016/j.cell.2013.05.002.
[24] P. Pietsch, Shufflebrain, Houghton Mifflin, Boston, 1981.
[25] P. Pietsch, C.W. Schneider, Brain transplantation in salamanders - an approach to memory transfer, Brain Res. 14 (1969) 707, https://doi.org/10.1016/0006-8993(69)90210-8.
[26] A. Bedecarrats, S. Chen, K. Pearce, D. Cai, D.L. Glanzman, RNA from trained Aplysia can induce an epigenetic engram for long-term sensitization in untrained Aplysia, eNeuro 5 (2018), https://doi.org/10.1523/ENEURO.0038-18.2018.
[27] H. Maldonado, A. Tablante, Behavioral transfer in praying mantis by injection of brain homogenate, Physiol. Behav. 16 (1976) 617–621.
[28] T. Saigusa, A. Tero, T. Nakagaki, Y. Kuramoto, Amoebae anticipate periodic events, Phys. Rev. Lett. 100 (2008), 018101.
[29] C.G. Langton, Artificial Life : an Overview, MIT Press, Cambridge, Mass, 1995.
[30] W.S. McCulloch, Embodiments of Mind, M.I.T. Press, Cambridge, Mass., 1988.
[31] R. Pfeifer, J. Bongard, S. Grand, How the Body Shapes the Way We Think : a New View of Intelligence, MIT Press, Cambridge, Mass, 2007.
[32] R. Pfeifer, M. Lungarella, F. Iida, Self-organization, embodiment, and biologically inspired robotics, Science 318 (2007) 1088–1093, https://doi.org/10.1126/science.1145803.
[33] T. Ziemke, What's that thing called embodiment? Avant 6 (2015) 161–174.
[34] I.D. Couzin, Collective cognition in animal groups, Trends Cognit. Sci. 13 (2009) 36–43, https://doi.org/10.1016/j.tics.2008.10.002. . S1364-6613(08)00252-0 [pii].
[35] I. Couzin, Collective minds, Nature 445 (2007) 715, 445715a [pii] 10.1038/445715a.
[36] T. Sakiyama, Y.P. Gunji, The kanizsa triangle illusion in foraging ants, Biosystems 142–143 (2016) 9–14, https://doi.org/10.1016/j.biosystems.2016.02.003.
[37] T. Sakiyama, Y.P. Gunji, The Muller-Lyer illusion in ant foraging, PLoS One 8 (2013), e81714, https://doi.org/10.1371/journal.pone.0081714.
[38] D.C. Dennett, Kinds of Minds : toward an Understanding of Consciousness, first ed., Basic Books, New York, 1996.
[39] I. Rahwan, M. Cebrian, N. Obradovich, J. Bongard, J.F. Bonnefon, C. Breazeal, J.W. Crandall, N.A. Christakis, I.D. Couzin, M.O. Jackson, N.R. Jennings, E. Kamar, I.M. Kloumann, H. Larochelle, D. Lazer, R. McElreath, A. Mislove, D.C. Parkes, A. Pentland, M.E. Roberts, A. Shariff, J.B. Tenenbaum, M. Wellman, Machine behaviour, Nature 568 (2019) 477–486, https://doi.org/10.1038/s41586-019-1138-y.
[40] G. Pezzulo, M. Levin, Re-membering the body: applications of computational neuroscience to the top-down control of regeneration of limbs and other complex organs, Integr. Biol. 7 (2015) 1487–1517, https://doi.org/10.1039/c5ib00221d.
[41] K. Haase, B.S. Freedman, Once upon a dish: engineering multicellular systems, Development vol. 147 (2020), https://doi.org/10.1242/dev.188573.
[42] M. Levin, A. Martinez Arias, Reverse-engineering growth and form in Heidelberg, Development vol. 146 (2019), https://doi.org/10.1242/dev.177261.
[43] F. Varenne, P. Chaigneau, J. Petitot, R. Doursat, Programming the emergence in morphogenetically architected complex systems, Acta Biotheor. 63 (2015) 295–308, https://doi.org/10.1007/s10441-015-9262-z.
[44] R. Doursat, C. Sanchez, Growing fine-grained multicellular robots, Soft Robot. 1 (2014) 110–121.
[45] J. Macia, B. Vidiella, R.V. Sole, Synthetic associative learning in engineered multicellular consortia, J. R. Soc. Interface 14 (2017), https://doi.org/10.1098/rsif.2017.0158.
[46] A. Urrios, J. Macia, R. Manzoni, N. Conde, A. Bonforti, E. de Nadal, F. Posas, R. Sole, A synthetic multicellular memory device, ACS Synth. Biol. 5 (2016) 862–873, https://doi.org/10.1021/acssynbio.5b00252.
[47] R. Sole, D.R. Amor, S. Duran-Nebreda, N. Conde-Pueyo, M. Carbonell-Ballestero, R. Montanez, Synthetic collective intelligence, Biosystems 148 (2016) 47–61, https://doi.org/10.1016/j.biosystems.2016.01.002.
[48] R.D. Kamm, R. Bashir, N. Arora, R.D. Dar, M.U. Gillette, L.G. Griffith, M.L. Kemp, K. Kinlaw, M. Levin, A.C. Martin, T.C. McDevitt, R.M. Nerem, M.J. Powers, T.A. Saif, J. Sharpe, S. Takayama, S. Takeuchi, R. Weiss, K.M. Ye, H.G. Yevick, M.H. Zaman, Perspective: the promise of multi-cellular engineered living systems, Apl. Bioeng. 2 (2018), https://doi.org/10.1063/1.5038337.
[49] R.D. Kamm, R. Bashir, Creating living cellular machines, Ann. Biomed. Eng. 42 (2014) 445–459, https://doi.org/10.1007/s10439-013-0902-7.
[50] B.A. Montgomery, Consciousness and Personhood in Split-Brain Patients, Dissertation, 2003.
[51] D.A. Parfit, Divided minds and the nature of persons, in: C. Blakemore, S.A. Greenfield (Eds.) Mindwaves, Blackwell1987.
[52] J. Perry, Can the self divide? J. Philos. 69 (1972) 463.
[53] D.J. Blackiston, M. Levin, Ectopic eyes outside the head in Xenopus tadpoles provide sensory data for light-mediated learning, J. Exp. Biol. 216 (2013) 1031–1040, https://doi.org/10.1242/jeb.074963.
[54] D.J. Blackiston, K. Vien, M. Levin, Serotonergic stimulation induces nerve growth and promotes visual learning via posterior eye grafts in a vertebrate model of induced sensory plasticity, npj Regen. Med, 2 (2017) 8, https://doi.org/10.1038/s41536-017-0012-5.
[55] D.J. Blackiston, G.M. Anderson, N. Rahman, C. Bieck, M. Levin, A novel method for inducing nerve growth via modulation of host resting potential: gap junction-mediated and serotonergic signaling mechanisms, Neurotherapeutics 12 (2015) 170–184, https://doi.org/10.1007/s13311-014-0317-7.
