

**Technological Approach to Mind Everywhere:
A Framework for Conceptualizing Goal-Directedness in Biology and Other Domains**

Michael Levin^{1,2,*} and David B. Resnik^{3*}

¹ Allen Discovery Center at Tufts University

² Wyss Institute for Bioinspired Engineering at Harvard University

³ National Institute of Environmental Health Ethics, National Institutes of Health

* Co-corresponding Authors:

Email: michael.levin@tufts.edu

Email: resnikd@niehs.nih.gov

Keywords: developmental biology, teleology,

Running title: Goal-directedness in biology

Abstract

What makes a system – evolved, engineered, or hybrid – describable by teleological and mentalistic terms such as intelligent, goal-directed, and cognitive? Here, we review classical thought on teleology in the life sciences and summarize ideas on goal directedness from an emerging field – diverse intelligence. This field seeks to characterize what all active agents, regardless of their composition or provenance, have in common. We emphasize: (1) empirical testability (not philosophical commitments to linguistic categories), (2) fecundity in discovery of new capabilities (not just reductive mechanistic explanations of results after they are made, but worldviews that facilitate and enable novel research), (3) operationalization of terminology by reference to conceptual and empirical toolkits shown to be effective for a given system (cognitive and teleological claims are really hypotheses of optimal interaction protocols), and (4) continuity of human goal-directedness with our unicellular origins (which implies a need for models of scaling of cognition). We describe in detail several recent examples of progress made by this framework which enables the application of powerful tools of cognitive neuroscience to the collective intelligence of cells navigating anatomical space, with applications in regenerative medicine, birth defects, cancer, and bioengineering. By abandoning teleophobia in favor of principled frameworks for understanding diverse minds embodied in the physical world, the plasticity and problem-solving competency of the agential material of life can provide fodder for advances in philosophical thought, as well as for biomedical and bioengineering applications.

1. Introduction: Teleology in Biology

Teleological concepts have played an essential role in biological explanation and discovery since the beginnings of scientific inquiry. Aristotle (384-322 BCE) held that to fully explain an event or process one must understand not only its material, efficient, and formal causes but also its final cause or *telos*, i.e. purpose [1, 2].¹ Purposes refer to the intentions, goals, or plans of intelligent beings, and functions are what things do to serve their purpose. On this view, artifacts serve human purposes, whereas natural things serve divine ones. Moreover, the moral or aesthetic value of a thing derives from its purpose. For example, a good flute is good at performing its function (i.e., to produce musical tones) and a good (or virtuous) person is good at performing the human function, which Aristotle understood to be rational activity of the soul [3].

Aristotelian ideas about scientific explanation and methodology held sway for nearly 2000 years until philosophers and scientists, such as Galileo Galilei (1564-1642), Descartes (1596-1650), Robert Boyle (1627-1691), and Isaac Newton (1643-1727), developed and experimentally tested laws and theories that did not refer to goals or purposes. By the end of the 1700s, many scientists viewed the universe as like a mechanical clock that operates according to mathematical principles of cause and effect [4]. Though most scientists still believed that God created the universe, they saw no need to appeal to divine purposes to understand events and processes within the universe, such as planetary motion, the refraction and reflection of light or chemical reactions. Interestingly however, the least action principle of Pierre Maupertius (1698-1759) introduced a kind of primitive goal-directedness into the very center of physics [5-7]².

While teleological thinking soon faded from many aspects of astronomy, physics, and chemistry, it did not dissipate from biology, medicine, and natural history, because many scientists still accepted the theological viewpoint, which had been forcefully defended by William Paley (1743-1805), that the only reasonable explanation of the appearance of design in livings that it is due to the operation of a divine designer. However, in 1859 Charles Darwin (1809-1882) dealt what seemed to be a fatal blow teleology in biology when he published the *Origin of Species*, a remarkable book that demonstrated, through rigorous arguments and copious evidence, that the appearance of design and order in the living world arises through random variation, adaptation, and differential reproduction and survival over geologic time (i.e., natural selection) and not as the result of any divine plan or purpose [1, 8, 9]. A key aspect of the conflict between these two world-views is the assumption that there is a categorical

¹ For an example of Aristotle's four causes consider the explanation of building a house. The wood, pipes, shingles, and other materials would be the material causes; the carpenters, plumbers, roofers, other builders would be the efficient causes; the blueprints would be the formal cause; and the end goal (the house itself) would be the final cause.

² Thus, these least action principles answer the question of "how far down does agency go?" – it goes all the way to the bottom and reveals the minimal lower bound on the spectrum of agential goal-directedness.

difference (that is a difference in natural kinds) between mechanistic and goal-directed systems. Prior to the establishment of cybernetics [10, 11], it was simply not clear how any understandable system (i.e., a machine) could have goals [12-15].

Although biology has become increasingly mechanistic since the advent of Darwinism in the late 1800s and the rise of genetics, biochemistry, biophysics, and molecular biology in mid-1900s, teleological thinking persists in biology because describing biological phenomena in terms of goals or functions is a useful—and some would say inescapable—way of thinking about the structure and behavior³ of cells, tissues, organisms, and other biological systems [17-19].⁴ To paraphrase a famous quote from evolutionary biologist Theodosius Dobzhansky (1900-1975), nothing in biology makes sense without teleology [22-24].

Despite its methodological value in biology, teleological thinking has faced numerous attacks over the years [19, 25]. One of the earliest critics of teleology, Francis Bacon (1561-1626), argued that explanations of scientific phenomena which refer to goals are useless expressions that do not advance our understanding of nature or make successful predications [26]. Clearly, Bacon raised an important point, since scientific concepts should help us to understand, predict, and control nature [27]. However, it is often the case that knowing that a biological system has a particular goal can provide us with useful information. For example, if we have seen little black ants (*Lasius niger*) in our kitchen and we know that these ants seek sugary foods, we can predict that if we leave an uncovered piece of cake on our kitchen countertop overnight it may be covered with black ants in the morning, and also that they may remove larger objects by rotating them through obstacles in very clever ways [28], and that the collective can be fooled by geometric illusions that also fool vertebrate nervous systems [29, 30]. Moreover, a main lesson of cybernetics, and of computer science in general, is that targeting the information structures that define a system's goals, instead of rewiring its hardware, can be an extremely valuable and powerful way to control its behavior.

A more fundamental objection to using teleological language in biology is that it violates the metaphysical axiom that causes must precede their effects [31-34]. Saying that a “an acorn germinates in order to become an oak tree” seems to imply that an effect (i.e., the goal of becoming an oak tree) exists prior to a cause that brings it about (i.e., germination). Although interactions at the quantum level of reality may sometimes violate the temporal order of causes and effects, interactions above this level do not [35]. This is a problem for simple systems, where the most explanatory story that can be told refers only to immediate causes; but for more complex ones, especially biologicals, it is often the case that the most effective

³ We will use the term ‘behavior’ in a very broad sense in this paper to include any form of activity associated with life, including but not limited to movement, energy utilization, metabolism, waste production, development, growth, reproduction, and evolution [16].

⁴ For a clear example of the role teleological thinking in biological discovery, consider inquiry into the chemical structure of DNA [20]. In constructing their model of DNA, James Watson and Francis Crick (1916-2004) were guided by assumptions concerning its biological function and purpose, e.g., “what must the chemical structure of DNA be like to enable it to serve the goals of information storage and be self-replication?” [21].

models for prediction and control emphasize the anticipatory or even counterfactual information that guides behavior⁵ [36-39].

Quantum physics aside, the most straightforward way of circumventing the backwards causation problem is to interpret teleological language mentalistically; that is, to understand goals as mental representations (such as desires, wants, intentions or preferences) that guide behavior [40].⁶ For example, if we observe a person folding a piece of paper into an origami crane, we might explain their behavior by saying that they have a goal of making the crane, which guides their behavior. In this case, there is no problem with backwards causation because the mental representation of the crane exists prior to the actions that create the crane. Woodfield [40] is one of the few contemporary philosophers to defend a mentalistic approach to teleology in science.⁷ Woodfield argues that notions of purpose and function apply primarily to purposive behavior in human beings and intelligent animals and that applications beyond this realm are metaphorical or derivative. Thus, when we say that “the purpose of the male Peacock’s tail feathers is to attract a mate” we mean this only metaphorically.⁸

A key problem with the mentalistic approach, according to many scientists and philosophers, is that it involves ascribing mental properties to things that clearly do not have minds [31, 43]. While most scientists will agree that it makes sense to say that human beings and other intelligent animals have minds that allow them to represent goals and think about how to seek them, they will not say that it makes sense to say the same things about cells, plants, insects, swarms of bees, or developing embryos.⁹ A paramecium that swims toward a food source is assumed not to think about where it is going; it simply acts on the basis of stimuli. To think otherwise is often seen as succumbing to the delusion of anthropomorphism¹⁰.

⁵ Indeed, it is a hallmark of agential systems that an effective explanation of what they are doing, and an effective strategy to manipulate their behavior, must involve events in a larger “cognitive light cone” around them than the local here-and-now. Local stimuli are sufficient to deal with a billiard ball, but events at a spatial distance, in the past, or in the future become crucial components of effective models of agents with memory, predictive capacity, and a radius of concern that is bigger than their immediate surface (which is already true for cells, and certainly for multicellular creatures).

⁶ We will say more about mental representation later in this paper. For now, we will say that we are justified in treating a system as if it has mental representations insofar as this assumption helps us to fruitfully describe, interpret, explain, predict, or control the behavior of the system [41].

⁷ See also Ducasse [42].

⁸ Of course, there is nothing inherently suspect about metaphors in science, since they are used all the time in the physical sciences for explaining and describing phenomena. For example, electrons are described as “jumping” between orbitals or forming a “cloud” around the nucleus. In immunology, antibodies attach to antigens like a “lock and key.”

⁹ We note that radical behaviorists, such as Skinner [44] do not accept the use of teleological language even to describe human behavior.

¹⁰ Of course, the charge of anthropomorphism is a compact way of smuggling in the pre-scientific notion that humans have a kind of magic inaccessible to other systems; this neglects our continuity with single cells (developmentally and evolutionarily). The project of modern teleology is not to confer human-style magic upon

Another objection to the use of teleological language in biology is that it is thought to imply a commitment to mysterious “vital forces” linking biological goals to their effects [18]. Although modern biologists resoundingly reject vitalism on the grounds that it is incompatible with materialist metaphysics, past prominent biologists and philosophers have defended this doctrine [1]. For example, the German embryologist Hans Driesch (1867-1941) argued that morphogenesis is so complex and multi-dimensional that one cannot adequately explain it unless one assumes that it is guided by vital forces (or entelechies) that guide cell differentiation, growth, and movement [45]. French philosopher Henri Bergson (1859-1941) argued that living things have an *Élan vital* (or vital force) that can produce creativity in evolution [46]. A key aspect of this field now is to show how the apparent entelechy can be compatible with the facts of chemistry and physics, much as a non-physical “algorithm” can be causal in making the electrons dance inside a computer circuit despite their obedience of Maxwell’s equations [47-54].

Although these objections have generated considerable philosophical and scientific discussion, they have not convinced most biologists to abandon teleology. Additionally, since the 1950s, prominent biologists and philosophers, including Ernest Nagel (1901-1985), Ernst Mayr (1904-2005), Jacques Monod (1910-1976), Colin Pittendrigh (1918-1976), Francesco Ayala (1934-2023), and many others, have helped to reduce the cognitive dissonance that can arise from using teleological language in biological inquiry by showing how to interpret teleology in a way that does not imply backwards causation, vitalism, or anything else that conflicts with scientific materialism. An essential part of this rapprochement is the idea that mentalistic approaches to teleology apply only to the behavior of human beings and some intelligent animals [19, 25, 40, 43].

Here, we argue that confining mentalism in this way is a mistake: it is an unnecessarily limiting view that creates pseudo-problems by positing sharply delimited natural kinds that are not supported by state-of-the-art biology and bioengineering [55]. It contributes to a kind of teleophobia that inhibits powerful research programs in regenerative medicine and synthetic morphoengineering. Recent advances in the fields of basal cognition and diverse Intelligence [56-59] show that it is useful to view many different biological systems, including molecular networks, cells, tissues, and organs – as well as organisms - as acting intelligently. *By ‘intelligence’ (or goal-directedness) we mean “the ability to achieve goals by different means”* (focusing on problem-solving in action spaces including but not limited to the familiar 3-dimensional space of conventional “behavior”) [60].

The degree of intelligence of a system falls on a spectrum (or relative scale), depending on the extent to which a system satisfies criteria associated with functional goal-directedness (Figure 1). Specifically, these criteria can be objectively demonstrated by the empirically-demonstrated degree of efficacy of different sets of tools applied to the system, ranging across

others but instead to naturalize human capacities and explain how the capacities attributed to humans have scaled up from minimal origins.

physical rewiring, cybernetics/control theory, behavioral science, linguistic commands, reasoning, and psychoanalysis. At one end of the spectrum are highly-intelligent agents, such as human beings, which demonstrate many different capacities related to the pursuit of goals, such as memory, learning, problem-solving, planning, self-awareness, meta-cognition, subjective experience, and language. Specifically, they have metacognitive loops that allow them to reason about their own goals and re-set some of them. At the other end of the spectrum are simpler agents, such as genetic-regulatory networks, which demonstrate only a few cognitive capacities, such as exploratory plasticity and learning [23, 60-63], and below that the least action behavior of passive matter¹¹. Somewhere between these two ends of the spectrum one may find agents with various goal-directedness traits, such as non-human mammals, developing embryos, ant colonies, and artificially intelligent machines and hybrids of biological and technological components [61, 69]. A key task of biology, then, is to determine the position of various systems on this spectrum, since the types of interventions that may be effective at controlling these systems will vary, depending on where they are on the spectrum [70]. This must be done empirically, by making hypotheses about action space, goals, and competencies to reach those goals, and then doing perturbative experiments to verify and improve our theory of mind about these systems – not by holding on to ancient categories and philosophical commitments about the systems allowed to be described by various cognitive terms.

¹¹ Even there, an engineer finds a degree of autonomy that can be exploited. For example, when building a roller coaster, one provides a mechanism to get it up the hill, but there is no mechanism needed to make sure it gets back down – it's an autonomous competency of the system to do that. Minimal, true, but not 0 and we hold a component of the capabilities (free energy minimization [64-68]) that when scaled up results in full-blown human metacognitive capacities.

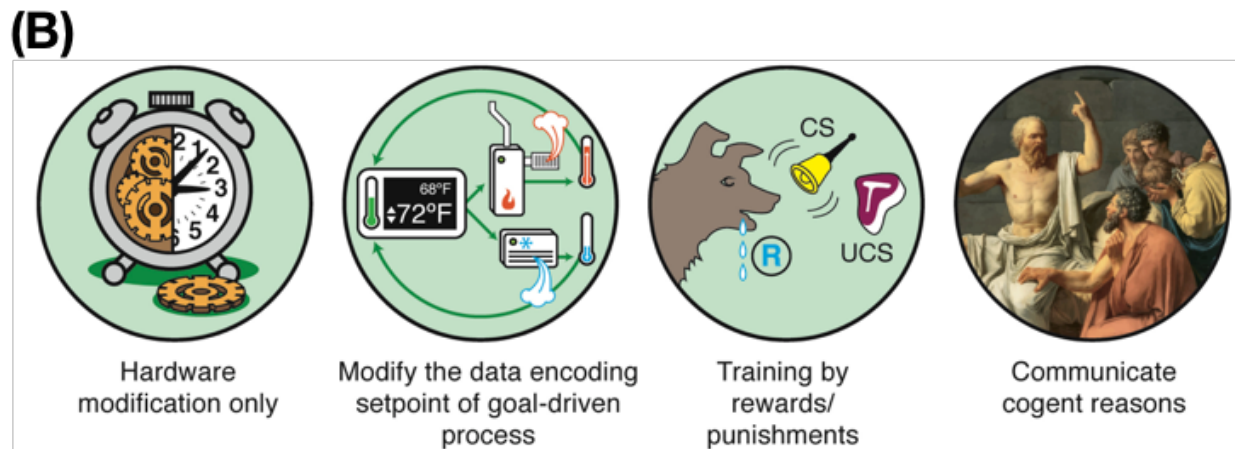
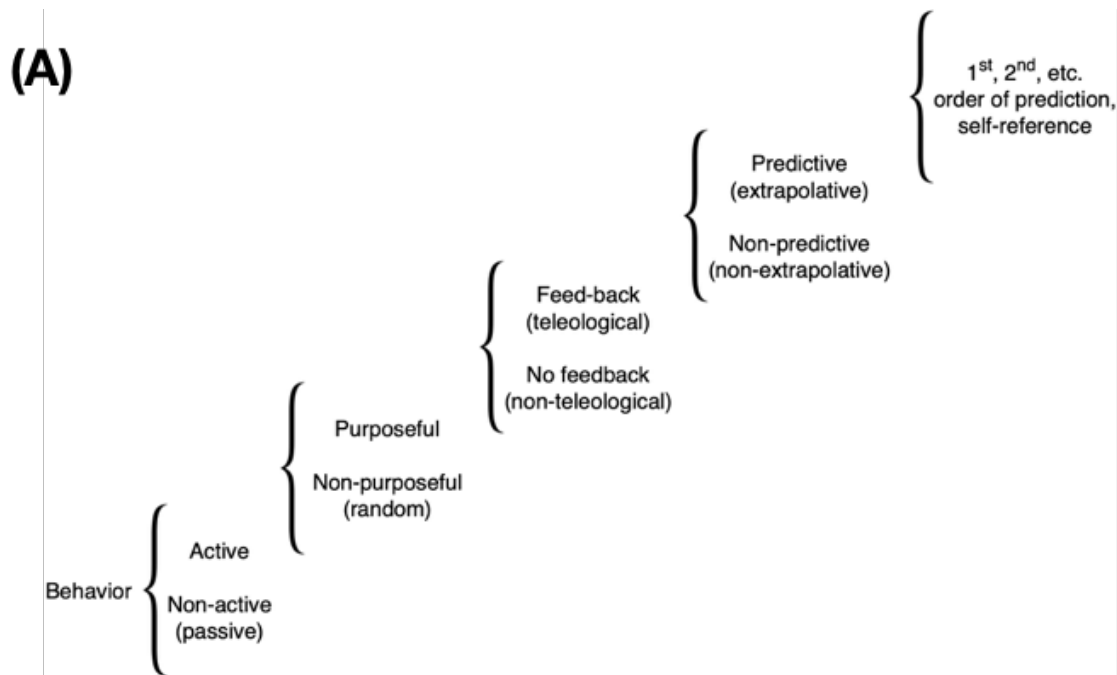


Figure 1: The continuum of cognitive properties. (A) A set of behavioral competencies, leading from passive matter to high-grade metacognitive intelligences (such as humans), illustrating great transitions in information processing from the cybernetic perspective. Taken with permission from [11]. (B) A spectrum of persuadability [60], which illustrates the concept that cognitive terms are interaction protocol claims: the cognitive status of any system, from simple mechanical devices that only follow least action laws to ones that can be predicted and controlled by the tools of cybernetics, behavior science, or psychoanalysis, can only be ascertained by function experiments in which one uses the tools appropriate to a given type of diverse intelligence and gauges the empirical efficacy of the interaction. Image in (B) by Jeremy Guay of Peregrine Creative, taken with permission from [60].

