

Collective Intelligence of Morphogenesis as a Teleonomic Process

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Abstract

Multiscale competency is a central phenomenon in biology: molecular networks, cells, tissues, and organisms all solve problems via behavior in various spaces (metabolic, physiological, anatomical, and the familiar 3D space of movement). These capabilities require being able to reach specific goal states despite perturbations and changes in their own parts and in the environment: effective teleonomy. Strong examples of the remarkable scaling of such goal states during teleonomic processes are seen across development, regeneration, and cancer suppression. I illustrate examples of regulative morphogenesis of multicellular bodies as the teleonomic behavior of a collective intelligence composed of cells. This perspective helps to unify many phenomena across multiscale biology, and suggests a framework for understanding how teleonomic capacity increased and diversified during evolution. Thus, teleonomy is a lynchpin concept that helps address key open questions around evolvability, biological plasticity, and basal cognition, and is a powerful invariant that drives novel empirical research programs.

Introduction

To paraphrase a famous quote (Dobzhansky 1973), nothing in biology makes sense except in light of teleonomy (Auletta 2011; Ellis, Noble, and O'Connor 2012; Noble 2011, 2010). Most observers, including biologists, physicists, and engineers, have watched with wonder as biological systems expend energy to achieve a specific state of affairs different than the current one, despite changing circumstances. This phenomenon includes workhorse concepts such as stress (the system-level effects of the inability to reach desired states, and the driver of change), memory (the ability to represent specific states that are not present right now), intelligence (competency in navigating problem spaces toward desired goals), and preferences (inherent valence of specific states over others). The capacity to work toward goals (preferred future states) is ubiquitous across the biosphere and present at all scales of organization, from the planning capacities of primates to the abilities of cellular collectives to modify their activity to achieve a specific embryonic anatomy despite perturbations. It is a defining feature of life, of great importance to evolutionary biologists (in their quest to understand the origin of various functions), exobiologists (seeking ways to recognize unconventional life forms), researchers in artificial intelligence, robotics, and artificial life (trying to develop autonomous synthetic systems), and workers in regenerative biomedicine (whose goal requires the reprogramming of cellular and tissue functions toward desired goal states associated with health). How living systems establish, encode, and pursue goals is a fundamental question at the heart of numerous fields, including biology, philosophy, cognitive science, and the information technology sciences.

Teleology and related concepts have been the subject of much debate (Turner 2017; McShea 2016; Lander 2004; Rosenblueth, Wiener, and Bigelow 1943; F.J. Varela, Thompson, and Rosch 1991; Maturana and Varela 1980b; F.G. Varela, Maturana, and Uribe 1974; F. Varela and Maturana 1972; Bertalanffy 195). Here, I focus on *teleonomy*: apparently purposeful behavior, emphasizing two aspects. “Apparent”, because it is to be measured and characterized from the perspective of an observer seeking a powerful way to understand the system (not some objective intrinsic fact about a system itself) (Ashby 1952). “Purposeful”, because great explanatory power and new research can be driven by a rigorous investigation of what states motivate a system to expend energy as it navigates various action spaces.

Teleonomy is a lens (akin to the pragmatic intentional stance (Dennett 1987)) through which scientists see biological systems, creatures see each other, and parts of living systems model other parts and themselves (Wood 2019; Mar et al. 2007). Here, I focus on teleonomy as a profound way to understand morphogenesis as the teleonomic behavior of a multiscale collective agent (molecular networks, cells, etc.). A key aim is to show that goal-directed function is not just the province of advanced brains with self-aware agency, but rather is a primary principle scaled up from basal functions in the most primitive life forms. More than that, it is an essential invariant that pervades, and reveals actionable symmetries across diverse aspects of biology.

The philosophical assumptions of this perspective (Levin 2022) can be explicitly stated as follows. First, there is a primary goal to drive empirical research, not to preserve philosophical positions that make “armchair” decisions on questions of agency in the absence of specific experiment. Second, there is a commitment to evolutionary continuity of bodies and minds and to a search for minimal examples of key capacities, which will

necessarily blur the boundaries between cognitive phenomena and “just physics”. Proposals for sharp phase transitions in terms of agency carry the burden of having to show how discrete changes across one generation create a novel agential capacity in offspring that didn’t exist in the parents. Thus, I assume gradualism and continuous (not binary) metrics of all important parameters, such as agency, cognition, intelligence, memory, goal-directedness, etc.