[56] P. Bach-y-Rita, C.C. Collins, F.A. Saunders, B. White, L. Scadden, Vision substitution by tactile image projection, Nature 221 (1969) 963–964.
[57] P. Bach-y-Rita, Sensory plasticity. Applications to a vision substitution system, Acta Neurol. Scand. 43 (1967) 417–426.
[58] Y. Danilov, M. Tyler, Brainport: an alternative input to the brain, J. Integr. Neurosci. 4 (2005) 537–550.
[59] T. Froese, M. McGann, W. Bigge, A. Spiers, A.K. Seth, The enactive torch: a new tool for the science of perception, Ieee T Haptics 5 (2012) 365–375, https://doi.org/10.1109/Toh.2011.57.
[60] T.B. DeMarse, K.P. Dockendorf, Adaptive flight control with living neuronal networks on microelectrode arrays, Ieee Ijcnn, 2005, pp. 1548–1551.
[61] A.L. Brueckner, Brains in a vat, J. Philos. 83 (1986) 148–167.
[62] E.M. Eisenstein, Aneural Organisms in Neurobiology, Plenum Press, New York, 1975.
[63] W.L. Lindsay, Mind in plants, J. Ment. Sci. 21 (1876) 513–532, https://doi.org/10.1192/bjp.21.96.513.
[64] J. Bose, Plant Response, Longmans, Green & Co, London, 1906.
[65] A. Damasio, G.B. Carvalho, The nature of feelings: evolutionary and neurobiological origins, Nat. Rev. Neurosci. 14 (2013) 143–152, https://doi.org/10.1038/nrn3403.
[66] M. Levin, The computational boundary of a "self": developmental bioelectricity drives multicellularity and scale-free cognition, Front. Psychol. 10 (2019), https://doi.org/10.3389/fpsyg.2019.02688.
[67] A.J. Trewavas, F. Baluska, The ubiquity of consciousness, EMBO Rep. 12 (2011) 1221–1225, https://doi.org/10.1038/embor.2011.218.
[68] F. Keijzer, M. van Duijn, P. Lyon, What nervous systems do: early evolution, input-output, and the skin brain thesis, Adapt. Behav. 21 (2013) 67–85, https://doi.org/10.1177/1059712312465330.
[69] P. Lyon, The cognitive cell: bacterial behavior reconsidered, Front. Microbiol. 6 (2015) 264, https://doi.org/10.3389/fmicb.2015.00264.
[70] C.Y. Yang, M. Bialecka-Fornal, C. Weatherwax, J.W. Larkin, A. Prindle, J. Liu, J. Garcia-Ojalvo, G.M. Suel, Encoding Membrane-Potential-Based Memory within a Microbial Community, Cell Syst. (2020), https://doi.org/10.1016/j.cels.2020.04.002.
[71] A. Prindle, J. Liu, M. Asally, S. Ly, J. Garcia-Ojalvo, G.M. Suel, Ion Channels Enable Electrical Communication in Bacterial Communities, Nature (2015), https://doi.org/10.1038/nature15709.
[72] J.P. Dexter, S. Prabakaran, J. Gunawardena, A complex hierarchy of avoidance behaviors in a single-cell eukaryote, Curr. Biol. 29 (2019) 4323–4329, https://doi.org/10.1016/j.cub.2019.10.059, e4322.
[73] M. Gagliano, C.I. Abramson, M. Depczynski, Plants learn and remember: lets get used to it, Oecologia 186 (2018) 29–31, https://doi.org/10.1007/s00442-017-4029-7.
[74] M. Gagliano, V.V. Vyazovskiy, A.A. Borbely, M. Grimonprez, M. Depczynski, Learning by association in plants, Sci. Rep. 6 (2016) 38427, https://doi.org/10.1038/srep38427.
[75] G. Nilsonne, A. Appelgren, J. Axelsson, M. Fredrikson, M. Lekander, Learning in a simple biological system: a pilot study of classical conditioning of human macrophages in vitro, Behav. Brain Funct. 7 (2011) 47, https://doi.org/10.1186/1744-9081-7-47.
[76] G. Balazsi, A. van Oudenaarden, J.J. Collins, Cellular decision making and biological noise: from microbes to mammals, Cell 144 (2011) 910–925, https://doi.org/10.1016/j.cell.2011.01.030. S0092-8674(11)00069-9 [pii].
[77] A. Linson, P. Calvo, Zoocentrism in the weeds? Cultivating plant models for cognitive yield, Biol. Philos. 35 (2020) 49, https://doi.org/10.1007/s10539-020-09766-y.
[78] C. Fields, J. Bischof, M. Levin, Morphological coordination: a common ancestral function unifying neural and non-neural signaling, Physiology 35 (2020) 16–30, https://doi.org/10.1152/physiol.00027.2019.
[79] M. Zoghi, Cardiac memory: do the heart and the brain remember the same? J. Intervent. Card Electrophysiol. 11 (2004) 177–182.
[80] C.H. Turner, A.G. Robling, R.L. Duncan, D.B. Burr, Do bone cells behave like a neuronal network? Calcif. Tissue Int. 70 (2002) 435–442.
[81] P. Goel, A. Mehta, Learning theories reveal loss of pancreatic electrical connectivity in diabetes as an adaptive response, PLoS One 8 (2013), e70366, https://doi.org/10.1371/journal.pone.0070366.
[82] Y. Katz, Embodying Probabilistic Inference in Biochemical Circuits, ArXiv,

2018.
[83] Y. Katz, M. Springer, Probabilistic adaptation in changing microbial environments, PeerJ. 4 (2016), e2716, https://doi.org/10.7717/peerj.2716.
[84] M. Emmons-Bell, F. Durant, A. Tung, A. Pietak, K. Miller, A. Kane, C.J. Martyniuk, D. Davidian, J. Morokuma, M. Levin, Regenerative Adaptation to Electrochemical Perturbation in Planaria: A Molecular Analysis of Physiological Plasticity, 2019, https://doi.org/10.1016/j.isci.2019.11.014 iScience in press.
[85] S. Stern, T. Dror, E. Stolovicki, N. Brenner, E. Braun, Genome-wide transcriptional plasticity underlies cellular adaptation to novel challenge, Mol. Syst. Biol. 3 (2007) 106, https://doi.org/10.1038/msb4100147.
[86] E. Ben-Jacob, Bacterial self-organization: co-enhancement of complexification and adaptability in a dynamic environment, Philos Trans A Math Phys Eng Sci 361 (2003) 1283–1312, https://doi.org/10.1098/rsta.2003.1199.
[87] E. Ben-Jacob, Bacterial wisdom, Godel's theorem and creative genomic webs, Physica A 248 (1998) 57–76, https://doi.org/10.1016/S0378-4371(97)00529-3.