Strong recent support for our position comes from experimental work in morphogenesis, synthetic biology, and other fields that study bioelectric networks outside the brain [62, 71, 72]. Some of the new discoveries about the plasticity of cell and tissue systems, and new ways to prompt them toward complex anatomical outcomes, were specifically made possible by a framework that implies that groups of cells act as agents in pursuit of collective goals and that the tools of computational neuroscience and behavioral science can be applied outside of their normal domain of brainy organisms navigating 3D space [62]. Although we maintain that our view is philosophically defensible, our main concern in this essay is to develop a position that has scientific and practical value. Our approach should be judged as successful to the extent that it yields testable, predictive, and explanatory hypotheses that lead to new ways of thinking in biology and have practical implications in medicine, bioengineering, robotics, and other fields [60, 61, 71, 73-75]. Finally, we also would like to stress that nothing in our view should be taken to imply vitalism, divine design, or other doctrines that involve a commitment to mysterious forces or phenomena that are incompatible with empirical science or limit rational inquiry and progress [61, 70].

Before we develop our position, it will be useful to briefly review some alternative approaches to goal-directedness in biology to provide a philosophical and scientific context for our view.

2. Brief Review of the Contemporary Debate about Biological Teleology

2.1 Teleology vs. Teleonomy

Although biologists and philosophers, including Immanuel Kant (1724-1804), Jean-Baptiste Lamarck (1744-1829), and Darwin have debated about the meaning of function and design in nature since Aristotle's time, contemporary inquiry into the problem of biological teleology began in the 1950s, when Pittendrigh [76] and Mayr [25, 77, 78] introduced the distinction between teleology and teleonomy as a way of talking about goals and functions in biology without presupposing mentalism, vitalism, or divine design [79].¹² Although both terms refer to goal-directedness in nature, one way distinguishing between teleology and teleonomy has to do with whether system itself has metacognition about its own goals, or whether the goals are only apparent to an outside observer. A strongly teleological system has components that can process information about (and perhaps re-set) its own goals – in a sense, it knows it has goals; in a more teleonomic system, an outside observer can determine that it has goals (by perturbational experiments that attempt to deviate the system from its goals) but no evidence suggests that the system is in any way representing or regulating its own the goals. For example, a person who folds a sheet of paper to produce an origami crane is a teleological

¹² Dresow and Love [79] refer to this philosophical inclination as “teleophobia.”

system because they have mental access to the represented goal (i.e., the goal of making the crane) that guides their behavior and do it with second-order intent to pursue a goal at all. In contrast, a 1st-generation thermostat relentlessly making sure the room is at the correct temperature might be merely teleonomic because, while it effectively pursues a goal, it lacks the apparatus to represent facts about goal-having or implement the stress mechanisms that motivate effort and plasticity when goals aren't being achieved, to change the setpoint according to larger-scale meta-goals, etc. In any case, determining the degree to which a system has true teleology, especially for unconventional and non-linguistic systems (or even linguistic ones, in the cases of robotically-embodied large language models), is not trivial and requires empirical experimentation.

Mayr [25, 77] argued that a teleonomic system must have an internal program (such as the genome) that produces goal-directed behavior. However, as we shall see below, there are many different approaches to teleonomy [79]. These approaches can be divided into two groups: ahistorical accounts, which hold that purposes, goals¹³, and functions can be defined without reference to their history; and historical (or etiological) accounts, which hold that purposes and function can be defined only by referring their history [80]. While the distinction between teleology and teleonomy has historical importance, it is not widely used in biology, despite some recent efforts to revive it [79]¹⁴. Therefore, in the remainder of this essay we will use term “goal-directedness” to refer to the phenomena that has been described as teleological or teleonomic.

2.2 Ahistorical Theories of Goal-Directedness

Building on the work of Sommerhof [83] and Braithwaite [84], Nagel [33, 85] defended an ahistorical account of goal-directedness based on concepts from cybernetics, the study of communication and control systems in animals and machines [10]. Nagel argued that two cybernetic notions are crucial for understanding goal-directedness in any system: persistence and plasticity. Persistence is the tendency for a system to produce or maintain a pattern of behavior despite external perturbations that could make it deviate from this pattern. Plasticity is the tendency of the system to produce a pattern of behavior from different starting points [86]. For example, a thermostat in a house exhibits persistence because it maintains a selected

¹³ We can define goals as concrete states within a problem space which a system expends effort to achieve (with some observable degree of competency despite barriers, interventions, and other novel scenarios). We can define purpose as a goal that a given system can reason about (metacognition) – the system represents itself as a goal-driven system and often can work to change those goals in accordance a more general ensemble of meta-goals.

¹⁴ It should be noted however that there is another use of the word teleonomy [23] which is not meant to diminish its reality or importance, but rather to emphasize (via the word “apparent”) the nature of an observer from whose vantage point the teleological behavior can be detected and exploited. This is the perspective of polycomputing [81] and more generally of observer-focused frameworks [70, 82] (and of course, complex agents are also observers of themselves, grounding their own teleonomy).

temperature in the house despite fluctuations in heat affecting the house. A thermostat exhibits plasticity because it can achieve the temperature setting from different starting points, i.e., initial temperature readings in the house. While Sommerhof, Braithwaite, and Nagel all agreed that goal-directedness involves persistence and plasticity, Nagel argued that one cannot infer goal-directedness only from only observing the behavior the system; one must also have evidence that the system has homeostatic mechanisms that produce goal-directed behavior [80]. For example, a thermostat exhibits persistence and plasticity because it has homeostatic mechanisms, including heat sensors, heating system control switches, and feedback loops, that enable it to control the temperature with the house.

A key assumption made by Nagel is that statements about functions and goals should explain why something exists or persists in a system. Hempel [87] and Cummins [88] criticized this view on the grounds that inquiring about the function of something does not necessarily tell us why it exists or persists. The statement “the function of the mammalian heart is to pump blood” does not tell precisely us why mammals have hearts because there are many different types of blood-pumping mechanisms that could perform this function, such as three-chambered pumps, multiple pumps, and so on. The term “heart” stands for a set of functional properties that can be realized in many different physical systems [18].

Based on this, as well as other criticisms of Nagel’s view, Cummins [88] developed a **causal role theory of goal-directedness**. The basic insight behind this theory is that functional statements explain what things do, not why they exist [89, 90]. Complex, biological systems have many different, interacting parts of various levels of organization. The parts of the system have capacities to produce or maintain various effects (or goals) within the system [91, 92]. For example, the human body has 11 different organ systems, composed of 78 organs, 206 bones, 600 muscles, 200 cell types, 30 trillion cells [93, 94].¹⁵ These parts of the human body work together to maintain life and health. To understand the function of any part in this system, one must determine what it does in the system and how it interacts with other parts. For example, macrophages are immune system cells that carry out several functions that help to promote the goal of protecting the body against disease. One of these functions is to phagocytize and degrade dead cells and foreign materials. Macrophages also interact with other immune system cells, including T-cells and B-cells, to protect the body against disease. For example, macrophages can activate T-cell responses by presenting them with antigens from pathogens or cancer cells and by secreting cytokines [102]. Macrophages are equipped with proteins that help them perform their functions, including receptor proteins that recognize molecular patterns of dead cells and foreign materials, enzymes that facilitate phagocytosis, and cytokines. These proteins are synthesized by ribosomes from genetic information encoded in the DNA [103].

¹⁵ Even something as “simple” as a yeast cell is composed of about 42 million protein molecules, consisting of 5858 different types of protein [95]; 6,000 genes [96]; and 200,000 ribosomes [97]. Additionally, cells can learn [98, 99] and anticipate future events [100, 101].

Like Cummins, McShea [86] also regards information about biological complexity and hierarchical organization as essential to understanding of goal-directedness, but he criticizes the causal role theory because it still involves statements about function and goals within systems and therefore risks sliding back into mentalism. McShea [86, 104], Lee and McShea [105], and Babcock and McShea [106] have developed an ahistorical view that explains persistence and plasticity in biological systems in terms of hierarchically organized structures, or **fields**, rather than goals and functions. A field can provide direction and control for entities affected by it. For example, a magnetic field can align iron filings in a particular position or deflect the solar wind. To illustrate the idea of field in biology, McShea [86] describe bacteria swimming toward a food source dissolved in water. The concentration gradient of the food in the water guides the bacteria to the source, not the goal of reaching the food. Moreover, the bacteria exhibit persistence and plasticity with respect to moving toward the food because they will move in the direction irrespective of perturbations in the system or different starting points. Phototropism is an example of a field because the position of a plant with respect to the source of light affects the direction of its growth. According to McShea, one can (in theory) understand almost any biological system, including ant colonies, human societies, ecosystems, in terms of fields and interactions between fields [106].

2.3 Historical Theories of Goal-Directedness

A key problem with the ahistorical approach to goal-directedness in biology, according to its critics, is that it does not provide sufficient context to distinguish between a) functions and accidents and b) functions and dysfunctions [32, 80, 107-110]. For example, the human heart produces sounds, which a doctor can listen to for diagnostic purposes. A heart murmur can indicate a serious problem, such as aortic stenosis [111]. Even though producing sound is a useful effect of the heart, physicians would not say that this is its function. It is, at best, a fortuitous accident that heart sounds can be used in medical diagnosis, since the heart's function is clearly to pump blood. Ahistorical approaches cannot support the obvious conclusion that the heart's function is not to make sound, since the heart is structured and organized so that it exhibits persistence and plasticity in producing this effect. With respect the function/dysfunction distinction, a normal, adult human heart beats at 55-85 beats per minute at rest [112]. If a person has a resting heart rate of 130 beats per minute, this would be regarded as unhealthy or dysfunctional, but is difficult to substantiate this claim without referring to contextual information if their heart is organized and structured so that it exhibits persistence and plasticity in producing this effect.

Proponents of historical theories of goal-directedness argue that history provides the context that is needed to distinguish between functions and accidents and functions and dysfunctions. For example, a historical theorist could claim that the function of the heart is to pump blood, as opposed to making sound, because this pumping blood contributed to the adaptive fitness of human beings with hearts, whereas making sound did not. A historical

theorist could also say that a human heart that beats 130 times per minute at rest is not functioning properly because this effect would have had a negative fitness.

Historical theories of goal-directedness in biology have been defended by Ayala [113], Wimsatt [114], Ruse [32], Wright [31], Boorse [115], Brandon [116], Millikan [107, 108], Neander [109], and Garson [110, 117]. Most proponents of the historical approach claim that biological functions are phenotypes or genotypes that persist in populations because they contributed to the fitness of the organisms that possessed them. That is, they are adaptations [116]. Thus, these historical accounts explain why something exists by referring to what it did in the past, i.e., how it affected fitness. However, some theorists (e.g., Millikan [108] and Garson [110, 117]) generalize this point and argue that any historical process that selects properties based on their effects can produce functions. For example, if a horse learns to avoid wire fences after receiving several shocks from a wire fence, one could say that the function of its wire fence-avoidance behavior is to protect the horse from electric shocks.

Critics of historical theories of goal-directedness argue that selection history provides neither necessary nor sufficient conditions for ascribing functions or goals to biological phenomena. It does not provide sufficient conditions because genotypes or phenotypes which are adaptations to past environments may no longer serve a function in their current environment (Garson 2016, 2019). For example, the hemoglobin beta (HB) mutation, which is common in populations that live in regions where malaria is endemic, such as parts of sub-Saharan Africa and the Middle East. The mutation changes in the shape of the hemoglobin protein and causes sickle cell disease in homozygotes but not heterozygotes. Since heterozygotes have a copy of the normal allele, they can produce normal red blood cells and do not develop sickle cell disease but they still have resistance to malaria. So, according to theories that define functions in terms of natural selection, the function of the mutation is to provide malaria resistance [118]. However, this mutation no longer serves that purpose in populations that have migrated from sub-Saharan Africa and now live in regions where malaria is not endemic. Historical theories do not provide necessary conditions for ascribing functions because some traits may contribute to reproduction and survival even though they have not yet been favored by natural selection. For example, suppose a mutation emerges in a population that confers resistance to an infectious disease, such as COVID-19, but has not been in the population long enough to be favored by natural selection. It seems plausible to claim that the function of the mutation is to provide resistance to COVID-19, but the historical view cannot countenance this hypothesis until the mutation persists and is selected for [119].

2.4 Pluralistic Theories of Goal-Directedness

Some authors have responded to the debate between ahistorical and historical theorists by arguing or suggesting that neither view entirely captures meaning of goal-directedness in biology and that the most reasonable way of thinking about this concept is to adopt a pluralistic

approach (Sober [120]; Griffiths [121]; Godfrey-Smith [122]; Brandon [123]; Garson [80, 124]). That is, ‘purpose,’ ‘function,’ and related terms can mean different things in biological research, depending on one’s epistemic aims and the types of questions being posed [125]. When the primary objective is to understand how something works (for example, when doing research in comparative anatomy or physiology), the ahistorical view may be most apt; however, when the primary objective is to understand why something exists or persists (for example, when doing research in evolutionary biology or ecology), the historical view would seem to be most useful. In many types of biological inquiry, both types of questions will arise and answers to one type of question may suggest answers to the other [80, 117]. For example, information about brain evolution can be useful in understanding the brain’s neural architecture and vice versa [126].

Table 1: Theories of Goal-Directedness in Biology

| Mentalistic Theories | Non-Mentalistic Theories |
|---|---|
| Aristotle [2, 3] Woodfield [40] Levin [60] Dennett [127] Deacon [128] Juarrero [129, 130] Love [79] | <p>Ahistorical Theories</p> Homeostatic mechanisms; Nagel [85] Genetic program; Mayr [25] Causal roles; Cummins [88], Amundson and Lauder [89] Physical or chemical fields; McShea [86] |
| | <p>Historical Theories</p> Natural selection; Ayala [113], Ruse [32], Wright [31], Brandon [116] Generalized selected effects; Millikan [108], Neander [109], Garson [110, 117] |
| | <p>Pluralistic Theories</p> Sober [120], Griffiths [121], Godfrey-Smith [122], Brandon [123], Garson [80, 124] |

Table 1: Theories of goal-directedness in biology. Theories of goal-directedness in biology can be classified as mentalistic theories, which explain purposes and functions by in terms of mental categories, such as mind, cognition, and problem-solving; and non-mentalistic theories, which do not explain teleology in terms of mental categories. Non-mentalistic theories can be subdivided into ahistorical theories, which explain the purpose or function of a thing in terms of its current causal role or place within a physical-mechanical system; and historical theories, which explain the purpose or function of the thing in terms of its history. Pluralistic theories combine historical and ahistorical accounts. Although we defend a mentalistic approach in this paper, our view could be characterized as pluralistic and pragmatic because we are not

rejecting these other approaches to goal-directedness and believe that the appropriateness of any approach depends on its ability to fruitfully guide experimentation and inquiry.

3. Brief Interlude

As one can see from the synopsis in Section 2, the leading theories of goal-directedness in biology fall roughly into three camps: the ahistorical approach, which interprets statements about goal-directedness as offering explanations of what things do or how they work; the historical approach, which interprets these statements as offering explanations of why things exist or persist; and pluralist approaches which regard both types of interpretations as acceptable, depending on scientific usage. These theories are non-mentalistic because they attempt to show how teleological terms can be understood without referring to minds or mental states. Although these different theories yield some useful insights into teleological thinking, it is not clear to us that any of these ways of talking about goal-directedness have gained widespread acceptance among biologists.¹⁶

While we think it is useful to review these leading approaches to biological goal-directedness because these provide context and background for our view, it is not our primary aim in this paper to adjudicate this debate, analyze what biologists mean by ‘purpose’ and ‘function,’ or explore the nuances of various arguments, definitions, counterexamples, or rhetorical moves. This is an important project, but it is not our project (see for example, [80, 131]). Rather, the main objective of this paper is to advance a framework for thinking about goal-directedness in biology that is in some ways a revival of an older, mentalistic approach. The rationale for this new approach comes not from philosophical analysis but from the empirical success of an alternative framework that has facilitated new experimental work in morphogenesis, synthetic biology, and bioelectric networks, which has wide-ranging implications for thinking about goal-directedness in biology and other domains. A new approach is required because non-mentalistic theories of goal-directedness do not provide an adequate explanation of these findings, nor do they offer fruitful guidance for future work in these and other areas involving the organization of complex behaviors.¹⁷ Our aim is to develop an approach to goal-directedness that will enhance our understanding of biological systems, open new avenues of inquiry, suggest novel ways of looking at old problems, and yield testable hypotheses with applications in medicine, bioengineering, other areas of science and technology. Before developing our view further, we will describe examples of experimental work in morphogenesis and synthetic biology that supports our view and explain why mainstream approaches to biological goal-directedness fail to provide optimal guidance for further progress in these fields.

¹⁶ During the 1970s, the term ‘teleonomy’ started to gain favor, but teleology is back in vogue [79].

¹⁷ This situation in biology is similar, we believe, to what happened in physics during the early 20th century, when the double-slit experiment required physicists to rethink their theories of light and matter [132].

4. New Experimental Results in Morphogenesis and Synthetic Biology

Every result in experimental biology can, after it is discovered, be said to be implemented by mechanical molecular processes underneath. The same is of course true of the most advanced, uncontroversial examples of human goal-directedness [133]. And this is not surprising: the mechanism is always going to be chemistry (or quantum foam, if one is truly committed to the reductionist project), never fairy-dust. However, we propose that a hallmark of a good philosophical framework is that it facilitates discovery of new capabilities and engenders new research programs, not just that it explain events after they've been produced. Here, we briefly describe some specific discoveries that were made precisely because of the use of a teleological framework that allowed the empirical testing of agential toolkits (primarily, from the cognitive and behavioral sciences) on novel substrates from which they were previously isolated due to the gatekeeping of allegiance to pre-scientific categories. Many more can be found in recent work [79, 134-160].