Teleonomy as a lens on collective intelligence

All agents are made of parts, which work together to solve problems with various degrees of competency (intelligence). Goals belong to agents at various scales, and it is imperative to understand how novel agents and their novel goals emerge from the cooperation of active subunits. The most obvious example is individual cognition arising from collections of neurons in a brain, but we must learn to recognize this phenomenon in unconventional guises as well. Cybernetics (Rosenblueth, Wiener, and Bigelow 1943; Wiener 1961) gives us a mature framework for understanding goal-directed behavior without resort to mysterianism, and dynamical systems and control theories offer rigorous formalisms in which attractor states are causes of system-level behavior (Manicka and Levin 2019). Indeed, the engineering advances of the last few decades have shifted the burden of magical thinking to those who believe that humans possess some sort of unique ability to pursue goals that can not exist in simpler life forms or bioengineered systems. “Anthropomorphism” as a critique of agential models in biology is a term often used to conceal a view of human capacity that is inconsistent with modern understanding of evolutionary origins of all capacities (Lyon 2015; Keijzer, van Duijn, and Lyon 2013; Lyon 2006; Balazsi, van Oudenaarden, and Collins 2011; Baluška and Levin 2016). A most important aspect of cybernetic approaches is that they are substrate-invariant, and remind us that no specific materials (cytoplasm, neurons, etc.) or scale of organization are required for a capacity as fundamental as teleonomic action. This independence from specific implementation details removes traditional cataracts from the lens through which we view “agents” that exhibit teleonomic behavior – self-imposed filters that have restricted research because our perceptual systems are tuned to recognize only some kinds of goal-directed behavior – familiar creatures acting in 3D space. Not only is there no unique material (brains) in which to find goal-directed behavior, but there is no unique spatio-temporal scale (Noble 2012). As occurred in physics (for quantum theory and relativity), we must go beyond the medium size, medium time-frame systems and be open to examining the evidence for agency in the very small (e.g., molecular networks), and the very large (e.g., whole lineages acting over evolutionary time scales) (C. Fields and Levin 2020b; C. Fields, Bischof, and Levin 2020; Friston 2013; Ramstead et al. 2019).

Teleonomy is not the final step on a continuum of agency – it is a primary capacity, present in many unconventional substrates, that makes all others possible and catalyzes the climb from self-maintaining metabolic cycles all the way through human-level cognition and beyond (Figure 1). Goal-directed behavior is, at the very least, uncontroversial in human animals. It is thought that this capacity is enabled by collectives of neurons (brains) exhibiting memory, error minimization capacity, and second-order metacognition that enables us to think about those goals (and perhaps re-set them) in addition to executing them. However, brains evolved from much more ancient bioelectric networks that are formed by all cells in the body, and are as old as bacterial biofilms (C.

Fields, Bischof, and Levin 2020; Prindle et al. 2015; Yang et al. 2020). These networks readily form circuits with memory that enables basal homeostatic function (Cervera et al. 2018; Pietak and Levin 2017; Cervera, Levin, and Mafe 2020; Cervera et al. 2019). The remarkable capacities for both robustness and novelty in morphogenesis reveals the central role of the *scaling of goals* as an explanatory, facilitating concept for new basic research and biomedical applications (Levin 2019), and the need to understand how evolution potentiates teleonomy.

Evolution scales up goal-directed activity: anatomical homeostasis

To recognize teleonomic behavior in unconventional contexts, it is helpful to start with the clear case of human goal-directed behavior and work backwards. Nervous systems exhibit specific structure-function relationships that bind collections of neural cells into coherent Selves with associative memories and goals that do not belong to any of the cells alone but only to the collective (i.e., all intelligences are collective intelligences). Complex brains enable memories of desired goal states and perceptual control loops which efficiently orchestrate behavior in 3D space in order to optimize specific parameters and satisfy drives (Pezzulo, Rigoli, and Friston 2015; Allen and Friston 2018; Powers 1973). However, this same basic scheme can be applied to action in many spaces, including metabolic, transcriptional, and physiological ones. On this view, “environment” is extended to include the internal affordances (components and their capacities) that molecular pathways, cells, and tissues have access to, and “embodiment” is extended to other problem spaces, not just familiar 3D space of motion. Indeed, William James’ definition of intelligence as the capacity of an agent to achieve “the same goal via different means” (James 1890) is suitably generic to encompass diverse intelligences of navigation of many different kinds of problem spaces. Here we consider one example, which likely served as the evolutionary origin for conventional goal-driven behaviors (C. Fields, Bischof, and Levin 2020): bioelectric networks of non-neural cells that enable metazoan organisms to navigate morphospace (Levin and Martyniuk 2018; Levin 2021a).