[88] Y. Soen, M. Knafo, M. Elgart, A principle of organization which facilitates broad Lamarckian-like adaptations by improvisation, Biol. Direct 10 (2015) 68, https://doi.org/10.1186/s13062-015-0097-y.
[89] M. Elgart, O. Snir, Y. Soen, Stress-mediated tuning of developmental robustness and plasticity in flies, Biochim. Biophys. Acta 1849 (2015) 462–466, https://doi.org/10.1016/j.bbagrm.2014.08.004.
[90] S. Manicka, M. Levin, Modeling somatic computation with non-neural bioelectric networks, Sci. Rep. 9 (2019) 18612, https://doi.org/10.1038/s41598-019-54859-8.
[91] S. Manicka, M. Levin, The Cognitive Lens: a primer on conceptual tools for analysing information processing in developmental and regenerative morphogenesis, Philos. Trans. R. Soc. Lond. B Biol. Sci. 374 (2019) 20180369, https://doi.org/10.1098/rstb.2018.0369.
[92] I. Bose, R. Karmakar, Simple models of plant learning and memory, Phys. Scripta T106 (2003) 9–12, https://doi.org/10.1238/Physica.Topical.106a00009.
[93] G.W. Bassel, Information processing and distributed computation in plant organs, Trends Plant Sci. (2018), https://doi.org/10.1016/j.tplants.2018.08.006.
[94] J. Lorber, Is your brain really necessary? Nurs. Mirror 152 (1981) 29–30.
[95] J. Lorber, Is your brain really necessary, Arch. Dis. Child. 53 (1978), 834-834.
[96] T. Campbell, J. McMahan, Animalism and the varieties of conjoined twinning, Theor. Med. Bioeth. 31 (2010) 285–301, https://doi.org/10.1007/s11017-010-9150-0.
[97] Y.M. Barilan, One or two: an examination of the recent case of the conjoined twins from Malta, J. Med. Philos. 28 (2003) 27–44, https://doi.org/10.1076/jmep.28.1.27.14176.
[98] A. Boussard, J. Delescluse, A. Perez-Escudero, A. Dussutour, Memory inception and preservation in slime moulds: the quest for a common mechanism, Philos. Trans. R. Soc. Lond. B Biol. Sci. 374 (2019) 20180368, https://doi.org/10.1098/rstb.2018.0368.
[99] A. Mitchell, G.H. Romano, B. Groisman, A. Yona, E. Dekel, M. Kupiec, O. Dahan, Y. Pilpel, Adaptive prediction of environmental changes by microorganisms, Nature 460 (2009) 220–224, https://doi.org/10.1038/nature08112.
[100] P. Brugger, E. Macas, J. Ihlemann, Do sperm cells remember? Behav. Brain Res. 136 (2002) 325–328.
[101] F. di Primio, B.S. Muller, J.W. Lengeler, Minimal cognition in unicellular organisms, in: Jean-Arcady Meyer, Alain Berthoz, Dario Floreano, in: Herbert L. Roitblat, S.W. Wilson (Eds.), SAB2000 Sixth International Conference on Simulation of Adaptive Behavior : FROM ANIMALS TO ANIMATS, 2000.
[102] P.G. Hepper, B. Waldman, Embryonic olfactory learning in frogs, Q. J. Exp. Psychol. B 44 (1992) 179–197.
[103] B.G. Dias, K.J. Ressler, Parental olfactory experience influences behavior and neural structure in subsequent generations, Nat. Neurosci. 17 (2014) 89–96, https://doi.org/10.1038/nn.3594.
[104] W.S. Mcculloch, Why the mind is in the head?, in: L.A. Jeffress (Ed.) Cerebral Mechanisms in Behavior: the Hixon Symposium1951, pp. 42–81.
[105] W.S. Mcculloch, A heterarchy of values determined by the topology of nervous nets, Bull. Math. Biophys. 7 (1945) 89–93.
[106] R.Y. Choi, A.S. Coyner, J. Kalpathy-Cramer, M.F. Chiang, J.P. Campbell, Introduction to machine learning, neural networks, and deep learning, Transl Vis Sci Technol 9 (2020) 14, https://doi.org/10.1167/tvst.9.2.14.
[107] W.C. Abraham, O.D. Jones, D.L. Glanzman, Is plasticity of synapses the mechanism of long-term memory storage? NPJ Sci Learn 4 (2019) 9, https://doi.org/10.1038/s41539-019-0048-y.
[108] F. Johansson, D.A. Jirenhed, A. Rasmussen, R. Zucca, G. Hesslow, Memory trace and timing mechanism localized to cerebellar Purkinje cells, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) 14930–14934, https://doi.org/10.1073/pnas.1415371111.
[109] F. Johansson, H.A. Carlsson, A. Rasmussen, C.H. Yeo, G. Hesslow, Activation of a temporal memory in purkinje cells by the mGluR7 receptor, Cell Rep. 13 (2015) 1741–1746, https://doi.org/10.1016/j.celrep.2015.10.047.
[110] D. Blackiston, T. Shomrat, M. Levin, The stability of memories during brain remodeling: a perspective, Commun. Integr. Biol. 8 (2015), e1073424, https://doi.org/10.1080/19420889.2015.1073424.
[111] D.J. Blackiston, E. Silva Casey, M.R. Weiss, Retention of memory through metamorphosis: can a moth remember what it learned as a caterpillar? PLoS One 3 (2008), e1736 https://doi.org/10.1371/journal.pone.0001736.
[112] T. Tully, V. Cambiazo, L. Kruse, Memory through metamorphosis in normal and mutant Drosophila, J. Neurosci. 14 (1994) 68–74.
[113] C.M. Goldsmith, H.R. Hepburn, D. Mitchell, Retention of an associative learning-task after metamorphosis in locusta-migratoria-migratorioides, J. Insect Physiol. 24 (1978) 737–741.
[114] R.R. Miller, A.M. Berk, Retention over metamorphosis in the African clawtoed frog, J. Exp. Psychol. Anim. Behav. Process. 3 (1977) 343–356.
[115] T.M. Alloway, Retention of learning through metamorphosis in grain beetle (Tenebrio-Molitor), Am. Zool. 12 (1972) 471–472.
[116] J.V. McConnell, J.M. Shelby, Memory transfer experiments in invertebrates, in: G. Ungar (Ed.), Molecular Mechanisms in Memory and Learning, Plenum Press, New York, 1970, pp. 71–101.
[117] R. Thompson, J.V. McConnell, Classical conditioning in the planarian Dugesia dorotocephala, J. Comp. Physiol. Psychol. 48 (1955) 65–68.
[118] J. Best, I. Rubenstein, Maze leaning and associated behavior in Planaria, J. Comp. Physiol. Psychol. (1962) 560–566.
[119] J.B. Best, Behaviour of planaria in instrumental learning paradigms, Ani. Behav. Supplement 13 (Suppl. 1) (1965) 69–75.