One example of practical implications of specific hypotheses about the intelligence of a given system is revealed by work on frog craniofacial morphogenesis. Every tadpole needs to rearrange its face to become a frog [161-163]. It was assumed that this is a hardwired process – every tadpole looks the same and every frog looks the same, so all evolution had to do was provide for mechanisms that reliably moved every organ in the right direction by the right amount. We (that is Dr. Levin's lab) decided to empirically test this assumption [164], suspecting that in fact the system may have more intelligence than that. Context-sensitive problem-solving competencies need to be revealed by perturbational experiments that probe what kind of goal-directedness a system might have, in addition to open-loop (feed-forward) emergence of complex outcomes from the rote execution of low-level mechanics. Thus, we created what we called "Picasso tadpoles" where the craniofacial structures were scrambled – the eye might be on top of the head, the mouth might be on the side, etc. It was found, using quantitative morphometrics [164, 165], that in fact these scrambled animals still made quite normal frogs, because the organs would go through novel paths (indeed, sometimes going too far and needing to double-back) to end up in the correct frog face target morphology. This example shows the ability of morphogenesis to reach a specific goal despite unexpected starting conditions (a more sophisticated way of navigating the anatomical morphospace), and more generally, the benefits of not assuming a system is at the very low end of problem-solving capabilities but of testing to see what behaviors it can muster to meet its normal end-state when circumstances change.

An even more drastic example can be seen in regenerating planaria. Planarian flatworms are an amazing creature – they regenerate every part of their body and can be cut into many pieces, each of which will form a perfect little worm [166]. Of course this process is studied today using conventional molecular biology and models of pathways [167]. However, there is an interesting aspect which is not predicted or implied by the standard worldview. Planaria are

not only highly regenerative, but also cancer-resistant and ageless (asexual planaria do not age and are basically immortal). Because they reproduce by fission and regeneration, they accumulate somatic mutations: for 400+ million years, every mutation that does not kill a stem cell is amplified into the next generation as the cells re-build new bodies after fission. They are mixoploid, with different numbers of chromosomes in their bodies (discussed in [168]). Of course this can be studied using molecular methods, but note that the modern paradigm of the genome as a mechanical orchestrator of biological events does not predict that the animal with the messiest genome should be the one with the most robust regeneration abilities and resistance to cancer and aging! It's the exact opposite prediction one would make from a genome-as-driver view. An explanation for this bizarre mismatch between expectation has finally been offered and simulated in computational experiments [169], and it relies on the *morphogenetic competency* of the cellular material: by conceptualizing evolution as producing problem-solving agents with ability to achieve specific goals in anatomical morphospace [63], the situation becomes clear. An unreliable material leads to selection for computational capability to achieve goals despite the presence of noise. Planarian tissue, due to the somatic inheritance of mutations, is ultimately unreliable and exerts significant pressure to evolve highly competent decision-making circuits to reach the normal target morphology despite novel circumstances. This gives rise to a feedback loop, because such regulative processes hide information from selection (a good embryo might be good because the structural genome is great, or because it wasn't great but the embryo fixed the problem on the fly, as often occurs [23]). This in turn means that evolution spends more time tuning the competency capability and not the baseline, default hardwired morphogenetic mechanisms.

One other interesting aspect that this line of thinking explains is the lack of transgenics in planaria. In other model systems, one can obtain mutant lines – fruit flies with curly wings, mice with unusual coat colors or skeletal malformations, etc. In planaria, not only is there no transgenesis available (despite 30+ years of attempts), but there are no mutant lines! Why? On the mechanistic view, this is a major puzzle. However, it makes perfect sense if one uses the concept of cell groups as a collective intelligence that solve anatomical problems (reviewed in [70, 170]): planaria have strongly de-emphasized their genetics, and instead leverage enormous autonomy and morphological intelligence (this is also seen in their ability to solve novel physiological problems [171]). Interestingly, there are 2 permanent lines of planaria that are not normal – but they are made by perturbing not genetic mechanisms, but the same kind of bioelectric signaling that underlies advanced animal cognition [172-175].

Planarian fragments can be induced to form 2 heads instead of one; the first 2-headed forms were made at the turn of the last century [176, 177]. However, to our knowledge, no one had *re-cut* the 2-headed forms to see what would happen, until our laboratory did it in 2009. Likely this was because it was perfectly obvious what would happen: the genetics are normal and therefore fragments would build what they always build, going back to 1 heads. Our framework instead led to a different prediction (Figure 2). First, we reasoned that the head-tail decision could not be local or determined by morphogen gradients (see [168] for explanation)

but must be a collective distributed decision. Electrical synapses are a powerful mechanism for ensuring collective decision-making in the brain [178], and thus we tested their roles in planaria, discovering that 2-headed worms could be made by perturbing the electrical synapses known as gap junctions [179]. Then, reasoning that this collective dynamic is likely to have the kind of memory seen in neural collectives (albeit in morphological space, not behavioral 3D space), we re-cut the 2-headed worms, discovering that the 2-headed state is *permanent* – in the absence of any further manipulations, 2-headed worms' fragments continue to regenerate as 2-headed [175]. This is a remarkable example of non-genetic inheritance of a different large-scale anatomy in a multicellular organism with a wild-type genome.

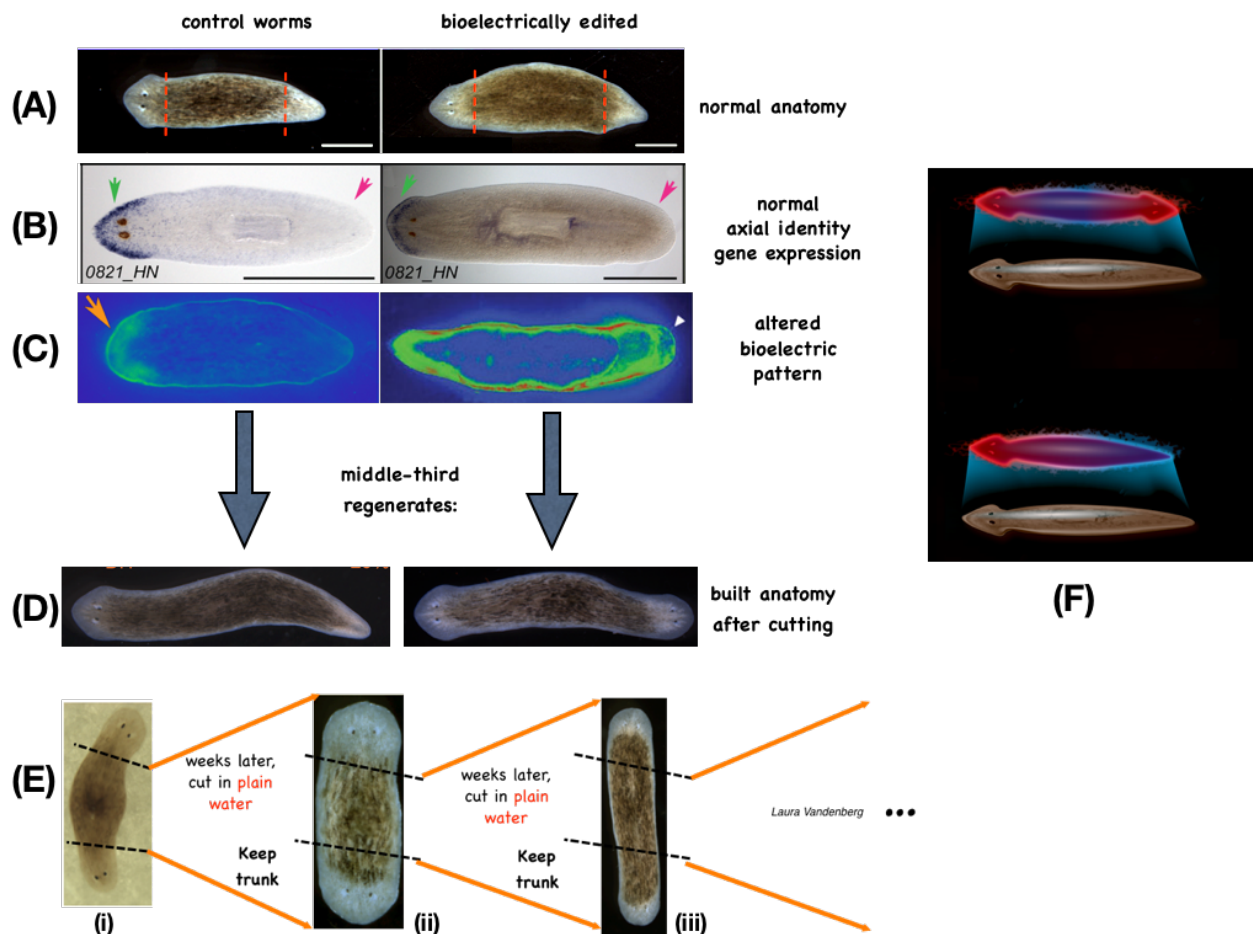


Figure 2: re-writing morphogenetic goals in regenerating planaria. Flatworms (in this case, *Dugesia japonica*) regenerate after amputation. The left columns in panels A-D show control worms, while the right panels show worms in which the endogenous bioelectric prepatter has been altered by exposure to a drug that alters resting potential of cells [172, 173]. (A) Planaria have head-identity genes (blue stain, in situ hybridization with an anterior marker) expressing in the correct side (anterior, not in the posterior tail region). (B) Voltage imaging with a fluorescent reporter dye [180] reveals the bioelectric pattern in which depolarized regions (green, left panel) specify that there should only be 1 head in normal worms. In a drug-

manipulated worm, (right panel) the pattern has been altered to encode the “2 heads” outcome. Both animals have normal anatomy - 1 head (oriented to the left), and 1 tail (on the opposite side). Red dashed lines indicate plane of amputation. (D) When those animals are cut, the middle fragments regenerate the number of heads consistent with the bioelectric pattern they had. (E) When 2-headed animals are amputated further, with no more exposure to bioelectric reagents, pieces continue to regenerate as 2-headed across generations (i,ii, iii) without limit. These data show that a bioelectric pattern stored in the tissue serves as the target to which the cells will build when needing to restore a whole body and that the pattern which determines this is not stored in the genetics – the same hardware can implement multiple outcomes (and stop when the outcome is achieved), as schematized in panel F where the same physical planarian body is shown storing multiple different representations of what the correct state is, which will guide repair and remodeling. The anatomical setpoint can be reset without changing the hardware of the system (as in any homeostatic system with a memory of goal state) and is persistent though re-writable (a key property of memory). Panels A, B taken with permission from [174]; Panels C, D, E taken with permission from [172, 175, 181]. Panel F by Jeremy Guay of Peregrine Creative.

We were also able to target the bioelectric circuits storing the number of heads to be made [173] (a literal encoding of a goal for the collective intelligence of cells – a biophysical mechanism of representation of the state toward which all the cells will work upon injury). Not only could we re-set it back to 1-headed [182], but we could also produce what in neuroscience is called perceptual bistability – an indecision and stochastic oscillation between 2 different interpretations of the same input [172]: we created worms whose fragments stochastically produce 1 or 2 heads [174]. A key aspect of this work is that what we re-write is a stable bioelectric state within tissue, and when we modify this pattern memory it stays latent: a 1-headed form, with normal anatomy and molecular marker expression, can be given a bioelectric pattern memory of “2 heads”. The memory and anatomy stay discordant until and unless it is injured, in which case the cells use this memory to know what to build (constructing 2-headed worms). In this sense, it is a truly counterfactual memory – it does not represent what is true about the animal’s body now, but what *will* be true if it gets injured, and in an important functional sense, the activity of the cells is controlled by internal representation of a future goal-state. That is, the teleology of the system is implemented by having an encoded state of the future (not backward causation at the level of physics, but at the level of information) that guides the morphogenesis toward a specific, encoded end.

These experiments demonstrate how an unconventional system (working in anatomical morphospace) can have a representation (or encoding) of a future state via the cellular collective of the body. It may represent an evolutionary precursor to the amazing “time travel” capacities of brains, which can think about situations that do not currently exist. This kind of representation of future or past goal states is an important component of concluding that a system has a degree of mind (without necessarily assuming meta-cognition or subjective experience, i.e. qualia). Indeed, if we were to try to visualize the basal forms from which

complex mammalian counterfactual representation might have evolved, this simple scheme would be the kind of thing we would imagine as the basic mechanisms that nervous systems later elaborated, amplified, and projected into the world of 3D behavior. The example also shows a specific, experimental approach to directly visualizing the encoded goal representations of unconventional systems, because the bioelectric voltage dye imaging reveals the (re-writable) goal state to an external observer much as neural decoding is supposed to give 3rd-person access to human mental goals and memories. Here, we know the goal exists because we can *see it* and *re-write* it, thus moving the question from a purely philosophical discussion of goals to a practical, empirical scenario.

Note what this example demonstrates: by developing tools to observe (bioelectric dye imaging) and re-write (targeting the ion channels in specific ways) the bioelectric pattern memories that serve as the future goals of the morphogenetic process, we reify the existence of goals, memories, and counterfactual states in an unconventional substrate. The best way to identify and prove the nature of a teleological system is by uncovering the ways in which goals are encoded (i.e., represented) and re-writing them, enabling the system to achieve novel behaviors not because its genetically-specified hardware was micromanaged to force it (like a mechanical clock) but because it was given a novel goal on which to exercise its autonomy (like a sophisticated thermostat circuit with multiple ways of maintaining a set temperature). We know these things exist, not metaphorically but in the most real sense of all – because using the tools and concepts of neuroscience we facilitate the ability to enable discovery and reach new capabilities by techniques used at the bench which were not facilitated by conventional approaches hyper-focused on bottom-up mechanistic causes. This research is just one example of the broader project of exploring bioelectric networks (and the capacities implemented by them) as a kind of cognitive glue that binds together active subunits, from neurons to bacteria [147, 148], toward the creation of emergent large-scale agents that have goals, competencies, memories, preferences, and top-down causal control than none of their parts have [183, 184].

Another example of the benefits of an engineering approach to teleology (goals as aspects of the materials' autonomy that can be targeted in effective interventions) concerns our attempts to use the bioelectric interface to communicate novel goals in vertebrate development (Figure 3). The face in frog embryos is defined by an instructive bioelectric prepatter that determines the location and number of eyes, mouth, and other organs [185]. When a similar pattern indicating the eye spot is introduced into other areas of the body, such as the gut, the cells build an ectopic eye [186]. This can even happen in posterior regions, which according to standard developmental biology is incompetent to form eye (this conclusion was reached because prior studies attempted to force eye development with the “master eye gene” *pax6*, which indeed doesn't work posterior to the neurectoderm at the front of the head; but the more convincing bioelectric prompt works everywhere). Note several key aspects which are facilitated by the hypothesis that cells are an agential material amenable to the tools of behavioral science – communication, goal-resetting, and collaboration – not just molecular micromanagement. First, it shows the bioelectric pattern memories are instructive, not

epiphenomenal – they are causal for changes in complex morphology not easily reachable by conventional means. Second, we did not force the construction of an eye by managing gene expression and painstakingly orchestrating the position of all the cell types. We didn't need to do this anymore than the humans of 5,000 years ago needed to know molecular mechanisms of neuroscience to communicate with dogs and horses. We provided a high-level prompt – a simple trigger stimulus which led to downstream complex behavior and the system managing its own molecular events to reach a goal in anatomical space that we specified (a dynamic well familiar to students of animal behavior). Third, targeting only a few cells is enough – they will autonomously recruit others, not initially targeted by us, to help complete the task. This of course also occurs in other collective intelligences like ants and termites who recruit conspecifics to help with a heavy carrying task. Taken together, these aspects illustrate how taking seriously the autonomy and competency of the material confers empirically-verifiable, practical advantages. Work is currently on-going to explore other aspects of neuroscience in these morphogenetic contexts, including the use of anxiolytics [187], hallucinogens [188], serotonergic modulators [189], memory blockers, and many other ways of modulating decision-making, perception, and memory in full-blown teleological agents in novel substrates to show the utility of this approach for novel discoveries.

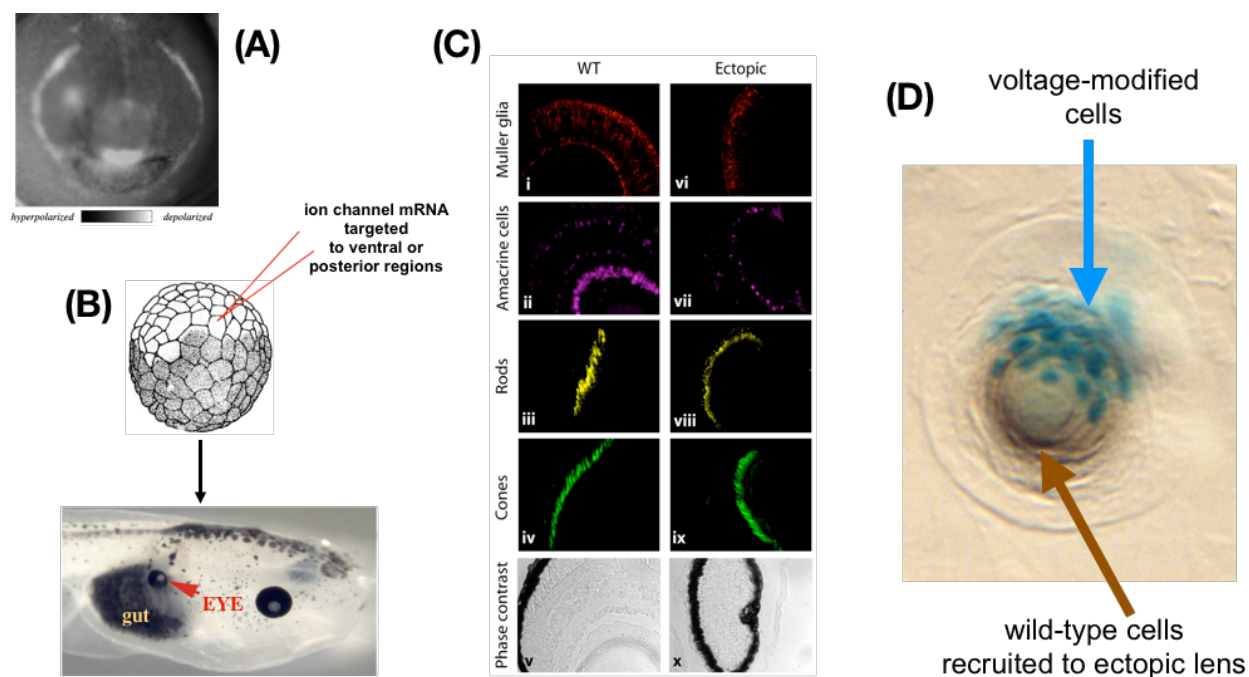


Figure 3: Resetting organ-level goals for cell groups in vivo. Normal craniofacial development in frog embryos is preceded by a bioelectric prepatter (A) in which the borders between depolarized (light) and hyperpolarized (dark) regions set the locations of the various organs of the face and head. We asked whether these bioelectric prepatters were instructive for the behavior of cell collectives. In order to reproduce the eye spot elsewhere in the body, we injected (B) an early embryo with mRNA encoding a potassium ion channel which would establish a specific bioelectric pattern in the posterior of the embryo. The result was eye

formation (red arrowhead) in regions such as the gut. Those eyes contained lens, retina, optic nerve, and other components (C, shown via immunohistochemical markers) even though all we provided was a very simple “make an eye here” prompt (a voltage state), not detailed instructions on how to micromanage the gene expression and cell differentiation needed to actually make an eye. When only a few cells were targeted (D, shown by the blue stain), they spontaneously recruited their un-modified neighbors to help in the task of making an ectopic lens in the animal’s flank. This illustrates the many competencies of the material: modularity, interpretation of simple stimuli via complex behavioral programs that are self-organized, scaling of resources appropriate to task, re-specification of collective goals on-the-fly, etc. Panel A taken with permission from [185]. Panels B,C taken with permission from [186]; Panel D taken with permission from [60].