[120] T. Shomrat, M. Levin, An automated training paradigm reveals long-term memory in planarians and its persistence through head regeneration, J. Exp. Biol. 216 (2013) 3799–3810, https://doi.org/10.1242/jeb.087809.
[121] G. Ungar, Chemical transfer of learning - its stimulus specificity, Fed. Proc. 25 (1966) 207.
[122] G. Ungar, L.N. Irwin, Transfer of acquired information by brain extracts, Nature 214 (1967) 453.
[123] R. Bisping, U. Oehlert, H. Reinauer, N. Longo, Negative and positive memory transfer through rna in instrumentally conditioned goldfish, Stud. Psychol. 13 (1971) 181–190.
[124] W.L. Byrne, D. Samuel, E.L. Bennett, M.R. Rosenzweig, E. Wasserman, A.R. Wagner, F. Gardner, R. Galambos, B.D. Berger, D.L. Margules, R.L. Fenichel, L. Stein, J.A. Corson, H.E. Enesco, S.L. Chorover, C.E. Holt, P.H. Schiller, L. Chiappet, M.E. Jarvik, R.C. Leaf, J.D. Dutcher, Z.P. Horovitz, P.L. Carlson, Memory transfer, Science 153 (1966) 658, https://doi.org/10.1126/science.153.3736.658.
[125] L. Carrier, Memory transfer in planaria, Ohio J. Sci. 79 (1979), 80-80.
[126] G.L. Holt, G. Bentz, Interanimal memory transfer of a barpress response through brain and liver rna injections, Bull. Psychonomic Soc. 21 (1983) 51–53.
[127] B.E. Miller, G.L. Holt, Memory transfer in rats by injection of brain and liver rna, J. Biol. Psychol. 19 (1977) 4–9.
[128] P.O. Peretti, H.G. Wakeley, Memory transfer in meal-worms, Psychonomic Sci. 15 (1969) 33, https://doi.org/10.3758/Bf03336182.
[129] P. Pietsch, C.W. Schneider, Brain transplantation in salamanders - an approach to memory transfer, Brain Res. 14 (1969) 707–715.
[130] X. Liu, S. Ramirez, S. Tonegawa, Inception of a false memory by optogenetic manipulation of a hippocampal memory engram, Philos. Trans. R. Soc. Lond. B Biol. Sci. 369 (2014) 20130142, https://doi.org/10.1098/rstb.2013.0142.
[131] S. Ramirez, X. Liu, P.A. Lin, J. Suh, M. Pignatelli, R.L. Redondo, T.J. Ryan, S. Tonegawa, Creating a false memory in the hippocampus, Science 341 (2013) 387–391, https://doi.org/10.1126/science.1239073.
[132] K. Ameriks, Personal identity and memory transfer, South. J. Philos. 14 (1976) 385–391, https://doi.org/10.1111/j.2041-6962.1976.tb01295.x.
[133] J. Vallverdu, O. Castro, R. Mayne, M. Talanov, M. Levin, F. Baluska, Y. Gunji, A. Dussutour, H. Zenil, A. Adamatzky, Slime mould: the fundamental mechanisms of biological cognition, Biosystems 165 (2018) 57–70, https://doi.org/10.1016/j.biosystems.2017.12.011.
[134] M. Beekman, T. Latty, Brainless but multi-headed: decision making by the acellular slime mould physarum polycephalum, J. Mol. Biol. 427 (2015) 3734–3743, https://doi.org/10.1016/j.jmb.2015.07.007.
[135] D. Vogel, A. Dussutour, Direct transfer of learned behaviour via cell fusion in non-neural organisms, Proc. Biol. Sci. 283 (2016), https://doi.org/10.1098/rspb.2016.2382.
[136] S. Braude, First Person Plural: Multiple Personality and the Philosophy of Mind, Rowman & Littlefield Publishers, Lanham, Md, 1995.
[137] A. Clark, D. Chalmers, The extended mind, Analysis 58 (1998) 7–19.
[138] R.A. Watson, C.L. Buckley, R. Mills, A. Davies, Associative Memory in Gene Regulation Networks, Artificial Life Conference XIIOdense, Denmark, 2010, pp. 194–201.
[139] N.R. Smalheiser, H. Manev, E. Costa, RNAi and brain function: was McConnell on the right track? Trends Neurosci. 24 (2001) 216–218. S0166-2236(00)01739-2 [pii].
[140] B. Setlow, Georges Ungar and memory transfer, J. Hist. Neurosci. 6 (1997) 181–192, https://doi.org/10.1080/09647049709525701.
[141] L.T. Smith, The interanimal transfer phenomenon: a review, Psychol. Bull. 81 (1974) 1078–1095.
[142] K.A. Wilmes, C. Clopath, Stability by Gating Plasticity in Recurrent Neural Networks, bioRxiv vol. 2020 (2020), https://doi.org/10.1101/2020.09.10.291120, 2009.2010.291120.
[143] J.E. Strassmann, D.C. Queller, The social organism: congresses, parties, and committees, Evolution 64 (2010) 605–616, https://doi.org/10.1111/j.1558-5646.2009.00929.x.
[144] V.O. Martinez, F.W. de Mendonca Lima, C.F. de Carvalho, J.A. Menezes-Filho, Toxoplasma gondii infection and behavioral outcomes in humans: a systematic review, Parasitol. Res. 117 (2018) 3059–3065, https://doi.org/10.1007/s00436-018-6040-2.
[145] G.L. Davidson, A.C. Cooke, C.N. Johnson, J.L. Quinn, The gut microbiome as a

driver of individual variation in cognition and functional behaviour, Philos. Trans. R. Soc. Lond. B Biol. Sci. 373 (2018), https://doi.org/10.1098/rstb.2017.0286.
[146] O. Nishimura, K. Hosoda, E. Kawaguchi, S. Yazawa, T. Hayashi, T. Inoue, Y. Umesono, K. Agata, Unusually large number of mutations in asexually reproducing clonal planarian dugesia japonica, PLoS One 10 (2015), e0143525, https://doi.org/10.1371/journal.pone.0143525.
[147] R.A. Firtel, Interacting signaling pathways controlling multicellular development in Dictyostelium, Curr. Opin. Genet. Dev. 6 (1996) 545–554, https://doi.org/10.1016/s0959-437x(96)80082-7.
[148] C. Tian, L. Liu, X. Ye, H. Fu, X. Sheng, L. Wang, H. Wang, D. Heng, L. Liu, Functional oocytes derived from granulosa cells, Cell Rep. 29 (2019) 4256–4267, https://doi.org/10.1016/j.celrep.2019.11.080, e4259.
[149] K. Hayashi, O. Hikabe, Y. Obata, Y. Hirao, Reconstitution of mouse oogenesis in a dish from pluripotent stem cells, Nat. Protoc. 12 (2017) 1733–1744, https://doi.org/10.1038/nprot.2017.070.