Another example comes from cancer research (Figure 4); whereas the planarian and eye induction examples showed re-writing the content of the represented morphogenetic goal, the following shows how the *scale* of cellular goals can be usefully manipulated. The bottom-up mechanical approach holds cancer to be an irrevocable result of genetic mutations spread as clonal populations from a single mutated cell (hardware defects). This has a practical implication (toxic chemotherapy to kill the cells), and a prediction: animals with ready access to proliferative, undifferentiated cells should be most prone to cancer. However, this prediction is wrong – the animals with the highest plasticity (planaria, salamanders) have very low incidence of cancer (reviewed in [190, 191]). An alternative model has been proposed [71, 192]: cancer as literally a dissociative identity disorder of the somatic collective intelligence. Cells which electrically disconnect from the tissue whose network stores very large morphogenetic goals (build a limb, or a liver, etc.) in effect roll back to the tiny cognitive light cones¹⁸ of single-cell amoebas, whose goals are metabolic, proliferative and migratory (i.e., metastasis). This view suggests an alternative to chemotherapy and a possibility that is not reachable from the conventional assumptions: that cancer can be reversed not by fixing the molecular hardware, but by re-scaling the *goals* of the system, enabling the cells to work towards larger goal states (organ maintenance). We tried this, and showed that: (1) carcinogenic defection can be seen early by tracking the bioelectrical states of cells [193], (2) metastatic melanoma can be induced in the absence of carcinogens, oncogenic mutations, or DNA damage – simply by disrupting the cellular bioelectric communication [194-196], and (3) cancer induced by potent oncogenes can be normalized into healthy tissue by forcibly re-establishing the correct bioelectric state of the collective, including at long range within tissue [197-199]. In parallel with re-setting the goals discussed in the section above, this research program reifies goal-directedness by showing that the *scale* of goals is a useful, practical target of interventions that enables biomedically-relevant progress.

¹⁸ The cognitive light cone (defined in [71]) demarcates the scale of the largest goal, in both space and time, which a system is capable of working towards.

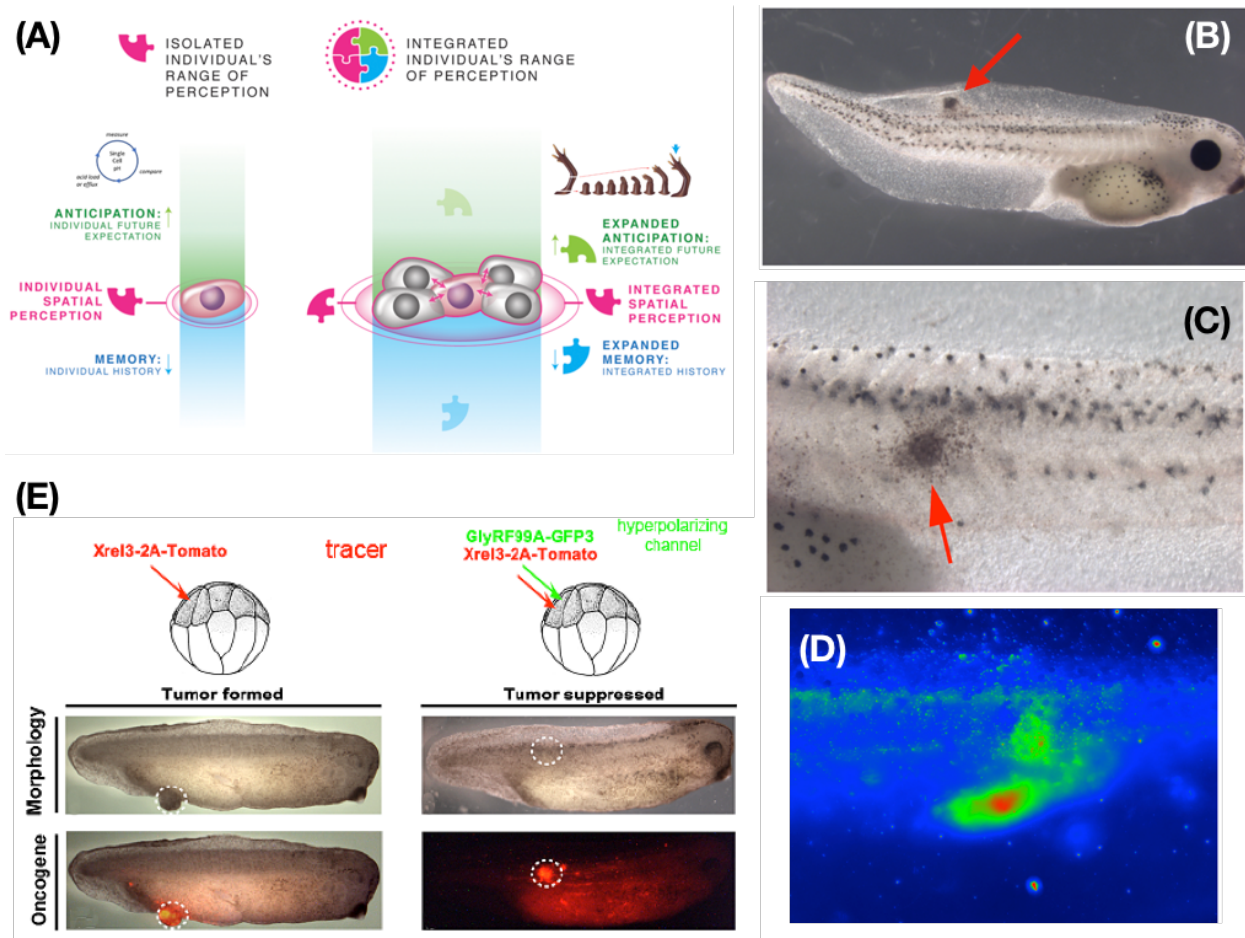


Figure 4: Cancer as a dissociative identity disorder of the collective morphogenetic intelligence. (A) Multicellular morphogenesis can be described as the enlargement of the goal states, from individual cells' modest homeostatic goals about pH and other values within the current cell boundary, cell groups pursue grandiose goals (such as making sure a salamander limb has the right shape and size). These are goal states in the sense that they guide the activity of cells and determine when they stop (when the error has been reduced sufficiently). This process of connecting cells into higher-order computational networks that can store and pursue larger goals in new spaces (anatomical space instead of the landscape of metabolic, physiological, and transcriptional goals) has a failure mode: cancer. When cells are disconnected from their collective by stress or oncogenes (such as the human oncogene injected into the frog embryo in panel B, which makes a tumor, red arrow), they revert back to their unicellular goals – a shrinkage of the boundary between self and world in which the cells no longer perceive their membership in a larger collective – a problem analogous to dissociative identity disorder in cognitive systems [192]. Closeup of the metastasizing tumor is seen in panel (C). This bioelectric disconnection is apparent using voltage reporter dyes (panel D), which indicate the abnormal bioelectric state of the nascent cancer cells. The use of this unconventional perspective on the cancer problem led to a specific treatment strategy (E): co-inject ion channels into the site of

oncogene function to force the correct bioelectric state: whereas the oncogene alone causes a tumor (morphology in top left panels, fluorescent tracer on the oncoprotein in bottom panels), it is prevented from doing so when co-injected with an ion channel mRNA – there may be no tumor (top right panel) even though the oncoprotein is strongly expressed (red tracer, bottom right panel). This shows that cancer is not simply a hardware disorder due to mutation but is fundamentally tractable using tools that target the size of cellular goal states. Images in Panel A by Jeremy Guay of Peregrine Creative, used with permission from [71, 183]. Panels B-E used with permission from [191]

The final example concerns the ability of unconventional biological agents to find *new goals*. The examples above showcased examples of exploiting the goal-directedness of the agential material of life [200]. But where do these goals come from? Some are shaped by evolution, the way that inborn instinctual behaviors are provided for some animals. But others are creatively developed in real-time, based on circumstances, as seen in many other examples of animal behavior. The conventional view sees morphology and behavior as driven by the genetics and shaped by a long history of selection. We pursued the idea that cell collectives are not only goal-seeking agents but have the ability to acquire novel behaviors that do not require eons of shaping to a specific environment (i.e., that evolution produces problem-solving agents not fixed solutions). First, by liberating epithelial cells from the other cells of a frog embryo (which normally induce them to have a boring life as the 2-dimensional outer surface of an embryo), we found that they spontaneously assemble into self-motile little constructs we dubbed Xenobots, which have novel capacities such as kinematic self-replication – ability to make copies of themselves by building with cells found in the environment [201-204]. To our knowledge there is no other creature that reproduces by kinematic self-replication and there have never been any Xenobots or selection to be a good Xenobot. They possess a highly altered transcriptome [205], despite the lack of any novel genes, synthetic biology circuits, scaffolds, or anything else – this is revealing the competencies and capabilities of the cell collective, and supports the view of the genome as a resource into which living beings dip as needed for their lifestyle, vs. a prescription of what and how to be. Next, while the conventional paradigm held that this was an unusual property of amphibian, embryonic cells, we explored the implications of the framework that sees plasticity as a fundamental aspect of minimal agents, and investigated the capabilities of *adult, human* cells. This led to the discovery of Anthrobots – self-motile proto-organisms made of adult human tracheal epithelial cells which, among other things, have the ability to heal wounds in surrounding neural tissue [206]. It is likely that this is just the beginning, and we have argued that complementing the field of synthetic biology (attempting to build functionality bottom-up), bioengineering and regenerative medicine both can take advantage of the competency and autonomy of the material [72, 170, 207, 208].

5. Goal-Directed Models as Contrast and Complement to Mechanistic Frameworks: Optimizing Experimental Fecundity

The current frameworks focus on the rules of chemical interactions within protein pathways, dynamical systems, and emergence via complexity arising from iteration of low-level rules in large numbers of parallel cells or networks (agent-based modeling, cellular automata, etc.). These approaches are dominated by discussions of signaling pathways, mechanical networks of forces, and other mechanistic metaphors, but also increasingly include gradients of attractive or repulsive stimuli, measurement, precision, and error, memory, decision-making across various landscapes [154, 209-214]. While very few explicitly emphasize the agency of the various biological components and use appropriate terms from behavior science to modulate them [183, 184], it is clear that even the current teleophobic paradigm is not as far from the right side of the spectrum of persuadability (Figure 1B) as one might think. What are the arguments for pushing further in that direction? Are not mechanistic molecular biology and genetics sufficient?

It is important to state clearly what we are not claiming. 1) We are not claiming that teleological terms should simply be added wherever possible for their own sake. Ours is a pragmatist claim: the applicability of mentalistic metaphors, at any level, needs to be backed up by experimental utility of doing so. They can be neither ruled out nor claimed in any particular case without experimental support. 2) We are also not using the very few examples covered above as the entire evidence for their utility. Those are representative examples but there is a huge field of work in diverse intelligence, evolutionary ecology, developmental biology, synthetic bioengineering, etc. in which many more examples have been and increasingly are found. These ideas do not stand or fall on the basis of any one experimental approach or dataset – they represent a philosophical perspective on the mechanistic and algorithmic continuity revealed by the evolutionary origins of the one uncontroversial example of goal-directed physical beings: brainy organisms. Bioelectricity, while a very convenient system in which to demonstrate the concepts we’re dealing with (because of its symmetry with neural processes), has no monopoly on these properties. Ultimately what we are describing is not the story of bioelectricity but the story of a continuum of cognitive capacities emerging in a wide range of embodiments [60]. And, 3) we are not claiming that any results in this field will be incompatible with the facts of molecular biology or other underlying mechanisms.

This last part is crucial: it is guaranteed that whatever remarkable example of goal-directed activity one studies, whether in the case of humans, tissues, or ant colonies, there will be some physical mechanism underneath. It will never be magic, and if one wants to look at the lowest level, one will always find chemistry (and quantum mechanics underneath that). What this fact does not warrant is an assumption that taking this level of description is optimal. First, because it is now known that some systems really do have causally-potent higher levels of organization [215-225] that do the work that their parts do not do. Second, telling stories consistent with molecular biology *after* something has been discovered is not the same as having a generative paradigm that leads to those discoveries in the first place. One feature that the above examples (Figures 2-4) have in common is that while of course all of these capabilities are consistent with the known properties of genes, proteins, etc. that implement

them, knowing those properties was not sufficient to discover them. They were found by making and testing hypotheses driven by the specific research program of extending mentalistic toolkits to other embodiments and to novel problem spaces (as guided by evolutionary and developmental continuity).

Thus, we argue that the common preference to give explanations at the lowest level of description should be moderated or replaced by the necessity of giving explanations that not only work backwards and are consistent with what was found but enable new findings in the future. We favor a pluralism in which different types of explanations can co-exist, but importantly, there are clear criteria for adjudicating among them. Fecundity is one, but it is only recognized on the scale of decades. Another, more immediate sign is *efficiency* of control: whereas the mainstream approach might call for careful control of a myriad of cells or genes to produce an eye [186] or regenerate a vertebrate leg over a year and a half by a stimulus provided over the first 24 hours [226], an approach focused on prompting the native problem-solving intelligence of cells does it with a very low information-content trigger. The ratio of information and effort put in, vs. obtained out, by the engineer or worker in regenerative medicine is a sure guide as to whether one has identified an optimal level at which to interact with a complex system. Knowing how much needs to be micromanaged and how much ingenuity, memory, autonomy, etc. can be expected from a system is the tractable research program of placing cells, tissues, etc. at the right place on the continuum (in turn, determined by whether you get better payoff from genomic rewiring or the use of tools like training paradigms, psychoactive compounds, communication protocols, etc., or both).

Regenerative medicine and bioengineering are areas in which the practical consequences of different philosophical frameworks play out [72, 208]. The conventional, non-mentalistic, approach to causation in biology, with emphasis on complex but mechanical (indirect, but not cognitive) linkage between genotype and phenotype does not facilitate discoveries regarding the wide plasticity and reprogrammability of life. The causal role approach, which construes goal-directedness as cause/effect relationships in hierarchically organized biological systems, does not suffice either. To detect, and functionally exploit goal-directedness, one needs an account of how information is represented in the network and how interventions at the level of the network can affect that information [60], but the causal role approach does not address this issue, because it treats biological systems as elaborately organized mechanisms, like clocks, rather than as information-processing systems which can implement different degrees of sophisticated, valenced, decision-making. A standard computationalist approach is likewise often insufficient, because biological systems operate with a polycomputing architecture where the mapping of physical events onto salience and meaning is performed by different observers at all scales within the body all of whom interpret it differently [81] based on their prior memories, goals, and cognitive capacities.

A proponent of the causal role theory could reply that the information contained in bioelectric networks could, in theory, be explained in terms of the electrical connections among

cells in the network. But the task of explaining problem-solving capacities of bioelectric or biochemical networks connections among cells would be equivalent to claiming that computer algorithms do not really exist and only Maxwell's equations should be used on the electron flows to understand and make use of computers [50-54]. For the same reason, no one has been able to show (yet) how to reduce information contained in highly complex bioelectric networks, such as brains, to physics or chemistry [41, 227-229]. In our critique of the causal role view, we are not assuming dualism, vitalism, or any type of exotic metaphysics. We are only claiming that to understand and fully exploit the remarkable capabilities of biological systems in novel circumstances, one must ascend above the level of physics and chemistry and consider how information in the networks is represented and processed [60].

Fields [230-232] are helpful contribution to project of explaining goal-directedness in biology. An epistemically sophisticated concept of a field (i.e., a field that contains information) can play a useful role in explaining the behavior of complex biological or mechanical systems. But like the local microenvironmental features that all cell biologists study, on their own fields do not suffice – it is still critical to understand how they are interpreted by the agential medium of life which makes decisions in light of past experience and preferred future states. Also, causal role theories can be useful in helping scientists to understand the relationship between different levels of organization in biological or mechanical systems. Borrowing a distinction from Mayr [25, 77] (see also Laland et al. [233]), we can say that history provides distal explanations of goal-directedness in mechanisms such as bioelectric networks, but the information contained in these networks and the molecular machinery that executes that executes it provides proximate explanations.

Historical approaches also can play an important role in helping biologists understand goal-directedness. Historical approaches might lead biologist to hypothesize that bioelectric networks have played an important role in macroevolution by providing organisms with tools for enhancing variation, adaptation, speciation, reproduction, and survival [62, 63, 234]. For example, bioelectric networks probably contributed to the success of the first multicellular organisms (about 600 million years ago) by facilitating the coordination and control of individual cells to achieve group goals [62, 63]. Evidence for this hypothesis comes from experiments showing the bacteria that grow in biofilms use bioelectric networks to regulate their behavior [62]. Fossil records indicate that organisms started forming biofilms shortly after life originated, about 3.8 billion years ago [235]. So, it is likely that bioelectric networks have evolved over time and become more sophisticated as life has increased in complexity [62]. The chemical and electrical activity in nerve tissue, brains, and other components of the nervous system is a natural extension of preexisting cellular networking capacities [62]. While biologists have long understood that even very simple nervous systems can store and process information, it is important to recognize that this ability is no different from cells have been able to do for eons. Recent computational modeling efforts have shown how the process of evolution is accelerated and made more robust when the material over which evolution

functions has active, computational, and agential properties in the layer between genotype and phenotype [169, 236].

6. A New Approach to Goal-Directedness in Biology

If leading approaches to goal-directedness cannot adequately explain how information guides cells in bioelectric networks, what kind of approach is up to this task? We believe that what is required is an approach that takes seriously the notion that biological systems can receive, store, process, and use information related to goals and use a variety of means to attain goals. That is, an approach that characterizes biological systems as goal-directed agents that have at least a rudimentary form of intelligence.

Because this approach signifies a partial return to the widely disfavored (and many would say, discredited), mentalistic approach to goal-directedness in biology, we need to clarify what we mean by 'intelligent,' 'goal-seeking,' 'agent', and other key concepts, in order to avert unfair critiques or misunderstandings of our view. The elements of our approach are as follows:

1. We follow William James [237] in defining intelligence as the capacity to achieve a goal by different means. Intelligence comes in degrees, depending on the capacities of the agent [61]. The highest forms of intelligence involve consciousness, perception, problem-solving, and metacognition, but lower forms need only involve persistence and plasticity with respect to goal-promotion. Thus, when we describe groups of cells as being goal-directed, we are not claiming that cells are goal-directed or intelligent in the way that human beings are, only that they have certain capacities related to achieving goals.
2. By an agent, we mean a system with the capacity to promote its goals. An agent could include a cell, organism, person, or social group [238]. Agents are always composed of parts, and collections of components are agents to the extent that the parts are sufficiently integrated and well-functioning to achieve the agent's goals – ones that are of a scale, or operate in a problem space, that differs from those of the parts. An agent need not be conscious or even alive to any significant degree; for example, agents could include viruses, computer programs, corporations, or robots. A significant agent executes a perceptual control loop, in which it takes measurements, compares to setpoint, and tries to minimize error with respect to its setpoint and prior expectations. Agents are demarcated by a cognitive light cone determined by the spatiotemporal size of the goals it can pursue (the area of spacetime in which states can motivate corrective action and stress). Higher-level agents sense, act, and make models of the world around them (and themselves). Agents can be described at multiple scales, including the microscopic scale that emphasizes determinism and backwards-looking explanations for events. Use of the word "Agent" refers to a frame that emphasizes: (A) 3rd person

recognition of a system with competency to navigate problem spaces. Low-agency tools (e.g., the tools of physics) are not good at detecting agency (this is why they see chemistry, not minds). Agency is best detected by another agent's cognitive processes in (i.e., external observers such as scientists, parasites, and conspecifics), via perturbational experiments). Detection of Agency is fallible, observer-dependent (not objective), and empirical. (B) 2nd person perspective - attempts to control other agents in a communication/instruction mode - tools along the Continuum of Persuadability (again, dependent on the skill of the observer to deploy the correct tools to exert control and hack the agent to desired outcomes).

3. A goal is an outcome, event, or situation promoted by an agent, such as energy acquisition, information maximization, a specific shape, a specific physiological state, nutrition, health, survival, reproduction, a temperature setting, shelter, territory, companionship, or profit. Goals can be formulated in very concrete spaces (e.g., the goal is drinking water from a stream) or in abstract ones (the goal of living a good life). Different types of agents have different types of goals, and agents expend energy to reach specific states (goals) in diverse problem spaces with different degrees of ingenuity. A goal exists whenever the tools of goal-based frameworks (e.g., cybernetics, control theory, behavioral science) provide good traction on the system (prediction and control). This does not need to be “purpose” (high-level goals where an agent has the meta-cognition to think about having goals and what they might be). The word “goal” is useful to indicate situations where an engineer, conspecific, parasite, or other agent does not need to micromanage some aspects of the system because they can offload that onto the system itself (when it has some ability to pursue goals without needing to be micromanaged at each step).
4. An agent promotes (or pursues) a goal by taking action(s) to achieve it, regardless of whether the agent obtains the goal or even can obtain it. For example, we would say that a developing human embryo has the goal of forming a human child even if the embryo spontaneously aborts. We would also say that a human organization has the goal of promoting a justice society, even if this goal cannot be fully achieved.
5. Goal-promoting comes in degrees, depending on the capacities of the agent. The most advanced forms of goal-promoting involve intentional (conscious, deliberate) action but less advanced forms need only involve persistence and plasticity with respect to a goal. For example, we would say that a thermostat in home is an agent that takes action to regulate temperature in the home by controlling the heating, ventilation, and air conditioning system in response to temperature readings provided by a sensor.
6. The degree to which an agent is intelligent corresponds (roughly) to its possession of some of the following proposed¹⁹ characteristics associated with intelligence:

¹⁹ This is proposal open to revision. We may have omitted some characteristics that should be on the list. See Gardner [239] for some criteria for human intelligence.

- a. **Persistence** [the agent can continue to work toward a goal for some extended time despite difficulties].
- b. **Plasticity** [the agent can achieve a goal from different starting points and is amenable to having the goal changed (not entirely hardwired)].
- c. **Diversity** [the agent has multiple ways of achieving the goal; for example, an organism may have several ways of regulating body temperature, such as sweating, panting, lowering its metabolism, sitting in the shade, etc., and cells can build a new kidney tubule using cell-to-cell communication or cytoskeletal bending mechanisms].
- d. **Information processing** [the agent can receive, store, process, and use information needed to promote its goals; for example, information about skin rupture triggers wound healing, and regeneration of just the right amount of limb tissue in a salamander is based on information about how much was removed and how much still remains].
- e. **Sensation** [the agent can receive sensory information about environment or its own internal states that it uses to promote its goals; for example, a cockroach runs away from a light source and cells move in response to chemical, mechanical, and electrical states of themselves and their neighboring cells].
- f. **Learning** [the agent's behavior and responses can be modified by past experience and change its behavior to achieve its goals; for example, a horse that learns to avoid an electric fence, a bee colony that learns the location of sources of nectar, or a gene regulatory network that learns to respond to a previously-neutral stimulus based on its past presentation with an effective stimulus (Pavlovian conditioning [240, 241])].
- g. **Ingenuity** [the agent can use different methods to achieve a goal, depending on the circumstances; for example, a bird may build a nest with pine needles or grass, depending on availability].
- h. **Novelty** [the agent can use new ways of achieving a goal that it has not had experience with before; for example, a bird that is trapped inside an airport builds a nest on a steel beam, or Xenobots perform kinematic self-replication when the normal frog mode of reproduction is not available to them. Novelty is different from diversity because an agent might have several ways of achieving a goal but none of them are new].
- i. **Organization** [the agent has multiple goals, including coordinated and interacting sub-goals; for example, when a gazelle flees from a cheetah, it must coordinate its breathing, heart rate, digestion, and sensory awareness to achieve the goal of survival; likewise, the process of morphogenesis must meet numerous anatomical, physiological, and metabolic constraints simultaneously].
- j. **Hierarchy** [the agent has a hierarchy of goals used to coordinate goals; for example, for gazelle fleeing from the cheetah, survival takes precedence over other goals it may have, such as feeding].

- k. **Consciousness** [the agent has first-person awareness of qualitative experiences, like pain, hunger, thirst, sensations, and emotions, including valence and affect for specific states].
- l. **Perception** [the agent interprets sensory information based on experience and functional awareness. Though perception involves sensation, it goes beyond sensation and involves a higher level of awareness. For example, a fly that darts from a moving object may be acting based on sensation and instinct, whereas a deer that learns to differentiate between people and other animals and flees from people is acting on perception].
- m. **Mental representation** [the agent forms a mental model of the world, and means of achieving goals; for example, a baby that grabs a teething ring and sticks it in its mouth to soothe its pain, or a planarian tissue that stores a bioelectrical pattern memory of what it should build if it gets injured in the future; mental representations need not necessarily be 2nd-order metacognitive or involve consciousness or subjective experience].
- n. **Self-awareness** [the agent's mental model includes a representation of itself and the has personal memory of its life history].
- o. **Other-awareness** [the agent understands that other agents have self-awareness and thoughts and feelings].
- p. **Planning** [the agent can execute sequential, composite, modular actions to achieve goals via subgoals, such as acquiring materials to make a tool to use in feeding].
- q. **Delayed gratification** [the agent can prioritize goals and delay gratification of needs, wants, or desires for longer term goals, and is able to move temporarily away from its goal in order to re-coup gains later].
- r. **Problem-solving** [the agent uses its memory, perception, and representational abilities to find different possible ways of achieving goals and outcomes; the agent might be a conventional group of cells in a body, for example, a crow that places pebbles in a pitcher to make the water level rise so as to obtain food or water [242], or a larger-scale swarm made of living bodies, such as a group of ants that is able to manipulate a geometric shape through a maze [28]. In each case, goals are defined with respect to different scales' agents and their problem-spaces.]
- s. **Language** [the agent can use symbols to communicate information, intentions, or emotions to other agents to achieve common goals; the agent can be persuaded by linguistic communication; sophisticated language entails the use of a generative grammar].
- t. **Selfhood** [broadly conceived, a Self is a term that emphasizes 1st-person inner perspective consisting of valence, attention, and decision-making. Selves are owners of goals, preferences, and memories that do not belong to any of their parts—an emergent whole implemented by an interlocked triad of: an option

space within which it operates, a cognitive light cone demarcating the size of goals in that space which the system can pursue, and a set of cognitive/computational processes that allow the system to navigate the space with some degree of competency). Selves live forward in time, being essentially decision-making systems that cannot be effectively described by deterministic backwards-looking causal stories. Selves arise when some collection of parts all buy in to the same shared story (model) of themselves and their environment (e.g., when cells become coupled by gap junctions, which allows them to share physiological engrams of experiences and thus build up the same internal models/memories, become a coherent emergent morphogenetic agent like an embryo). A defining feature of significant Selves is that they do not try to observe reality "as it is" (preserving the fidelity of information about the environment's microstates) but instead compress and coarse-grain it into memories that will allow their future instances to preserve adaptive salience, not detail [243]. Selves interpret and reinterpret their memory engrams as they do with any input or signal, not being tied to how the sender (including their own past Selflet) meant it but doing the best they can to extract adaptive meaning in current internal and external circumstances (this is an example of Polycomputing). Selves are primarily sense-making systems, which reinforce their own reality via models of the world in which they exist].

- u. **Abstract thinking** [the agent can mentally represent and manipulate abstract concepts, such as numbers, shapes, words, time, and so on].
- v. **Realism** [the agent makes use of categories for distinguishing between reality and fantasy, truth and lies].
- w. **Reasoning** [the agent can use deductive or inductive reasoning to make inferences, construct arguments, solve mathematical equations, draw connections between ideas, test hypotheses, design artifacts; the agent can be persuaded by abstract arguments].
- x. **Emotional maturity** [the agent has the ability to understand and manage its emotions and react appropriately to others' emotions].
- y. **Meta-cognition** [the agent can think about its own thinking, is critically aware of itself and its environment, and choose its own goals, including abstract goals, such as finding meaning and purpose in existence].
- z. **Morality** [the agent has moral agency; that is, the agent can act according to moral standards, use moral standard to evaluate other agents or situations, develop and critically reflect on moral standards].

7. A key task of biology and other sciences is to understand an agent's capacities (or its place on spectrum of intelligence) because information about these capacities is crucial for

explaining, predicting, and manipulating the agent's behavior [23, 60, 62].²⁰ If an agent is not capable of understanding language, then there is little point in using language to try to influence the agent's behavior. If an agent is capable of understanding language, then using language to influence their behavior may be preferable to using brute force. There is a spectrum of persuadability corresponding to the spectrum of intelligence [60] (see Figure 1). Highly intelligent agents, such as human beings, can be persuaded by language and rational arguments, while mechanical devices with no software, such as clocks, can be persuaded only by mechanistic interventions (i.e., brute force). Some animals, such as dogs, horses, and mice, can be persuaded by operant conditioning. As we saw in Section 4, cells connected by bioelectric networks can be persuaded by modifying their stored information. In Section 7, we will discuss how understand the behavior of bioelectric networks and developing methods for persuading (or "hacking") them may have important applications in regenerative medicine, oncology, and other disciplines.

8. Contemporary literature on teleology and teleonomy has focused on trying to establish necessary and sufficient conditions for ascribing functions to traits. The approach has generated a barrage of definition, counterexamples, and refinements. We are not interested in engaging in this dialectic because we believe that the term 'function', like many other important concepts in science and philosophy, has multiple meanings and therefore may be impossible to define by means of rigid rules.²¹ We view goal-directedness, functionality, and related ideas family-resemblance concepts [244, 245]; that is, one can develop a list of characteristics associated with these concepts, but not a set of necessary and sufficient conditions for applying them. We are more interested in developing a concept of goal-directedness that has scientific and practical value than in promulgating a definition that is impervious to semantic critiques.
9. Although we have developed our approach to goal-directedness in biology to describe, explain, and predict the behavior of bioelectric networks in morphogenesis, the list of characteristics associated with goal-directedness does not depend on the method of control. Biological systems have many different methods of coordinating behavior to attain goals, including chemical signaling, physical control, behavioral communication, and symbolic language. Since our approach to goal-directedness is not tied to any of these methods, it can be applied to various systems, including ant colonies, genetic regulatory networks, bird flocks, economies, ecologies, and so on. It could also be applied to alien life

²⁰ Lee and McShea [105] have developed a methodology for measuring goals-directedness. While we think that measurement can play a key role in advancing our understanding of goal-directedness, we are not sure whether it is possible to accurately, precisely, and consistently measure goal-directedness when a system has more than a rudimentary level of intelligence, due to the complexity of the system and the number of different metrics that might apply. Rather than trying to assign a numeric value to the goal-directedness of a system, it may be more fruitful to describe the system's capacities and place it on a relative scale. That is, to measure goal-directedness qualitatively rather than quantitatively.

²¹ 'Life' may also resist definition by means of rigid rules [16].

forms and non-biological systems, such as artificially intelligent machines, robots, swarms of nanobots, and so on.

10. While we are claiming that intelligence comes in degrees, we are not claiming all matter has some degree of intelligence. To have some degree of intelligence, a system must at least have persistence and plasticity. A thermostat has such qualities, but a chunk of granite or even a diamond, does not. While we want to extend the scope of mental concepts, we are not defending panpsychism.
11. Although we believe that subjective, qualitative experience emerges at some point on the spectrum of intelligence, we do not have a view on why or how this happens. We are not addressing the “hard problem of consciousness” [228]. We are only dealing with “easy” problems related to intelligence, such as agency, information processing, memory, problem-solving, cognition, and language.

7. Applications: looking toward the future

The validity of conceptual frameworks is recognizable from the novel research programs they facilitate and new capabilities that they enable to be visualized and pursued. We envision a number of new research directions made possible by unleashing powerful concepts from behavioral and cognitive sciences on problems ranging across biomedicine, bioengineering, ecology, evolution, and AI.

First, the recognition of problem-solving capacities in cells and tissues opens the way to research in how they perform computations that are currently intractable to our biomedicine and drug discovery efforts. For example, newt cells can build a correctly sized and shaped body despite large variability in the ploidy of cells, adapting to new copy number of DNA and drastic changes in cell size by using novel molecular mechanisms as needed to create the same structures [246, 247]. Likewise, planaria exposed to barium experience a drastic degeneration of the entire head (as barium abrogates necessary potassium exchange), but quickly regenerate a new, barium-adapted head by finding just a handful of genes among their genome whose up-regulation enables them to solve this completely novel physiological stressor [171, 248]. Understanding how cells find solutions, in very large problem spaces, to novel challenges involving their own parts and the external environment could revolutionize the biomedical search for interventions to disease states. We currently have few algorithms that can systematically identify such solutions (often relying on expensive screens), and the tools of cognitive and behavioral science are an extremely promising avenue to creating bio-inspired ways to find therapeutics.

More broadly, the many examples of plasticity of form and function with unchanged genetics [175, 249] enable the same kind of powerful reprogrammability afforded by brain-based flexibility of behavior. This bodes well for coaxing new outcomes without gene therapy and intractable attempts to guess the necessary genetic changes for desired complex system-level outcomes [250]. Applications in cancer and birth defects [198, 199, 251, 252] have already

shown a roadmap for how the same genetically-encoded hardware can be modified and repaired by signals and stimuli that exploit the agential material of life top-down [183].

Second, we have argued [72, 208] for a novel path to definitive regenerative medicine but not for micromanaging symptoms, with the attendant side effects and unpredictable efficacy, but true solutions to injury, degeneration, aging, and cancer. This requires the discovery of storage and encoding of goal states (bioelectrical and other) which can be re-written by therapeutics, in effect getting buy-in from the cells (vs. unwanted compensatory responses). A broader version of this research program expands from directly re-writing goal states to actual training protocols in which cells' and tissues' basal cognition processes [59, 253, 254] are exploited via positive and negative reinforcement and behavior shaping protocols [255] toward desired physiological and anatomical outcomes too complex to micromanage with current tools. Indeed, it is possible to train not only cells and tissues but molecular pathways within cells, opening the path for drug conditioning and many applications in novel use of pharmaceuticals [207].

Third, a broader development and use of tools from the sciences of mind impact bioengineering and the development of synthetic living machines [256-259], with the realization that we must manage not only emergent form and function but also emergent cognition. We envision a new set of tools for programming biobots with stimuli and experiences, not only synthetic biology circuits. Beyond the utility of these machines for us, the realization of degrees of mind in unconventional embodiments [69, 260] forces sharper questions of ethics and what we owe the agents that we create. No longer is it sufficient to compare organoids to human brains, or to assume that lack of conventional sense organs and motility in an in vitro construct means that it's not "embodied" (not running perception-action goal-directed loops in physiological and other spaces that are hard for us to see) [70]. Moving away from human cognition as a standard in ethical models toward a realization of diverse embodiments gives rise to a robust research program to expand ethical frameworks built on unsustainable ancient binary categories and update it in light of the recent science of diverse intelligence.

An important frontier for combating the mind-blindness and teleophobia that has held back progress is the development of conceptual and practical tools for communication and collaboration with unconventional and non-linguistic systems. The future use of AI and other tools as a kind of translator module between radically different kinds of minds will enable a new frontier of more ethical synthbiosis with being from bioengineered life to entire ecosystems. Especially critical is the fact that this set of frameworks enables a much more natural expansion of ethical, legal, and social structures to encompass the forthcoming cyborgs, hybrot, and other composite beings that cannot readily be assigned to the human (or life) vs. machine categories. The forthcoming variety of human and non-human minds, far broader than Darwin's original "endless forms most beautiful" [55], require a more sophisticated framework and cannot be dealt with by current binary categorizations.

8. Objections

Before concluding our essay, we would like to address a few key objection to help build that case for our view and help the reader understand it.

First objection: You are implying that scientists and philosophers should abandon current approaches to goal-directedness, which seem to do a pretty good job of explaining some important cases, such as homeostatic regulation and the evolution of biological adaptations. Why throw out the baby with the bathwater?

Reply: As we stressed in Section 5, we are not arguing that these other the approaches should be rejected, but we are arguing they cannot adequately explain, and more importantly, extend, the experimental approaches described in Section 4 and therefore a new approach, which more effectively drives research into the competencies of unconventional embodiments of mind (with its many practical applications), is needed. Current approaches could be used, depending on that type of goal-directedness that scientists are trying to understand. Some types of low-level of goal-directedness, such as homeostasis, might be best explained in terms of causal roles and relationships with no mention of agency or intelligence. Biological adaptations, in many cases, could be explained in terms of the operation of natural selection over time and nothing more. We see no need to interfere with the use of explanatory frameworks that yield fruitful results. Since we accept multiple approaches to goal-directedness, our view could be characterized as pluralistic and inclusive, even though it represents a conceptual shift toward mentalism. We argue that, on the spectrum of agency, the goal should be to empirically determine the optimal position for a given system – not intentionally skew low (Morgan’s Canon [261]) nor high (animism) but use experiments to determine which discipline (ranging across physics, cybernetics, behavioral science, psychoanalysis, etc.) provides the most payoff in terms of prediction, control, and synthetic discovery of new vistas of research.