[150] O. Hikabe, N. Hamazaki, G. Nagamatsu, Y. Obata, Y. Hirao, N. Hamada, S. Shimamoto, T. Imamura, K. Nakashima, M. Saitou, K. Hayashi, Reconstitution in vitro of the entire cycle of the mouse female germ line, Nature 539 (2016) 299–303, https://doi.org/10.1038/nature20104.
[151] T. Russell, T. Madsen, F. Thomas, N. Raven, R. Hamede, B. Ujvari, Oncogenesis as a selective force: adaptive evolution in the face of a transmissible cancer, Bioessays 40 (2018), https://doi.org/10.1002/bies.201700146.
[152] B. Ujvari, A.T. Papenfuss, K. Belov, Transmissible cancers in an evolutionary context, Bioessays 38 (Suppl 1) (2016) S14–S23, https://doi.org/10.1002/bies.201670904.
[153] G. Pezzulo, M. Levin, Top-down models in biology: explanation and control of complex living systems above the molecular level, J. R. Soc. Interface 13 (2016), https://doi.org/10.1098/rsif.2016.0555.
[154] K.D. Birnbaum, A.S. Alvarado, Slicing across kingdoms: regeneration in plants and animals, Cell 132 (2008) 697–710.
[155] K. Pinet, K.A. McLaughlin, Mechanisms of physiological tissue remodeling in animals: manipulating tissue, organ, and organism morphology, Dev. Biol. (2019), https://doi.org/10.1016/j.ydbio.2019.04.001.
[156] A. Voskoboynik, N. Simon-Blecher, Y. Soen, B. Rinkevich, A.W. De Tomaso, K.J. Ishizuka, I.L. Weissman, Striving for normality: whole body regeneration through a series of abnormal generations, Faseb. J. 21 (2007) 1335–1344, fj.06-7337com [pii.
[157] L.N. Vandenberg, D.S. Adams, M. Levin, Normalized shape and location of perturbed craniofacial structures in the Xenopus tadpole reveal an innate ability to achieve correct morphology, Dev. Dynam. 241 (2012) 863–878, https://doi.org/10.1002/dvdy.23770.
[158] K. Pinet, M. Deolankar, B. Leung, K.A. McLaughlin, Adaptive Correction of Craniofacial Defects in Pre-metamorphic Xenopus laevis Tadpoles Involves Thyroid Hormone-independent Tissue Remodeling, Development vol. 146 (2019), https://doi.org/10.1242/dev.175893.
[159] G. Fankhauser, Maintenance of normal structure in heteroploid salamander larvae, through compensation of changes in cell size by adjustment of cell number and cell shape, J. Exp. Zool. 100 (1945) 445–455, https://doi.org/10.1002/jez.1401000310.
[160] P. Fontes, J. Komori, R. Lopez, W. Marsh, E. Lagasse, Development of ectopic livers by hepatocyte transplantation into swine lymph nodes, Liver Transplant. (2020), https://doi.org/10.1002/lt.25872.
[161] E.J. Slijper, Biologic anatomical investigations on the bipedal gait and upright posture in mammals - with special reference to a little goat born without forelegs II, Proc. K. Ned. Akad. Wet. 45 (1942) 407–415.
[162] C.L. Yntema, Blastema formation in sparsely innervated and aneurogenic forelimbs of amblystoma larvae, J. Exp. Zool. 142 (1959) 423–439.
[163] I. Slavkov, D. Carrillo-Zapata, N. Carranza, X. Diego, F. Jansson, J. Kaandorp, S. Hauert, J. Sharpe, Morphogenesis in robot swarms, Sci Robot 3 (2018), https://doi.org/10.1126/scirobotics.aau9178. ARTN eaau9178.
[164] C. Fields, M. Levin, Multiscale Memory and Bioelectric Error Correction in the Cytoplasm–Cytoskeleton-Membrane System, Wiley Interdisciplinary Reviews: Systems Biology and Medicine, 2017, p. e1410, https://doi.org/10.1002/wsbm.1410.
[165] A. Livshits, L. Shani-Zerbib, Y. Maroudas-Sacks, E. Braun, K. Keren, Structural inheritance of the actin cytoskeletal organization determines the body Axis in regenerating Hydra, Cell Rep. 18 (2017) 1410–1421, https://doi.org/10.1016/j.celrep.2017.01.036.
[166] K.G. Sullivan, M. Emmons-Bell, M. Levin, Physiological inputs regulate species-specific anatomy during embryogenesis and regeneration, Commun. Integr. Biol. 9 (2016), e1192733, https://doi.org/10.1080/19420889.2016.1192733.
[167] K. Williams, J. Bischof, F. Lee, K. Miller, J. LaPalme, B. Wolfe, M. Levin, Regulation of axial and head patterning during planarian regeneration by a commensal bacterium, Mech. Dev. (2020) 103614, https://doi.org/10.1016/j.mod.2020.103614.
[168] J.B. Benoit, A. Vigneron, N.A. Broderick, Y. Wu, J.S. Sun, J.R. Carlson, S. Aksoy, B.L. Weiss, Symbiont-induced odorant binding proteins mediate insect host hematopoiesis, Elife 6 (2017), https://doi.org/10.7554/eLife.19535.
[169] D. Osman, N. Buchon, S. Chakrabarti, Y.T. Huang, W.C. Su, M. Poidevin, Y.C. Tsai, B. Lemaitre, Autocrine and paracrine unpaired signaling regulate intestinal stem cell maintenance and division, J. Cell Sci. 125 (2012) 5944–5949, https://doi.org/10.1242/jcs.113100.
[170] C.A. Mangold, M.J. Ishler, R.G. Loreto, M.L. Hazen, D.P. Hughes, Zombie ant death grip due to hypercontracted mandibular muscles, J. Exp. Biol. 222 (2019), https://doi.org/10.1242/jeb.200683.
[171] R.G. Loreto, D.P. Hughes, The metabolic alteration and apparent preservation of the zombie ant brain, J. Insect Physiol. 118 (2019) 103918, https://doi.org/10.1016/j.jinsphys.2019.103918.
[172] D.P. Hughes, J.P. Araujo, R.G. Loreto, L. Quevillon, C. de Bekker, H.C. Evans, From so simple a beginning: the evolution of behavioral manipulation by fungi, Adv. Genet. 94 (2016) 437–469, https://doi.org/10.1016/bs.adgen.2016.01.004.
[173] R.C. da Silva, H. Langoni, Toxoplasma gondii: host-parasite interaction and behavior manipulation, Parasitol. Res. 105 (2009) 893–898, https://doi.org/10.1007/s00436-009-1526-6.
[174] O.A. Pilling, A.J. Rogers, B. Gulla-Devaney, L.A. Katz, Insights into trans-generational epigenetics from studies of ciliates, Eur. J. Protistol. (2017), https://doi.org/10.1016/j.ejop.2017.05.004.