Second Objection: Your approach is incompatible with scientific materialism because it involves mentalism, which is too high a price to pay for explaining experimental results. Scientists and philosophers have worked hard since the 1950s to show how to teleonomic language in biology provide materialistic explanations of goal-directedness and your approach would undo all that.

Reply: As we have argued earlier, we think that our approach is compatible with scientific materialism, because we are not assuming the existence of metaphysically irreducible minds. We hold that mind, intelligence, and agency, related terms are ultimately compatible with the objects, processes, and properties belonging to physics and chemistry [60, 61]. While cognitive scientists, neuroscientists, and philosophers have made tremendous progress toward the goal of understanding how the human mind functions in the last 50 years, its achievement is decades away. We readily acknowledge that the mind-body problem remains one of science’s great mysteries [228, 262], but we argue that the way to make progress on this and other problems is to move away from the implicit dualism of artificial sharp boundaries between

canonical mind-ful entities and their more primitive origins and instead develop principled research programs that seek to understand the scaling and transformation of diverse cognitive capacities on evolutionary and ontogenic timescales.

Third Objection: The use of the word Intelligence and other cognitive terms applied outside of its familiar context of brainy animals immediately raises questions: might not these terms be misused? Are not morphogenetic systems simply following the rules of chemistry – why anthropomorphize them?

Reply: First, in the modern age, we must accept that *all* cognitive systems – ourselves included – exhibit chemistry, not magic, when one drills down to examine the lower levels. Thus, there simply is no special human category which one can correctly anthropomorphize as somehow being beyond the laws of physics at its base. We argue that this word is an anachronism and needs to be retired in favor of an empirically-grounded view, updated with the latest findings in causal information theory [215-220, 263], in which it is perfectly possible (in fact, unavoidable) for a system to both, be subject to chemistry, and also to possess additional levels of description and control whose recognition affords novel benefits. We offer two points in clarifying our use of this terminology (developed in detail in [60]). An uncontroversial aspect of our view is that claims of intelligence (and other cognitive terms), like all others, must be based on rigorous experiment, supported or ruled out by the degree of objective benefit that a given framing affords in terms of a) prediction and control, and b) future discovery (and new research programs) it suggests. The latter is most significant, because almost any paradigm can be rescued by enough epicycles; indeed, after one has discovered a new effect or reached a new capability, it is easy to drill down to the chemistry and – looking backwards – claim that there is no intelligence here because it mechanically follows the laws of physics. The same is true for any act of a complex human brain-body system – if one insists on a view from the level of particles, it will always be there. The key question is: does that level of perspective provide the most interesting platform from which to make the next discovery or develop the most effective control policy? The emphasis should be on novel capabilities, and new research programs facilitated (or suppressed) by a given perspective. Thus, we propose that attempts to mine the rich toolbox of behavioral science to understand and exploit capabilities of morphogenetic systems will continue to pay off in many (but no doubt, not all) cases. We have fleshed out the prior gains facilitated by this view, and the promises for regenerative medicine, elsewhere [72, 207]. The less conventional, and sometimes uncomfortable, aspect of our position is that the empirical utility of framings needs to be applied fearlessly, and followed wherever it may lead: its empirical consequences must be taken seriously even when they contradict long-cherished a priori commitments to how non-intelligent a non-brainy system must be. In other words, if a specific framing, which uses tools normally reserved for brains, results in fruitful new research programs on bacterial biofilms [147-149], plant roots [264-270], the training of gene-regulatory networks [240, 241, 271, 272], or developmental/regenerative biology [75], then the scientific approach requires that we consider those systems to be bona fide subjects of that corner of the

natural world that is supposed to be described by the behavioral science of a spectrum of minds.

Fourth objection: aren't you mistaking emergent complexity and unpredictability for intelligence? Is there really a research program here?

Reply: explicitly, we hold that the reason to attribute intelligence to a process such as morphogenesis is *not* because it looks complex, unpredictable, agential, or anything else. The only reason to attribute a specific degree of intelligence (and claim specific capabilities as listed above) is to do perturbative experiments that reveal them. These competencies cannot be inferred from strictly observational data, and complexity alone is insufficient – different types of problem-solving capacities need to be explicitly demonstrated in functional experiments. Likewise, they cannot be ruled out based on philosophical commitments or classical categories and colloquial language use but must be argued against based on experimental evidence. The research program we propose is rigorously focused on empirically testing, not historically assuming, the boundaries between disciplines that have suppressed new discoveries by the gate-keeping threat of “category errors”. The categories must evolve with the science, not be maintained for historical reasons. Just as people are using tools of cognitive science to rigorously test the capacities of swarm intelligence [28, 273, 274] in collectives of animals (going up a level from conventional individuals), we emphasize the utility of testing these tools in novel substrates and at novel scales [23, 101, 151, 253, 254, 275-282]. In all of these cases, an operational, pragmatic view of cognitive terms suggests that when their application results in progress and new discoveries, they are legitimately applicable.

Fifth Objection: isn't it odd to expect cognition in non-brainy substrates – why would it be there?

Reply: on the contrary, taking evolution seriously requires that there be ancestral functions leading up to the development of the most obvious features of brains. Indeed, it is now known [283, 284] that all of the mechanisms used by the brain to carry out its amazing functions – ion channels, electrical synapses, neurotransmitters – are evolutionarily ancient and are already doing brain-like signaling in bacterial biofilms. Not only the mechanisms, but many of the algorithms around information processing, active inference, etc. are widely conserved beyond brains [64, 184, 285]. Thus, if either mechanistic composition or functional behavior are taken as the kinds of things that provide evidence for cognition, there should be no surprise to find it in the living material that was speed-optimized and augmented to become the central nervous system.

9. Conclusion

Returning to where we began in this paper, since Aristotle's time, scientists have been trying to understand purposiveness in the living world. Attempts to banish teleological

concepts from the life sciences have proven to be largely unsuccessful because life exhibits myriad forms of goal-directedness that cannot be easily explained in causal-mechanical terms and teleological concepts, such as goal, purpose, and function, are useful in hypothesis formation, model building, and experimental design. In response to this predicament, scientists and philosophers have proposed theories of biological teleology that avoid the use of methodologically “dubious” mentalistic concepts and explain goal-directedness by referring to properties, processes, and objects that seem to be compatible with a mechanistic worldview, such as genetic program, causal role, adaptation, and field. While these non-mentalistic approaches to teleology can account for many phenomena in biology and other domains, they are not capable of adequately explaining ground-breaking experimental results in morphogenesis, synthetic biology, and other fields, described in this paper, which involve the manipulation of cells and tissues connected by bioelectric networks. In this paper, we have defended a mentalistic approach to goal-directedness to account for these and other experimental results, but the view also applies to other biological systems that exhibit complex, goal-directed behaviors, such as ant colonies, economies, and genetic regulatory networks. Our view is motivated not by the desire to prove any philosophical points but by the practical necessity of developing concepts that can fruitfully guide inquiry in these fields of research and suggest testable hypotheses and explanatorily robust models and theories.

Based on the arguments and conceptual clarifications we have made in this paper, and examples of real research programs that are not only consistent with, but actually driven by, the ideas we have defended, it is clear that a continuous, pluralistic, and pragmatic approach to agency, mind, and cognition beyond the brain is possible. The field of diverse intelligence offers numerous opportunities to move beyond the increasingly limiting teleophobia and animism of the past, toward developing principled theories that port tools and concepts across the increasingly blurring boundaries of disciplines that were established centuries ago. Truly transdisciplinary work spanning science and philosophy can now be done, to positively impact clarity about the status of embodied minds and the biomedicine, engineering, and other practical advances that await our ability to optimally interact with intelligence in unfamiliar guises.

Acknowledgements:

Dr. Resnik’s research is supported by the Intramural Program of the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH). Dr. Levin thanks Eugene Jhong for his support. We thank Julia Poirier for editorial assistance with the manuscript. The views expressed in this paper do not represent the views of the NIEHS, NIH, or U.S. government.

References

1. Mayr, E., *The Growth of Biological Thought*. 1982, Cambridge, MA: Harvard University Press.
2. Aristotle, *Physics*. MIT Classics. 2009 [350 BCE].
3. Aristotle, *Nicomachean Ethics*. 2009 [350 BCE].
4. Jacob, M., *The Scientific Revolution: A Brief History with Document*. 2nd ed. 2018, London, UK: Bedford/St. Martin's.
5. Georgiev, G. and I. Georgiev, *The least action and the metric of an organized system*. Open Systems & Information Dynamics, 2002. **9**(4): p. 371-380.
6. Annala, A., *Least-time paths of light*. Monthly Notices of the Royal Astronomical Society, 2011. **416**(4): p. 2944-2948.
7. Ogborn, J., J. Hanc, and E. Taylor. *Action on stage: historical introduction*. in *2006 GIREP Conference, Modeling in Physics and Physics Education*. 2006. Amsterdam.
8. Dennett, D.C., *Darwin's Dangerous Idea: Evolution and the Meanings of Life*. 1995, New York, NY: Simon & Schuster.
9. Darwin, C., *On the Origin of Species by Means of Natural Selection*. 1859, John Murray, Albemarle Street: London.
10. Weiner, N., *Cybernetics: Or Control and Communication in the Animal and the Machine*. 1948, Paris, France: Hermann & Cie.
11. Rosenblueth, A., N. Wiener, and J. Bigelow, *Behavior, purpose, and teleology*. Philos Sci, 1943. **10**(1): p. 18-24.
12. McShea, D.W., *Machine wanting*. Stud Hist Philos Biol Biomed Sci, 2013. **44**(4 Pt B): p. 679-87.
13. Nechansky, H., *Elements of a cybernetic epistemology*. Kybernetes, 2007. **36**(2): p. 157-174.
14. Bussieniers, E., T. Veloz, and F. Heylighen, *Goal Directedness, Chemical Organizations, and Cybernetic Mechanisms*. Entropy (Basel), 2021. **23**(8).
15. Heylighen, F., *The meaning and origin of goal-directedness: a dynamical systems perspective*. Biological Journal of the Linnean Society, 2023. **139**(4): p. 370-387.
16. Gómez-Márquez, J., *What is life?* Mol Biol Rep, 2021. **48**(8): p. 6223-6230.
17. Monod, J., *Chance and necessity: An essay on the Natural Philosophy of Modern Biology*. 1972: Vintage Books.
18. Rosenberg, A., *The Structure of Biological Science*. 1985, Cambridge, UK: Cambridge University Press.
19. Allen, C. and J. Neal, *Teleological notions in biology*, in *Stanford Encyclopedia of Philosophy*, E.N. Zalta, Editor. 2020, Metaphysics Research Lab, Stanford University: Stanford, CA.
20. Resnik, D.B., *Functional language and biological discovery*. Journal for General Philosophy of Science, 1995. **26**: p. 119-134.
21. Watson, J.D., *The Double Helix*. 2001, New York, NY: Touchstone.
22. Toepfer, G., *Teleology and its constitutive role for biology as the science of organized systems in nature*. Stud Hist Philos Biol Biomed Sci, 2012. **43**(1): p. 113-9.
23. Levin, M., *Collective Intelligence of Morphogenesis as a Teleonomic Process*, in *Evolution "On Purpose"*, C.A. Corning, et al., Editors. 2023, MIT Press: Cambridge, MA. p. 175-198.
24. Dobzhansky, T., *Nothing in biology makes sense except in the light of evolution*. American Biology Teacher, 1973. **35**(3): p. 125-129.
25. Mayr, E., *The Idea of Teleology*. Journal of the History of Ideas, 1992. **53**(1): p. 117-135.
26. Bacon, F., *The Advancement of Learning*, H. Morley, Editor. 1605.
27. Haack, S., *Defending Science - Within Reason: Between Scientism And Cynicism*. 2007, New York, NY: Prometheus Books.

28. Dreyer, T., et al., *Comparing cooperative geometric puzzle solving in ants versus humans*. Proc Natl Acad Sci U S A, 2025. **122**(1): p. e2414274121.
29. Sakiyama, T. and Y.P. Gunji, *The Kanizsa triangle illusion in foraging ants*. Biosystems, 2016. **142-143**: p. 9-14.
30. Sakiyama, T. and Y.P. Gunji, *The Muller-Lyer illusion in ant foraging*. PLoS One, 2013. **8**(12): p. e81714.
31. Wright, L., *Teleological Explanations*. 1976, Los Angeles, CA: University of California Press.
32. Ruse, M.E., *The Philosophy of Biology*. 1973, Atlantic Highlands, NJ: Humanities Press.
33. Nagel, E., *Teleology Revisited and Other Essays in the Philosophy and History of Science*. 1979, New York, NY: Columbia University Press.
34. Pearl, J., M. Glymour, and N.P. Jewell, *Causal Inference in Statistics*. 2016, New York, NY: Wiley.
35. Wolchover, N. *Quantum mischief rewrites the laws of cause and effect*. Quanta Magazine, 2021.
36. Friston, K. and P. Ao, *Free energy, value, and attractors*. Comput Math Methods Med, 2012. **2012**: p. 937860.
37. Friston, K., *Life as we know it*. J R Soc Interface, 2013. **10**(86): p. 20130475.
38. Rosen, R., *Anticipatory systems : philosophical, mathematical, and methodological foundations*. 1985, Oxford, England ; New York: Pergamon Press.
39. Rosen, R., *Anticipatory Systems in Retrospect and Prospect*. Gen Syst, 1979. **24**: p. 11-23.
40. Woodfield, A., *Teleology*. 1976, Cambridge, UK: Cambridge University Press.
41. Dennett, D.C., *The Intentional Stance*. 1989, Cambridge, MA: The MIT Press.
42. Ducasse, C.J., *Explanation, Mechanism, and Teleology*. The Journal of Philosophy, 1925. **22**(6): p. 150-155.
43. Bedau, M., *Where's the good in teleology?* Philosophy and Phenomenological Research, 1992. **52**(4): p. 781-806.
44. Skinner, B.F., *Beyond Freedom and Dignity*. 1971, New York, NY: Alfred A Knopf.
45. Driesch, H., *The History and Theory of Vitalism*. 1914, London: MacMillan.
46. Bergson, H., *Creative Evolution*. 1911, New York, NY: Henry Holt and Company.
47. Ellis, G. and B. Drossel, *How Downwards Causation Occurs in Digital Computers*. Foundations of Physics, 2019. **49**(11): p. 1253-1277.
48. Walker, S.I., P.C.W. Davies, and G.F.R. Ellis, *From matter to life : information and causality*. 2017, Cambridge, United Kingdom: Cambridge University Press. xxii, 494 pages.
49. Ellis, G.F.R., D. Noble, and T. O'Connor, *Top-down causation: an integrating theme within and across the sciences?* Interface Focus, 2011. **2**(1): p. 1-3.
50. Ellis, G.F., *Top-down causation and emergence: some comments on mechanisms*. Interface Focus, 2012. **2**(1): p. 126-40.
51. Ellis, G.F.R. and C.S. Bloch, *Top-Down Causation, Adaptive Selection, and Their Consequences*. Human Development, 2011. **54**(2): p. 93-100.
52. Ellis, G.F.R., *Top-Down Causation and the Human Brain*. Downward Causation and the Neurobiology of Free Will, 2009: p. 63-81.
53. Ellis, G.F.R., *On the nature of causation in complex systems*. Transactions of the Royal Society of South Africa, 2008. **63**(1): p. 69-84.
54. Auletta, G., G.F. Ellis, and L. Jaeger, *Top-down causation by information control: from a philosophical problem to a scientific research programme*. J R Soc Interface, 2008. **5**(27): p. 1159-72.
55. Clawson, W.P. and M. Levin, *Endless forms most beautiful 2.0: teleonomy and the bioengineering of chimaeric and synthetic organisms*. Biological Journal of the Linnean Society, 2023. **139**(4): p. 457-486.

56. Baluška, F. and M. Levin, *On Having No Head: Cognition throughout Biological Systems*. Front Psychol, 2016. **7**: p. 902.
57. Lyon, P., *The biogenic approach to cognition*. Cogn Process, 2006. **7**(1): p. 11-29.
58. Lyon, P., *Of what is "minimal cognition" the half-baked version?* Adaptive Behavior, 2020. **28**(6): p. 407-424.
59. Lyon, P., *The cognitive cell: bacterial behavior reconsidered*. Front Microbiol, 2015. **6**: p. 264.
60. Levin, M., *Technological Approach to Mind Everywhere: An Experimentally-Grounded Framework for Understanding Diverse Bodies and Minds*. Front Syst Neurosci, 2022. **16**: p. 768201.
61. Levin, M. and D.C. Dennett *Cognition All the Way Down*. Aeon, 2020.
62. Levin, M., *Bioelectric networks: the cognitive glue enabling evolutionary scaling from physiology to mind*. Anim Cogn, 2023. **26**(6): p. 1865-1891.
63. Levin, M., *Darwin's agential materials: evolutionary implications of multiscale competency in developmental biology*. Cell Mol Life Sci, 2023. **80**(6): p. 142.
64. Kuchling, F., et al., *Morphogenesis as Bayesian inference: A variational approach to pattern formation and control in complex biological systems*. Phys Life Rev, 2020. **33**: p. 88-108.
65. Ramstead, M.J.D., et al., *Variational ecology and the physics of sentient systems*. Phys Life Rev, 2019. **31**: p. 188-205.
66. Ramstead, M.J.D., P.B. Badcock, and K.J. Friston, *Answering Schrodinger's question: A free-energy formulation*. Phys Life Rev, 2018. **24**: p. 1-16.
67. Kirchhoff, M., et al., *The Markov blankets of life: autonomy, active inference and the free energy principle*. J R Soc Interface, 2018. **15**(138).
68. Allen, M. and K.J. Friston, *From cognitivism to autopoiesis: towards a computational framework for the embodied mind*. Synthese, 2018. **195**(6): p. 2459-2482.
69. Rouleau, N. and M. Levin, *The Multiple Realizability of Sentience in Living Systems and Beyond*. eNeuro, 2023. **10**(11): p. ENEURO.0375-23.2023
70. Fields, C. and M. Levin, *Competency in Navigating Arbitrary Spaces as an Invariant for Analyzing Cognition in Diverse Embodiments*. Entropy (Basel), 2022. **24**(6): p. 819.
71. Levin, M., *The Computational Boundary of a "Self": Developmental Bioelectricity Drives Multicellularity and Scale-Free Cognition*. Front Psychol, 2019. **10**(2688): p. 2688.
72. Lagasse, E. and M. Levin, *Future medicine: from molecular pathways to the collective intelligence of the body*. Trends Mol Med, 2023. **29**(9): p. 687-710.
73. Levin, M., *Morphogenetic fields in embryogenesis, regeneration, and cancer: non-local control of complex patterning*. Biosystems, 2012. **109**(3): p. 243-61.
74. Levin, M., *Life, death, and self: Fundamental questions of primitive cognition viewed through the lens of body plasticity and synthetic organisms*. Biochem Biophys Res Commun, 2021. **564**: p. 114-133.
75. Levin, M., *Bioelectric signaling: Reprogrammable circuits underlying embryogenesis, regeneration, and cancer*. Cell, 2021. **184**(8): p. 1971-1989.
76. Pittendrigh, C.S., *Adaptation, natural selection and behavior*, in *Behavior and Evolution*, A. Roe and G.G. Simpson, Editors. 1958, Yale University Press: New Haven, CT. p. 390-416.
77. Mayr, E., *Cause and effect in biology*. Science, 1961. **134**(3489): p. 1501-6.
78. Mayr, E., *Teleological and teleonomic, a new analysis*, in *Methodological and Historical Essays in the Natural and Social Sciences*, R.S. Cohen and M.W. Wartofsky, Editors. 1974, Springer: Dordrecht, The Netherlands. p. 91-117.
79. Dresow, M. and A.C. Love, *Teleonomy: Revisiting a Proposed Conceptual Replacement for Teleology*. Biol Theory, 2023. **18**(2): p. 101-113.
80. Garson, J., *A Critical Overview of Biological Functions*. 2016, Dordrecht, the Netherlands: Springer.

81. Bongard, J. and M. Levin, *There's Plenty of Room Right Here: Biological Systems as Evolved, Overloaded, Multi-Scale Machines*. Biomimetics (Basel), 2023. **8**(1).
82. Fields, C., et al., *A free energy principle for generic quantum systems*. Prog Biophys Mol Biol, 2022. **173**: p. 36-59.
83. Sommerhoff, G., *Analytical Biology*. 1950, London, UK: Oxford University Press.
84. Braithwaite, R.B., *Scientific Explanation*. 1953, Cambridge, UK: Cambridge University Press.
85. Nagel, E., *The Structure of Science*. 1961, New York, NY: Harcourt.
86. McShea, D.W., *Upper-directed systems: a new approach to teleology in biology*. Biology & Philosophy, 2012. **27**(5): p. 663-684.
87. Hempel, C.G., *Aspects of Scientific Explanation: And Other Essays in the Philosophy of Science*. 1965, New York, NY: Free Press.
88. Cummins, R., *Functional Analysis*. The Journal of Philosophy, 1975. **72**(20): p. 741-765.
89. Amundson, R. and G.V. Lauder, *Function without purpose*. Biology & Philosophy, 1994. **9**(4): p. 443-469.
90. Couch, M.B., *Causal role theories of functional explanation*, in *Internet Encyclopedia of Philosophy*. 2023.
91. Wimsatt, W.C. *Complexity and organization*. in *Philosophy of Science Association 1972*. 1972. Lansing, MI: D. Reidel.
92. Eronen, M.I. and D.S. Brooks, *Levels of organization in biology*, in *Stanford Encyclopedia of Philosophy*, E.N. Zalta and U. Nodelman, Editors. 2024, Metaphysics Research Lab, Stanford University: Stanford, CA.
93. Sender, R., S. Fuchs, and R. Milo, *Revised Estimates for the Number of Human and Bacteria Cells in the Body*. PLoS Biol, 2016. **14**(8): p. e1002533.
94. Marieb, E. and K. Hoehn, *Human Anatomy & Physiology*. 11th ed. 2018, London, UK: Pearson.
95. Ho, B., A. Baryshnikova, and G.W. Brown, *Unification of Protein Abundance Datasets Yields a Quantitative Saccharomyces cerevisiae Proteome*. Cell Syst, 2018. **6**(2): p. 192-205 e3.
96. Institute, N.H.G.R. 1966: *Yeast genome sequenced*. [website] 2013; Available from: <https://www.genome.gov/25520379/online-education-kit-1996-yeast-genome-sequenced>
97. Woolford, J.L., Jr. and S.J. Baserga, *Ribosome biogenesis in the yeast Saccharomyces cerevisiae*. Genetics, 2013. **195**(3): p. 643-81.
98. Gershman, S.J., et al., *Reconsidering the evidence for learning in single cells*. Elife, 2021. **10**.
99. Kukushkin, N.V., et al., *The massed-spaced learning effect in non-neural human cells*. Nat Commun, 2024. **15**(1): p. 9635.
100. Pershin, Y.V., S. La Fontaine, and M. Di Ventra, *Memristive model of amoeba learning*. Phys Rev E Stat Nonlin Soft Matter Phys, 2009. **80**(2 Pt 1): p. 021926.
101. Saigusa, T., et al., *Amoebae anticipate periodic events*. Phys Rev Lett, 2008. **100**(1): p. 018101.
102. Guerriero, J.L., *Macrophages: Their Untold Story in T Cell Activation and Function*. Int Rev Cell Mol Biol, 2019. **342**: p. 73-93.
103. Lendeckel, U., S. Venz, and C. Wolke, *Macrophages: shapes and functions*. ChemTexts, 2022. **8**(2): p. 12.
104. McShea, D.W., *Evolutionary trends and goal directedness*. Synthese, 2023. **201**(5): p. 178.
105. Lee, J.G. and D.W. McShea, *Operationalizing Goal Directedness: An Empirical Route to Advancing a Philosophical Discussion*. Philosophy, Theory, and Practice in Biology, 2020. **12**(20220112): p. 5.
106. Babcock, G. and D.W. McShea, *An externalist teleology*. Synthese, 2021. **199**(3-4): p. 8755-8780.
107. Millikan, R., *Language, Thought and Other Biological Categories*. 1984, Cambridge, MA: MIT Press.
108. Millikan, R.G., *In Defense of Proper Functions*. Philosophy of Science, 1989. **56**(2): p. 288-302.

109. Neander, K., *Functions as selected effects*. Philosophy of Science, 1991. **58**(2): p. 168–184.
110. Garson, J., *A Generalized Selected Effects Theory of Function*. Philosophy of Science, 2017. **84**(3): p. 523-543.
111. Medicine, P. *Heart murmurs*. 2023; Available from: <https://www.pennmedicine.org/for-patients-and-visitors/patient-information/conditions-treated-a-to-z/heart-murmur>.
112. Lewine, H.E. *What is a normal heart rate?* . Harvard Health News 2023.
113. Ayala, F.J., *Teleological Explanations in Evolutionary Biology*. Philosophy of Science, 1970. **37**(1): p. 1-15.
114. Wimsatt, W.C., *Teleology and the logical structure of function statements*. Studies in History and Philosophy of Science Part A, 1972. **3**: p. 1-80.
115. Boorse, C., *Health as a Theoretical Concept*. Philosophy of Science, 1977. **44**(4): p. 542-573.
116. Brandon, R.N., *Biological teleology: Questions and explanations*. Studies in History and Philosophy of Science Part A, 1981. **12**(2): p. 91-105.
117. Garson, J., *What Biological Functions Are and Why They Matter*. 2019, Cambridge, UK: Cambridge University Press.
118. Sabeti, P., *Natural selection: uncovering mechanisms of evolutionary adaptation to infectious disease*. Nature Education, 2008. **1**(1): p. 13.
119. Bigelow, J. and R. Pargetter, *Functions*. The Journal of Philosophy, 1987. **84**(4): p. 181-196.
120. Sober, E., *Philosophy of Biology*. 1993, Boulder, CO: Westview Press.
121. Griffiths, P.E., *Functional Analysis and Proper Functions*. The British Journal for the Philosophy of Science, 1993. **44**(3): p. 409-422.
122. Godfrey-Smith, P., *Functions: Consensus without Unity*. Pacific Philosophical Quarterly, 1993. **74**(3): p. 196-208.
123. Brandon, R.N., *A General Case for Functional Pluralism*, in *Functions: selection and mechanisms*, P. Huneman, Editor. 2013, Springer: Dordrecht, Netherlands. p. 97-104.
124. Garson, J., *How to Be a Function Pluralist*. The British Journal for the Philosophy of Science, 2018. **69**(4): p. 1101-1122.
125. Salmon, W., *Scientific Explanation and the Causal Structure of the World*. 1984, Princeton, NJ: Princeton University Press.
126. Verendeef, A. and C.C. Sherwood, *Human Brain Evolution*. Curr Opin Behav Sci, 2017. **16**: p. 41-45.
127. Dennett, D.C., *The intentional stance*. 1987, Cambridge, Mass.: MIT Press. xi, 388 p.
128. Deacon, T.W., *Incomplete nature : how mind emerged from matter*. 1st ed. 2012, New York: W.W. Norton & Co. xv, 602 p.
129. Juarrero, A., *What does the closure of context-sensitive constraints mean for determinism, autonomy, self-determination, and agency?* Prog Biophys Mol Biol, 2015. **119**(3): p. 510-21.
130. Juarrero, A., *Context changes everything : how constraints create coherence*. 2023, The MIT Press,: Cambridge, Massachusetts. p. 1 online resource.
131. Wouters, A., *The function debate in philosophy*. Acta Biotheor, 2005. **53**(2): p. 123-51.
132. Allori, V., *Quantum Mechanics and Paradigm Shifts*. Topoi, 2015. **34**(2): p. 313-323.
133. Sapolsky, R.M., *Determined : a science of life without free will*. 2023, New York: Penguin Press. 511 pages.
134. DiFrisco, J., G.P. Wagner, and A.C. Love, *Reframing research on evolutionary novelty and co-option: Character identity mechanisms versus deep homology*. Semin Cell Dev Biol, 2023. **145**: p. 3-12.
135. Brigandt, I. and A.C. Love, *Conceptualizing evolutionary novelty: moving beyond definitional debates*. J Exp Zool B Mol Dev Evol, 2012. **318**(6): p. 417-27.

136. Love, A.C., *Idealization in evolutionary developmental investigation: a tension between phenotypic plasticity and normal stages*. Philos Trans R Soc Lond B Biol Sci, 2010. **365**(1540): p. 679-90.
137. Noble, D., *How the Hodgkin cycle became the principle of biological relativity*. J Physiol, 2022. **600**(24): p. 5171-5177.
138. Noble, D., *Modern physiology vindicates Darwin's dream*. Exp Physiol, 2022. **107**(9): p. 1015-1028.
139. Noble, D., *The role of stochasticity in biological communication processes*. Prog Biophys Mol Biol, 2021. **162**: p. 122-128.
140. Noble, D., *A theory of biological relativity: no privileged level of causation*. Interface Focus, 2012. **2**(1): p. 55-64.
141. Noble, D., *The aims of systems biology: between molecules and organisms*. Pharmacopsychiatry, 2011. **44 Suppl 1**: p. S9-S14.
142. Noble, D., *Biophysics and systems biology*. Philos Trans A Math Phys Eng Sci, 2010. **368**(1914): p. 1125-39.
143. Sultan, S.E., A.P. Moczek, and D. Walsh, *Bridging the explanatory gaps: What can we learn from a biological agency perspective?* Bioessays, 2022. **44**(1): p. e2100185.
144. McFadden, P.N. and D.E. Koshland, Jr., *Habituation in the single cell: diminished secretion of norepinephrine with repetitive depolarization of PC12 cells*. Proc Natl Acad Sci U S A, 1990. **87**(5): p. 2031-5.
145. Koshland, D.E., *The bacterium as a model neuron*. Trends in Neurosciences, 1983. **6**(4): p. 133-137.
146. Koshland, D.E., Jr., *Bacterial chemotaxis in relation to neurobiology*. Annu Rev Neurosci, 1980. **3**: p. 43-75.
147. Prindle, A., et al., *Ion channels enable electrical communication in bacterial communities*. Nature, 2015. **527**(7576): p. 59-63.
148. Martinez-Corral, R., et al., *Metabolic basis of brain-like electrical signalling in bacterial communities*. Philos Trans R Soc Lond B Biol Sci, 2019. **374**(1774): p. 20180382.
149. Yang, C.Y., et al., *Encoding Membrane-Potential-Based Memory within a Microbial Community*. Cell Syst, 2020. **10**(5): p. 417-423 e3.
150. Moczek, A.P., et al., *The role of developmental plasticity in evolutionary innovation*. Proc Biol Sci, 2011. **278**(1719): p. 2705-13.
151. Zakirov, B., et al., *Active perception during angiogenesis: filopodia speed up Notch selection of tip cells in silico and in vivo*. Philos Trans R Soc Lond B Biol Sci, 2021. **376**(1821): p. 20190753.
152. Bentley, K. and S. Chakravartula, *The temporal basis of angiogenesis*. Philos Trans R Soc Lond B Biol Sci, 2017. **372**(1720).
153. Bentley, K., A. Philippides, and E. Ravasz Regan, *Do endothelial cells dream of eclectic shape?* Dev Cell, 2014. **29**(2): p. 146-58.
154. Bugaj, L.J., G.P. O'Donoghue, and W.A. Lim, *Interrogating cellular perception and decision making with optogenetic tools*. J Cell Biol, 2017. **216**(1): p. 25-28.
155. Koseska, A. and P.I. Bastiaens, *Cell signaling as a cognitive process*. EMBO J, 2017. **36**(5): p. 568-582.
156. Baluška, F., S. Lev-Yadun, and S. Mancuso, *Swarm intelligence in plant roots*. Trends Ecol Evol, 2010. **25**(12): p. 682-3.
157. Baluška, F. and S. Mancuso, *Deep evolutionary origins of neurobiology: Turning the essence of 'neural' upside-down*. Commun Integr Biol, 2009. **2**(1): p. 60-5.
158. Grémiaux, A., et al., *Plant anesthesia supports similarities between animals and plants: Claude Bernard's forgotten studies*. Plant Signal Behav, 2014. **9**(1): p. e27886.

159. Kelz, M.B. and G.A. Mashour, *The Biology of General Anesthesia from Paramecium to Primate*. Curr Biol, 2019. **29**(22): p. R1199-R1210.
160. Baluška, F., et al., *Understanding of anesthesia - Why consciousness is essential for life and not based on genes*. Commun Integr Biol, 2016. **9**(6): p. e1238118.
161. Tata, J.R., *Amphibian metamorphosis: An exquisite model for hormonal regulation of postembryonic development in vertebrates*. Dev Growth Differ, 1996. **38**(3): p. 223-231.
162. Shi, Y.B., et al., *Tadpole competence and tissue-specific temporal regulation of amphibian metamorphosis: roles of thyroid hormone and its receptors*. Bioessays, 1996. **18**(5): p. 391-9.
163. Kanamori, A. and D.D. Brown, *The analysis of complex developmental programmes: amphibian metamorphosis*. Genes Cells, 1996. **1**(5): p. 429-35.
164. Vandenberg, L.N., D.S. Adams, and M. Levin, *Normalized shape and location of perturbed craniofacial structures in the Xenopus tadpole reveal an innate ability to achieve correct morphology*. Dev Dyn, 2012. **241**(5): p. 863-78.
165. Pinet, K., et al., *Adaptive correction of craniofacial defects in pre-metamorphic Xenopus laevis tadpoles involves thyroid hormone-independent tissue remodeling*. Development, 2019. **146**(14).
166. Saló, E., et al., *Planarian regeneration: achievements and future directions after 20 years of research*. Int J Dev Biol, 2009. **53**(8-10): p. 1317-27.
167. Owlarn, S. and K. Bartscherer, *Go ahead, grow a head! A planarian's guide to anterior regeneration*. Regeneration (Oxf), 2016. **3**(3): p. 139-55.
168. Levin, M., A.M. Pietak, and J. Bischof, *Planarian regeneration as a model of anatomical homeostasis: Recent progress in biophysical and computational approaches*. Semin Cell Dev Biol, 2019. **87**: p. 125-144.
169. Shreesha, L. and M. Levin, *Cellular Competency during Development Alters Evolutionary Dynamics in an Artificial Embryogeny Model*. Entropy (Basel), 2023. **25**(1): p. 131.
170. McMillen, P. and M. Levin, *Collective intelligence: A unifying concept for integrating biology across scales and substrates*. Commun Biol, 2024. **7**(1): p. 378.
171. Emmons-Bell, M., et al., *Regenerative Adaptation to Electrochemical Perturbation in Planaria: A Molecular Analysis of Physiological Plasticity*. iScience, 2019. **22**: p. 147-165.
172. Pezzulo, G., et al., *Bistability of somatic pattern memories: stochastic outcomes in bioelectric circuits underlying regeneration*. Philos Trans R Soc Lond B Biol Sci, 2021. **376**(1821): p. 20190765.
173. Durant, F., et al., *The Role of Early Bioelectric Signals in the Regeneration of Planarian Anterior/Posterior Polarity*. Biophys J, 2019. **116**(5): p. 948-961.
174. Durant, F., et al., *Long-Term, Stochastic Editing of Regenerative Anatomy via Targeting Endogenous Bioelectric Gradients*. Biophys J, 2017. **112**(10): p. 2231-2243.
175. Oviedo, N.J., et al., *Long-range neural and gap junction protein-mediated cues control polarity during planarian regeneration*. Dev Biol, 2010. **339**(1): p. 188-99.
176. Morgan, T.H., *Experimental studies of the regeneration of Planaria maculata*. Arch Entwicklungsmech Org, 1898. **7**: p. 364-397.
177. Child, C.M., *Studies on the dynamics of morphogenesis and inheritance in experimental reproduction the I Axial gradient in planaria dorotocephala as a limiting factor in regulation*. Journal of Experimental Zoology, 1913. **10**(3): p. 265-320.
178. Palacios-Prado, N. and F.F. Bukauskas, *Heterotypic gap junction channels as voltage-sensitive valves for intercellular signaling*. Proc Natl Acad Sci U S A, 2009. **106**(35): p. 14855-60.
179. Nogi, T. and M. Levin, *Characterization of innexin gene expression and functional roles of gap-junctional communication in planarian regeneration*. Dev Biol, 2005. **287**(2): p. 314-35.
180. Oviedo, N.J., et al., *Live Imaging of Planarian Membrane Potential Using DiBAC4(3)*. CSH Protoc, 2008. **2008**: p. pdb prot5055.