[175] J. Beisson, T.M. Sonneborn, Cytoplasmic inheritance of the organization of the cell cortex in paramecium aurelia, Proc. Natl. Acad. Sci. U. S. A. 53 (1965) 275–282.
[176] M. Levin, A.M. Pietak, J. Bischof, Planarian regeneration as a model of anatomical homeostasis: recent progress in biophysical and computational approaches, Semin. Cell Dev. Biol. (2018), https://doi.org/10.1016/j.semcdb.2018.04.003.
[177] F. Durant, J. Bischof, C. Fields, J. Morokuma, J. LaPalme, A. Hoi, M. Levin, The role of early bioelectric signals in the regeneration of planarian anterior/posterior polarity, Biophys. J. 116 (2019) 948–961, https://doi.org/10.1016/j.bpj.2019.01.029.
[178] N.J. Oviedo, J. Morokuma, P. Walentek, I.P. Kema, M.B. Gu, J.M. Ahn, J.S. Hwang, T. Gojobori, M. Levin, Long-range neural and gap junction protein-mediated cues control polarity during planarian regeneration, Dev. Biol. 339 (2010) 188–199, https://doi.org/10.1016/j.ydbio.2009.12.012. S0012-1606(09)01402-X [pii].
[179] F. Durant, J. Morokuma, C. Fields, K. Williams, D.S. Adams, M. Levin, Long-term, stochastic editing of regenerative anatomy via targeting endogenous bioelectric gradients, Biophys. J. 112 (2017) 2231–2243, https://doi.org/10.1016/j.bpj.2017.04.011.
[180] J.X. Zhou, L. Cisneros, T. Knijnenburg, K. Trachana, P. Davies, S. Huang, Phylostratigraphic analysis of tumor and developmental transcriptomes reveals relationship between oncogenesis, phylogenesis and ontogenesis, Convergent Science Physical Oncology 4 (2018), https://doi.org/10.1088/2057-1739/aab1b0. UNSP 025002.
[181] P.C.W. Davies, C.H. Lineweaver, Cancer tumors as Metazoa 1.0: tapping genes of ancient ancestors, Phys. Biol. 8 (2011), https://doi.org/10.1088/1478-3975/8/1/015001. Artn 015001.
[182] B. Chernet, M. Levin, Endogenous voltage potentials and the microenvironment: bioelectric signals that reveal, induce and normalize cancer, J Clin Exp Oncol Suppl 1 (2013), https://doi.org/10.4172/2324-9110.S1-002.
[183] D. Moore, S.I. Walker, M. Levin, Cancer as a disorder of patterning information: computational and biophysical perspectives on the cancer problem, Convergent Sci. Phys. Oncol. 3 (2017), 043001.
[184] B. Mintz, K. Illmensee, Normal genetically mosaic mice produced from malignant teratocarcinoma cells, Proc. Natl. Acad. Sci. U. S. A. 72 (1975) 3585–3589.
[185] M.J. Hendrix, E.A. Seftor, R.E. Seftor, J. Kasemeier-Kulesa, P.M. Kulesa, L.M. Postovit, Reprogramming metastatic tumour cells with embryonic microenvironments, Nat. Rev. Canc. 7 (2007) 246–255.
[186] B.T. Chernet, M. Levin, Transmembrane voltage potential of somatic cells controls oncogene-mediated tumorigenesis at long-range, Oncotarget 5 (2014) 3287–3306.
[187] B.T. Chernet, M. Levin, Transmembrane voltage potential is an essential cellular parameter for the detection and control of tumor development in a Xenopus model, Dis. Mod. Mech. 6 (2013) 595–607, https://doi.org/10.1242/dmm.010835.
[188] J.S. Turner, Termites as models of swarm cognition, Swarm Intell-Us 5 (2011) 19–43, https://doi.org/10.1007/s11721-010-0049-1.
[189] W. Roux, Der Kampf der Theile im Organismus, W. Engelmann, Leipzig, Germany., 1881.
[190] M. Miyamoto, M. Hattori, K. Hosoda, M. Sawamoto, M. Motoishi, T. Hayashi, T. Inoue, Y. Umesono, The pharyngeal nervous system orchestrates feeding behavior in planarians, Sci Adv 6 (2020), eaaz0882, https://doi.org/10.1126/sciadv.aaz0882.
[191] G.M. Edelman, Neural Darwinism: selection and reentrant signaling in higher brain function, Neuron 10 (1993) 115–125.
[192] A. Livnat, N. Pippenger, An optimal brain can be composed of conflicting agents, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 3198–3202, https://doi.org/10.1073/pnas.0510932103.
[193] P.Y. Lwigale, R.A. Schneider, Other chimeras: quail-duck and mouse-chick, Methods Cell Biol. 87 (2008) 59–74, https://doi.org/10.1016/S0091-679X(08)00203-3.
[194] F. Suchy, H. Nakauchi, Interspecies chimeras, Curr. Opin. Genet. Dev. 52 (2018) 36–41, https://doi.org/10.1016/j.gde.2018.05.007.
[195] L.I. Korochkin, [New approaches in developmental genetics and gene therapy: xenotransplantation of Drosophila embryonic nerve cells into the brain of vertebrate animals], Genetika 36 (2000) 1436–1442.
[196] H.T. Greely, M.K. Cho, The Henrietta Lacks legacy grows, EMBO Rep. 14 (2013) 849, https://doi.org/10.1038/embor.2013.148.

[197] F. Baluska, K. Yokawa, S. Mancuso, K. Baverstock, Understanding of anesthesia - why consciousness is essential for life and not based on genes, Commun. Integr. Biol. 9 (2016), e1238118, https://doi.org/10.1080/19420889.2016.1238118.
[198] A. Gremiaux, K. Yokawa, S. Mancuso, F. Baluska, Plant anesthesia supports similarities between animals and plants: claude Bernard's forgotten studies, Plant Signal. Behav. 9 (2014).
[199] M.B. Kelz, P.S. Garcia, G.A. Mashour, K. Solt, Escape from oblivion: neural mechanisms of emergence from general anesthesia, Anesth. Analg. 128 (2019) 726–736, https://doi.org/10.1213/ANE.0000000000004006.
[200] V.C. Muller, M. Hoffmann, What is morphological computation? On how the body contributes to cognition and control, Artif. Life 23 (2017) 1–24, https://doi.org/10.1162/ARTL_a_00219.
[201] F. Corucci, N. Cheney, H. Lipson, C. Laschi, J.C. Bongard, Material properties affect evolution's ability to exploit morphological computation in growing soft-bodied creatures, in: The Fifteenth International Conference on the Synthesis and Simulation of Living Systems, ALIFE XV), 2015.
[202] R. Pfeifer, F. Iida, M. Lungarella, Cognition from the bottom up: on biological inspiration, body morphology, and soft materials, Trends Cognit. Sci. 18 (2014) 404–413, https://doi.org/10.1016/j.tics.2014.04.004.
[203] R. Pfeifer, G. Gomez, Morphological computation - connecting brain, body, and environment, creating brain-like intelligence: from basic principles to complex, Intelligent Systems 5436 (2009) 66–83.
[204] J. Bongard, Morphological change in machines accelerates the evolution of robust behavior, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 1234–1239, https://doi.org/10.1073/pnas.1015390108.
[205] V. Chan, K. Park, M.B. Collens, H. Kong, T.A. Saif, R. Bashir, Development of miniaturized walking biological machines, Sci. Rep. 2 (2012) 857, https://doi.org/10.1038/srep00857.
[206] S.J. Park, M. Gazzola, K.S. Park, S. Park, V. Di Santo, E.L. Blevins, J.U. Lind, P.H. Campbell, S. Dauth, A.K. Capulli, F.S. Pasqualini, S. Ahn, A. Cho, H. Yuan, B.M. Maoz, R. Vijaykumar, J.W. Choi, K. Deisseroth, G.V. Lauder, L. Mahadevan, K.K. Parker, Phototactic guidance of a tissue-engineered soft-robotic ray, Science 353 (2016) 158–162, https://doi.org/10.1126/science.aaf4292.
[207] S. Kriegman, D. Blackiston, M. Levin, J. Bongard, A scalable pipeline for designing reconfigurable organisms, Proc. Natl. Acad. Sci. U. S. A. 117 (2020) 1853–1859, https://doi.org/10.1073/pnas.1910837117.
[208] F. Varenne, P. Chaigneau, J. Petitot, R. Doursat, Programming the emergence in morphogenetically architected complex systems, Acta Biotheor. 63 (2015) 295–308.
[209] J.A. Arias Del Angel, V. Nanjundiah, M. Benítez, S.A. Newman, Interplay of mesoscale physics and agent-like behaviors in the parallel evolution of aggregative multicellularity, EvoDevo 11 (2020) 21, https://doi.org/10.1186/s13227-020-00165-8.
[210] J. Bongard, V. Zykov, H. Lipson, Resilient machines through continuous self-modeling, Science 314 (2006) 1118–1121, https://doi.org/10.1126/science.1133687.
[211] G. Pezzulo, F. Rigoli, K. Friston, Active Inference, homeostatic regulation and adaptive behavioural control, Prog. Neurobiol. (2015), https://doi.org/10.1016/j.pneurobio.2015.09.001.
[212] K. Friston, B. Sengupta, G. Auletta, Cognitive dynamics: from attractors to active inference, Proc. IEEE 102 (2014) 427–445, https://doi.org/10.1109/Jproc.2014.2306251.
[213] K. Friston, M. Levin, B. Sengupta, G. Pezzulo, Knowing one's place: a free-energy approach to pattern regulation, J. R. Soc. Interface 12 (2015), https://doi.org/10.1098/rsif.2014.1383.
[214] F. Kuchling, K. Friston, G. Georgiev, M. Levin, Morphogenesis as Bayesian inference: a variational approach to pattern formation and control in complex biological systems, Phys. Life Rev. 33 (2020) 88–108, https://doi.org/10.1016/j.plrev.2019.06.001.
[215] M. Bonzanni, N. Rouleau, M. Levin, D.L. Kaplan, Optogenetically induced cellular habituation in non-neuronal cells, PLoS One 15 (2020), e0227230, https://doi.org/10.1371/journal.pone.0227230.
[216] M. Bonzanni, N. Rouleau, M. Levin, D.L. Kaplan, On the generalization of habituation: how discrete biological systems respond to repetitive stimuli: a novel model of habituation that is independent of any biological system, Bioessays 41 (2019), e1900028, https://doi.org/10.1002/bies.201900028.
[217] B.D. Reger, K.M. Fleming, V. Sanguineti, S. Alford, F.A. Mussa-Ivaldi, Connecting brains to robots: an artificial body for studying the computational properties of neural tissues, Artif. Life 6 (2000) 307–324.
[218] S. Tsuda, S. Artmann, K.-P. Zauner, The phi-bot: a robot controlled by a slime mould, in: A. Adamatzky, M. Komosinski (Eds.) Artificial Life Models in Hardware, Springer London2009, pp. 213-232.
[219] F. Keijzer, Moving and sensing without input and output: early nervous systems and the origins of the animal sensorimotor organization, Biol. Philos. 30 (2015) 311–331, https://doi.org/10.1007/s10539-015-9483-1.
[220] G. Jekely, F. Keijzer, P. Godfrey-Smith, An option space for early neural evolution, Philos. Trans. R. Soc. Lond. B Biol. Sci. 370 (2015), https://doi.org/10.1098/rstb.2015.0181.
[221] J.S. Torday, W.B. Miller Jr., On the evolution of the mammalian brain, Front. Syst. Neurosci. 10 (2016) 31, https://doi.org/10.3389/fnsys.2016.00031.
[222] V.P. Pai, S. Aw, T. Shomrat, J.M. Lemire, M. Levin, Transmembrane voltage potential controls embryonic eye patterning in Xenopus laevis, Development 139 (2012) 313–323, https://doi.org/10.1242/dev.073759.
[223] M. Levin, C.J. Martyniuk, The bioelectric code: an ancient computational medium for dynamic control of growth and form, Biosystems 164 (2018) 76–93, https://doi.org/10.1016/j.biosystems.2017.08.009.
[224] A. Pietak, M. Levin, Bioelectrical control of positional information in development and regeneration: a review of conceptual and computational advances, Prog. Biophys. Mol. Biol. 137 (2018) 52–68, https://doi.org/10.1016/j.pbiomolbio.2018.03.008.
[225] B.T. Chernet, D.S. Adams, M. Lobikin, M. Levin, Use of genetically encoded, light-gated ion translocators to control tumorigenesis, Oncotarget 7 (2016) 19575–19588, https://doi.org/10.18632/oncotarget.8036.
[226] D.S. Adams, J.M. Lemire, R.H. Kramer, M. Levin, Optogenetics in Developmental Biology: using light to control ion flux-dependent signals in Xenopus embryos, Int. J. Dev. Biol. 58 (2014) 851–861, https://doi.org/10.1387/ijdb.140207ml.
[227] M. Levin, G.A. Buznikov, J.M. Lauder, Of minds and embryos: left-right asymmetry and the serotonergic controls of pre-neural morphogenesis, Dev. Neurosci. 28 (2006) 171–185.
[228] J.M. Lauder, Neurotransmitters as growth regulatory signals: role of receptors and second messengers, Trends Neurosci. 16 (1993) 233–240, https://doi.org/10.1016/0166-2236(93)90162-f.
[229] E. Ralston, S. Beushausen, T. Ploug, Expression of the synaptic vesicle proteins VAMPs/synaptobrevins 1 and 2 in non-neural tissues, J. Biol. Chem. 269 (1994) 15403–15406.