181. Fields, C. and M. Levin, *Multiscale memory and bioelectric error correction in the cytoplasm-cytoskeleton-membrane system*. Wiley Interdiscip Rev Syst Biol Med, 2018. **10**(2): p. e1410.
182. Beane, W.S., et al., *A chemical genetics approach reveals H,K-ATPase-mediated membrane voltage is required for planarian head regeneration*. Chem Biol, 2011. **18**(1): p. 77-89.
183. Pezzulo, G. and M. Levin, *Top-down models in biology: explanation and control of complex living systems above the molecular level*. J R Soc Interface, 2016. **13**(124).
184. Pezzulo, G. and 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 (Camb), 2015. **7**(12): p. 1487-517.
185. Vandenberg, L.N., R.D. Morrie, and D.S. Adams, *V-ATPase-dependent ectodermal voltage and pH regionalization are required for craniofacial morphogenesis*. Dev Dyn, 2011. **240**(8): p. 1889-904.
186. Pai, V.P., et al., *Transmembrane voltage potential controls embryonic eye patterning in Xenopus laevis*. Development, 2012. **139**(2): p. 313-23.
187. Shreesha, L. and M. Levin, *Stress sharing as cognitive glue for collective intelligences: A computational model of stress as a coordinator for morphogenesis*. Biochem Biophys Res Commun, 2024. **731**: p. 150396.
188. Sullivan, K.G. and M. Levin, *Neurotransmitter signaling pathways required for normal development in Xenopus laevis embryos: a pharmacological survey screen*. J Anat, 2016. **229**(4): p. 483-502.
189. Levin, M., G.A. Buznikov, and J.M. Lauder, *Of minds and embryos: left-right asymmetry and the serotonergic controls of pre-neural morphogenesis*. Dev Neurosci, 2006. **28**(3): p. 171-85.
190. Moore, D., S.I. Walker, and M. Levin, *Cancer as a disorder of patterning information: computational and biophysical perspectives on the cancer problem*. Convergent Science Physical Oncology, 2017. **3**: p. 043001.
191. Chernet, B. and M. Levin, *Endogenous Voltage Potentials and the Microenvironment: Bioelectric Signals that Reveal, Induce and Normalize Cancer*. J Clin Exp Oncol, 2013. **Suppl 1**: p. S1-002.
192. Levin, M., *Bioelectrical approaches to cancer as a problem of the scaling of the cellular self*. Prog Biophys Mol Biol, 2021. **165**: p. 102-113.
193. Chernet, B.T. and M. Levin, *Transmembrane voltage potential is an essential cellular parameter for the detection and control of tumor development in a Xenopus model*. Dis Model Mech, 2013. **6**(3): p. 595-607.
194. Blackiston, D., et al., *Transmembrane potential of GlyCl-expressing instructor cells induces a neoplastic-like conversion of melanocytes via a serotonergic pathway*. Dis Model Mech, 2011. **4**(1): p. 67-85.
195. Lobikin, M., et al., *Selective depolarization of transmembrane potential alters muscle patterning and muscle cell localization in Xenopus laevis embryos*. Int J Dev Biol, 2015. **59**(7-9): p. 303-11.
196. Lobikin, M., et al., *Serotonergic regulation of melanocyte conversion: A bioelectrically regulated network for stochastic all-or-none hyperpigmentation*. Sci Signal, 2015. **8**(397): p. ra99.
197. Chernet, B.T., et al., *Use of genetically encoded, light-gated ion translocators to control tumorigenesis*. Oncotarget, 2016. **7**(15): p. 19575-88.
198. Chernet, B.T., C. Fields, and M. Levin, *Long-range gap junctional signaling controls oncogene-mediated tumorigenesis in Xenopus laevis embryos*. Front Physiol, 2014. **5**: p. 519.
199. Chernet, B.T. and M. Levin, *Transmembrane voltage potential of somatic cells controls oncogene-mediated tumorigenesis at long-range*. Oncotarget, 2014. **5**(10): p. 3287-306.
200. Davies, J. and M. Levin, *Synthetic morphology with agential materials*. Nature Reviews Bioengineering, 2023. **1**: p. 46-59.
201. Blackiston, D., et al., *Biological Robots: Perspectives on an Emerging Interdisciplinary Field*. Soft Robot, 2023. **10**(4): p. 674-686.

202. Kriegman, S., et al., *Kinematic self-replication in reconfigurable organisms*. Proc Natl Acad Sci U S A, 2021. **118**(49).
203. Blackiston, D., et al., *A cellular platform for the development of synthetic living machines*. Sci Robot, 2021. **6**(52): p. eabf1571.
204. Kriegman, S., et al., *A scalable pipeline for designing reconfigurable organisms*. Proc Natl Acad Sci U S A, 2020. **117**(4): p. 1853-1859.
205. Pai, V.P., et al. *Basal Xenobot Transcriptomics: Gene Expression Changes in wildtype cells comprising one form of biobot*. OSF Preprints, 2024. DOI: 10.31219/osf.io/n2jre.
206. Gumuskaya, G., et al., *Motile Living Biobots Self-Construct from Adult Human Somatic Progenitor Seed Cells*. Adv Sci (Weinh), 2024. **11**(4): p. e2303575.
207. Mathews, J., et al., *Cellular signaling pathways as plastic, proto-cognitive systems: Implications for biomedicine*. Patterns (N Y), 2023. **4**(5): p. 100737.
208. Levin, M., *The Multiscale Wisdom of the Body: Collective Intelligence as a Tractable Interface for Next-Generation Biomedicine*. Bioessays, 2024: p. e202400196.
209. Rabinowitz, J.S., et al., *Transcriptomic, proteomic, and metabolomic landscape of positional memory in the caudal fin of zebrafish*. Proc Natl Acad Sci U S A, 2017. **114**(5): p. E717-E726.
210. Moris, N., C. Pina, and A.M. Arias, *Transition states and cell fate decisions in epigenetic landscapes*. Nat Rev Genet, 2016. **17**(11): p. 693-703.
211. Eritano, A.S., et al., *Tissue-Scale Mechanical Coupling Reduces Morphogenetic Noise to Ensure Precision during Epithelial Folding*. Dev Cell, 2020. **53**(2): p. 212-228 e12.
212. Tamari, Z. and N. Barkai, *Improved readout precision of the Bicoid morphogen gradient by early decoding*. J Biol Phys, 2012. **38**(2): p. 317-29.
213. Spirov, A.V. and D.M. Holloway, *Making the body plan: precision in the genetic hierarchy of Drosophila embryo segmentation*. In Silico Biol, 2003. **3**(1-2): p. 89-100.
214. Houchmandzadeh, B., E. Wieschaus, and S. Leibler, *Establishment of developmental precision and proportions in the early Drosophila embryo*. Nature, 2002. **415**(6873): p. 798-802.
215. Hoel, E. and M. Levin, *Emergence of informative higher scales in biological systems: a computational toolkit for optimal prediction and control*. Commun Integr Biol, 2020. **13**(1): p. 108-118.
216. Hoel, E.P., *Agent Above, Atom Below: How Agents Causally Emerge from Their Underlying Microphysics*, in *Wandering Towards a Goal*, A. Aguirre, B. Foster, and Z. Merali, Editors. 2018, Springer International Publishing: Cham. p. 63-76.
217. Hoel, E., *When the Map Is Better Than the Territory*. Entropy, 2017. **19**(5).
218. Albantakis, L., et al., *What caused what? An irreducible account of actual causation*. arXiv, 2017. **arXiv:1708.06716**.
219. Hoel, E.P., et al., *Can the macro beat the micro? Integrated information across spatiotemporal scales*. Neurosci Conscious, 2016. **2016**(1): p. niw012.
220. Hoel, E.P., L. Albantakis, and G. Tononi, *Quantifying causal emergence shows that macro can beat micro*. Proc Natl Acad Sci U S A, 2013. **110**(49): p. 19790-5.
221. Cliff, O.M., et al., *Quantifying Long-Range Interactions and Coherent Structure in Multi-Agent Dynamics*. Artif Life, 2017. **23**(1): p. 34-57.
222. Wibrat, M., et al., *Local active information storage as a tool to understand distributed neural information processing*. Front Neuroinform, 2014. **8**: p. 1.
223. Lizier, J.T., *JIDT: An Information-Theoretic Toolkit for Studying the Dynamics of Complex Systems*. Frontiers in Robotics and AI, 2014. **1**(11).
224. Wang, X.R., et al., *Quantifying and tracing information cascades in swarms*. PLoS One, 2012. **7**(7): p. e40084.

225. Lizier, J.T., et al., *Multivariate information-theoretic measures reveal directed information structure and task relevant changes in fMRI connectivity*. J Comput Neurosci, 2011. **30**(1): p. 85-107.
226. Murugan, N.J., et al., *Acute multidrug delivery via a wearable bioreactor facilitates long-term limb regeneration and functional recovery in adult Xenopus laevis*. Sci Adv, 2022. **8**(4): p. eabj2164.
227. Penrose, R., *The Emperor's New Mind: Concerning Computers, Minds, and the Laws of Physics*. 1989, New York, NY: Oxford University Press.
228. Chalmers, D., *The Conscious Mind: In Search of a Fundamental Theory*. 1997, New York, NY; Oxford, UK: Oxford University Press.
229. Searle, J., *Mind: A Brief Introduction*. 2005, New York, NY: Oxford University Press.
230. Wartlick, O., A. Kicheva, and M. González-Gaitán, *Morphogen gradient formation*. Cold Spring Harb Perspect Biol, 2009. **1**(3): p. a001255.
231. Wolpert, L., *Positional information and the spatial pattern of cellular differentiation*. J Theor Biol, 1969. **25**(1): p. 1-47.
232. Grodstein, J., P. McMillen, and M. Levin, *Closing the loop on morphogenesis: a mathematical model of morphogenesis by closed-loop reaction-diffusion*. Front Cell Dev Biol, 2023. **11**: p. 1087650.
233. Laland, K.N., et al., *Cause and effect in biology revisited: is Mayr's proximate-ultimate dichotomy still useful?* Science, 2011. **334**(6062): p. 1512-6.
234. Levin, M., *Endogenous bioelectrical networks store non-genetic patterning information during development and regeneration*. J Physiol, 2014. **592**(11): p. 2295-305.
235. Römling, U., *Is biofilm formation intrinsic to the origin of life?* Environ Microbiol, 2023. **25**(1): p. 26-39.
236. Hartl, B., S. Risi, and M. Levin, *Evolutionary Implications of Self-Assembling Cybernetic Materials with Collective Problem-Solving Intelligence at Multiple Scales*. Entropy, 2024. **26**(7): p. 532.
237. James, W., *Principles of Psychology*. 1890, New York, NY: Henry Holt.
238. Schlosser, M., *Agency*, in *Stanford Encyclopedia of Philosophy*, E.N. Zalta, Editor. 2019, Metaphysics Research Lab, Stanford University: Stanford, CA.
239. Gardner, H., *Frames of Mind: The Theory of Multiple Intelligences*. 2011, New York, NY: Basic Books.
240. Biswas, S., W. Clawson, and M. Levin, *Learning in Transcriptional Network Models: Computational Discovery of Pathway-Level Memory and Effective Interventions*. Int J Mol Sci, 2022. **24**(1): p. 285.
241. Biswas, S., et al., *Gene regulatory networks exhibit several kinds of memory: quantification of memory in biological and random transcriptional networks*. iScience, 2021. **24**(3): p. 102131.
242. Bird, C.D. and N.J. Emery, *Rooks use stones to raise the water level to reach a floating worm*. Curr Biol, 2009. **19**(16): p. 1410-4.
243. Levin, M., *Self-Improvising Memory: A Perspective on Memories as Agential, Dynamically Reinterpreting Cognitive Glue*. Entropy (Basel), 2024. **26**(6).
244. Wittgenstein, L., *Philosophical Investigations*. 1953, Oxford, UK: Blackwell.
245. Biletzki, A. and A. Matar, *Ludwig Wittgenstein*, in *Stanford Encyclopedia of Philosophy*. 2023, Metaphysics Research Lab, Stanford University: Stanford, CA.
246. Fankhauser, G., *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, 1945. **100**(3): p. 445-55.
247. Fankhauser, G., *The Effects of Changes in Chromosome Number on Amphibian Development*. The Quarterly Review of Biology, 1945. **20**(1): p. 20-78.

248. Cervera, J., M. Levin, and S. Mafé, *Multicellular adaptation to electrophysiological perturbations analyzed by deterministic and stochastic bioelectrical models*. Sci Rep, 2024. **14**(1): p. 27608.
249. Sullivan, K.G., M. Emmons-Bell, and M. Levin, *Physiological inputs regulate species-specific anatomy during embryogenesis and regeneration*. Commun Integr Biol, 2016. **9**(4): p. e1192733.
250. Lobo, D., et al., *A linear-encoding model explains the variability of the target morphology in regeneration*. J R Soc Interface, 2014. **11**(92): p. 20130918.
251. Pai, V.P. and M. Levin, *HCN2 channel-induced rescue of brain, eye, heart and gut teratogenesis caused by nicotine, ethanol and aberrant notch signalling*. Wound Repair Regen, 2022. **30**(6): p. 681-706.
252. Pai, V.P., et al., *Endogenous gradients of resting potential instructively pattern embryonic neural tissue via Notch signaling and regulation of proliferation*. J Neurosci, 2015. **35**(10): p. 4366-85.
253. Baluška, F., W.B. Miller, and A.S. Reber, *Cellular and evolutionary perspectives on organismal cognition: from unicellular to multicellular organisms*. Biological Journal of the Linnean Society, 2023. **139**(4): p. 503-513.
254. Reber, A.S. and F. Baluška, *Cognition in some surprising places*. Biochem Biophys Res Commun, 2021. **564**: p. 150-157.
255. Abramson, C.I. and M. Levin, *Behaviorist approaches to investigating memory and learning: A primer for synthetic biology and bioengineering*. Commun Integr Biol, 2021. **14**(1): p. 230-247.
256. Ebrahimkhani, M.R. and M. Levin, *Synthetic living machines: A new window on life*. iScience, 2021. **24**(5): p. 102505.
257. Ebrahimkhani, M.R. and M. Ebisuya, *Synthetic developmental biology: build and control multicellular systems*. Curr Opin Chem Biol, 2019. **52**: p. 9-15.
258. Kamm, R.D., et al., *Perspective: The promise of multi-cellular engineered living systems*. APL Bioeng, 2018. **2**(4): p. 040901.
259. Kamm, R.D. and R. Bashir, *Creating living cellular machines*. Ann Biomed Eng, 2014. **42**(2): p. 445-59.
260. Rouleau, N. and M. Levin, *Discussions of machine versus living intelligence need more clarity*. Nature Machine Intelligence, 2024. **6**(12): p. 1424-1426.
261. Morgan, C.L., *Other minds than ours*, in *An Introduction to Comparative Psychology*, W. Scott, Editor. 1903. p. 59-.
262. Chalmers, D., *The Character of Consciousness*. 2010, New York, NY; Oxford, UK: Oxford University Press.
263. Moore, D.G., et al., *Inform: Efficient Information-Theoretic Analysis of Collective Behaviors*. Front Robot AI, 2018. **5**(60): p. 60.
264. Davis, G.V., et al., *Toward uncovering an operating system in plant organs*. Trends Plant Sci, 2024. **29**(7): p. 742-753.
265. Johnston, I.G. and G.W. Bassel, *Identification of a bet-hedging network motif generating noise in hormone concentrations and germination propensity in Arabidopsis*. J R Soc Interface, 2018. **15**(141).
266. Bassel, G.W., *Information Processing and Distributed Computation in Plant Organs*. Trends Plant Sci, 2018. **23**(11): p. 994-1005.
267. Topham, A.T., et al., *Temperature variability is integrated by a spatially embedded decision-making center to break dormancy in Arabidopsis seeds*. Proc Natl Acad Sci U S A, 2017. **114**(25): p. 6629-6634.
268. Yokawa, K., et al., *Anaesthetics stop diverse plant organ movements, affect endocytic vesicle recycling and ROS homeostasis, and block action potentials in Venus flytraps*. Ann Bot, 2018. **122**(5): p. 747-756.

269. Ciszak, M., et al., *Plant shoots exhibit synchronized oscillatory motions*. Commun Integr Biol, 2016. **9**(5): p. e1238117.
270. Calvo, P., F. Baluška, and A. Sims, "*Feature Detection*" vs. "*Predictive Coding*" Models of Plant Behavior. Front Psychol, 2016. **7**: p. 1505.
271. Gyurkó, D.M., et al., *Adaptation and learning of molecular networks as a description of cancer development at the systems-level: potential use in anti-cancer therapies*. Semin Cancer Biol, 2013. **23**(4): p. 262-9.
272. Csermely, P., et al., *Learning of Signaling Networks: Molecular Mechanisms*. Trends Biochem Sci, 2020. **45**(4): p. 284-294.
273. Couzin, I., *Collective minds*. Nature, 2007. **445**(7129): p. 715.
274. Couzin, I.D., *Collective cognition in animal groups*. Trends Cogn Sci, 2009. **13**(1): p. 36-43.
275. Deisboeck, T.S. and I.D. Couzin, *Collective behavior in cancer cell populations*. Bioessays, 2009. **31**(2): p. 190-7.
276. Reid, C.R., et al., *Amoeboid organism uses extracellular secretions to make smart foraging decisions*. Behavioral Ecology, 2013. **24**(4): p. 812-818.
277. Mori, Y. and A. Koaze, *Cognition of different length by Physarum polycephalum: Weber's law in an amoeboid organism*. Mycoscience, 2013. **54**(6): p. 426-428.
278. Vallverdú, J., et al., *Slime mould: The fundamental mechanisms of biological cognition*. Biosystems, 2018. **165**: p. 57-70.
279. Baluška, F. and A.S. Reber, *Cellular and organismal agency - Not based on genes: A comment on Baverstock*. Prog Biophys Mol Biol, 2021. **167**: p. 161-162.
280. Calvo, P., et al., *Plants are intelligent, here's how*. Ann Bot, 2020. **125**(1): p. 11-28.
281. Calvo, P., V.P. Sahi, and A. Trewavas, *Are plants sentient?* Plant Cell Environ, 2017. **40**(11): p. 2858-2869.
282. Trewavas, A., *Intelligence, Cognition, and Language of Green Plants*. Front Psychol, 2016. **7**: p. 588.
283. Keijzer, F., M. van Duijn, and P. Lyon, *What nervous systems do: early evolution, input-output, and the skin brain thesis*. Adaptive Behavior, 2013. **21**(2): p. 67-85.
284. Fields, C., J. Bischof, and M. Levin, *Morphological Coordination: A Common Ancestral Function Unifying Neural and Non-Neural Signaling*. Physiology (Bethesda), 2020. **35**(1): p. 16-30.
285. Friston, K., et al., *Knowing one's place: a free-energy approach to pattern regulation*. J R Soc Interface, 2015. **12**(105).