[230] I. Wessler, H. Kilbinger, F. Bittinger, R. Unger, C.J. Kirkpatrick, The non-neuronal cholinergic system in humans: expression, function and pathophysiology, Life Sci. 72 (2003) 2055–2061, https://doi.org/10.1016/s0024-3205(03)00083-3.
[231] M. Emmons-Bell, F. Durant, J. Hammelman, N. Bessonov, V. Volpert, J. Morokuma, K. Pinet, D.S. Adams, A. Pietak, D. Lobo, M. Levin, Gap junctional blockade stochastically induces different species-specific head anatomies in genetically wild-type girardia dorotocephala flatworms, Int. J. Mol. Sci. 16 (2015) 27865–27896, https://doi.org/10.3390/ijms161126065.
[232] K. Wentlandt, M. Samoilova, P.L. Carlen, H. El Beheiry, General anesthetics inhibit gap junction communication in cultured organotypic hippocampal slices, Anesth. Analg. 102 (2006) 1692–1698, https://doi.org/10.1213/01.ane.0000202472.41103.78.
[233] D.S. He, J.M. Burt, Mechanism and selectivity of the effects of halothane on gap junction channel function, Circ. Res. 86 (2000) E104–E109.
[234] J.W. Larkin, X. Zhai, K. Kikuchi, S.E. Redford, A. Prindle, J. Liu, S. Greenfield, A.M. Walczak, J. Garcia-Ojalvo, A. Mugler, G.M. Suel, Signal Percolation within a Bacterial Community, Cell Syst. (2018), https://doi.org/10.1016/j.cels.2018.06.005.
[235] J. Liu, R. Martinez-Corral, A. Prindle, D.D. Lee, J. Larkin, M. Gabalda-Sagarra, J. Garcia-Ojalvo, G.M. Suel, Coupling between distant biofilms and emergence of nutrient time-sharing, Science 356 (2017) 638–642, https://doi.org/10.1126/science.aah4204.
[236] H.M. McNamara, R. Salegame, Z.A. Tanoury, H. Xu, S. Begum, G. Ortiz, O. Pourquie, A.E. Cohen, Bioelectrical domain walls in homogeneous tissues, Nat. Phys. 16 (2020) 357–364, https://doi.org/10.1038/s41567-019-0765-4.
[237] H.M. McNamara, R. Salegame, Z.A. Tanoury, H. Xu, S. Begum, G. Ortiz, O. Pourquie, A.E. Cohen, Bioelectrical Signaling via Domain Wall Migration, bioRxiv (2019) 570440, https://doi.org/10.1101/570440.
[238] H.M. McNamara, S. Dodson, Y.L. Huang, E.W. Miller, B. Sandstede, A.E. Cohen, Geometry-Dependent arrhythmias in electrically excitable tissues, Cell Syst. 7 (2018) 359–370, https://doi.org/10.1016/j.cels.2018.08.013, e356.
[239] S. Grossberg, Communication, memory, and development, in: R. Rosen, F. Snell (Eds.), Progress in Theoretical Biology, 1978.
[240] G. Pezzulo, J. Lapalme, F. Durant, M. Levin, Bistability of somatic pattern memories: stochastic outcomes in bioelectric circuits underlying regeneration, Philosophical Proceedings of the Royal Society B in press, 2020.
[241] P.B. Shull, D.D. Damian, Haptic wearables as sensory replacement, sensory augmentation and trainer - a review, J. NeuroEng. Rehabil. 12 (2015) 59, https://doi.org/10.1186/s12984-015-0055-z.
[242] J.L. Collinger, B. Wodlinger, J.E. Downey, W. Wang, E.C. Tyler-Kabara, D.J. Weber, A.J. McMorland, M. Velliste, M.L. Boninger, A.B. Schwartz, High-performance neuroprosthetic control by an individual with tetraplegia, Lancet 381 (2013) 557–564, https://doi.org/10.1016/S0140-6736(12)61816-9.
[243] M. Velliste, S. Perel, M.C. Spalding, A.S. Whitford, A.B. Schwartz, Cortical control of a prosthetic arm for self-feeding, Nature 453 (2008) 1098–1101, https://doi.org/10.1038/nature06996.
[244] M.J. Giummarra, N. Georgiou-Karistianis, M.E. Nicholls, S.J. Gibson, J.L. Bradshaw, The phantom in the mirror: a modified rubber-hand illusion in amputees and normals, Perception 39 (2010) 103–118, https://doi.org/10.1068/p6519.
[245] M.P. Kammers, F. de Vignemont, L. Verhagen, H.C. Dijkerman, The rubber hand illusion in action, Neuropsychologia 47 (2009) 204–211, https://doi.org/10.1016/j.neuropsychologia.2008.07.028.
[246] H. Ramakonar, E.A. Franz, C.R. Lind, The rubber hand illusion and its application to clinical neuroscience, J. Clin. Neurosci. 18 (2011) 1596–1601, https://doi.org/10.1016/j.jocn.2011.05.008.
[247] A. Asher, W.A. Segal, S.A. Baccus, L.P. Yaroslavsky, D.V. Palanker, Image processing for a high-resolution optoelectronic retinal prosthesis, IEEE Trans. Biomed. Eng. 54 (2007) 993–1004, https://doi.org/10.1109/TBME.2007.894828.

[248] R. Sole, Synthetic transitions: towards a new synthesis, Philos. Trans. R. Soc. Lond. B Biol. Sci. 371 (2016), https://doi.org/10.1098/rstb.2015.0438.
[249] M. Egeblad, E.S. Nakasone, Z. Werb, Tumors as organs: complex tissues that interface with the entire organism, Dev. Cell 18 (2010) 884–901, https://doi.org/10.1016/j.devcel.2010.05.012.
[250] C.E. Boklage, How New Humans Are Made : Cells and Embryos, Twins and Chimeras, Left and Right, Mind/self\soul, Sex, and Schizophrenia, World Scientific, Singapore ; Hackensack, NJ, 2010.
[251] A.M. Boddy, A. Fortunato, M. Wilson Sayres, A. Aktipis, Fetal microchimerism and maternal health: a review and evolutionary analysis of cooperation and conflict beyond the womb, Bioessays 37 (2015) 1106–1118, https://doi.org/10.1002/bies.201500059.
[252] A. Rosenblueth, N. Wiener, J. Bigelow, Behavior, purpose, and teleology, Philos. Sci. 10 (1943) 18–24.
[253] R.P. Boisseau, D. Vogel, A. Dussutour, Habituation in non-neural organisms: evidence from slime moulds, Proc. Biol. Sci. 283 (2016), https://doi.org/10.1098/rspb.2016.0446.
[254] K. Friston, Life as we know it, J. R. Soc. Interface/the Royal Society 10 (2013) 20130475, https://doi.org/10.1098/rsif.2013.0475.
[255] K. Friston, Active inference and free energy, Behav. Brain Sci. 36 (2013) 212–213, https://doi.org/10.1017/S0140525X12002142.