Morphospace is the space of possible anatomical configurations that any group of cells can achieve (Stone 1997). Multicellular organisms move through morphospace during embryogenesis, regeneration, and remodeling such as metamorphosis. Because genomes encode micro-level protein hardware, not directly specifying growth and form, it is essential to understand not only molecular mechanisms *necessary* for morphogenesis, but also the information-processing dynamics that are *sufficient* for the swarm intelligence of cell groups to create, repair, and reconstruct large-scale anatomical features (Pezzulo and Levin 2016, 2015; Friston et al. 2015). Examples abound of cellular collectives being able to reach the desired region of morphospace despite diverse starting positions and perturbations along the way – an activity which is strongly isomorphic to aspects of cognitive and behavioral science (Friston et al. 2015; Grossberg 1978).

Embryogenesis itself is often thought about in terms of pure emergence – complex forms appear via the parallel action of large numbers of cells following local rules. However, it is not at all as brittle as this kind of emergent cellular automata paradigm would predict. Mammalian embryos cut in half produce monozygotic twins (not half-embryos), and embryos created with radically different numbers of cells still produce properly-scaled bodies (Cooke 1981). Perhaps the most instructive example from the perspective of teleonomy is that of the kidney tubule in the newt. Kidney tubules of the

correct cross-sectional geometry and diameter typically arise from numerous cells working together. However, if the cells are made to be very large, just one cell will bend around itself to create the same structure (Fankhauser 1945b, 1945a). This reveals that diverse underlying molecular mechanisms (cell:cell communication vs. cytoskeletal bending) can be called up as needed, diverging from the normal course of events in embryogenesis, in the service of a large-scale goal in anatomical morphospace. The ability to achieve the same outcome with highly altered components, requiring no re-training on ontogenetic or phylogenetic time-scales, is something our engineering and machine learning technologies cannot yet achieve.

Development is thus incredibly reliable, producing bodies to very tight tolerance despite considerable deviations and noise at the level of gene expression and cellular activity (Gonze et al. 2018; Eritano et al. 2020; Simon, Hadjantonakis, and Schroter 2018). This robustness, and its occasional failure in the case of birth defects immediately suggests teleonomic perspectives because only goal-directed agents can make mistakes; biophysics alone cannot make mistakes – every micro-scale process proceeds according to the laws of physics and chemistry. Developmental defects are mistakes relative to the correct outcome toward which they strive. Embryonic bodies do a remarkable job of detecting and correcting such mistakes; for example, embryonic salamander tails grafted to the flank slowly remodel into a limb – altering the existing tissue structure to become correct with respect to the large-scale body plan (Farinella-Ferruzza 1956). But this capacity is not just for the rare cases of teratogenic influences: it may drive all of development. From the perspective of each embryonic stage, the prior stage has incorrect anatomy – it is a “birth defect” that must be corrected by actuation of gene expression, physiology, and cell movement. One can view the progression of development as a series of repairs that drive the system toward the correct anatomical setpoint.

Regulative development is thus a special case of the more generic process of regeneration: moving an incorrect state closer to the target setpoint (Figure 2). Many organisms can do this as adults, repairing drastic injury. Examples include salamanders (which can regenerate eyes, limbs, jaws, and other organs) and planarian flatworms (which regenerate every part of the body from even small fragments, while scaling the remaining tissue down so that perfect proportion results) (W. S. Beane et al. 2013; Oviedo, Newmark, and Sanchez Alvarado 2003). Regeneration offers numerous examples of teleonomic activity (Figure 2). First and most remarkably, it stops. The rapid growth and remodeling of regeneration (which can be as fast as any tumor) stops precisely when a correct organ shape has been achieved – the collective can certainly detect when its goal has been achieved, which results in the cessation of numerous molecular-biological and biophysical processes. Second, it achieves its goal from diverse starting positions, as a limb can be cut at any point along the proximo-distal axis and results in only as much growth and morphogenesis as is necessary to rebuild itself. Third, it can take diverse paths through morphospace: for example, when frog leg regeneration is induced by bioelectric state change, it does not proceed along the developmental path that normally forms frog limbs.

Two other cases are instructive, because they emphasize knowledge gaps with respect to how teleonomy in anatomical space relates to genomes (Figure 3). Planarian regeneration is extremely stable, invariably resulting in a perfect little worm from almost

any kind of cut. Because of their reproduction by fission and regeneration, some species of planaria do not use Weissman's Barrier: every mutation that doesn't kill a stem cell is amplified in the soma in the subsequent generations. As a result of this (reviewed in (Levin, Pietak, and Bischof 2018)), their genomes are incredibly messy and their constituent cells are mixoploid (bearing different numbers of chromosomes). This illustrates the remarkable ability to reliably implement the same anatomy despite chaos within the underlying molecular components. A different kind of chaos is tamed by frog metamorphosis. In order to build a frog face, the face of the tadpole must be strongly remodeled. However, it is now clear that this is not achieved by some sort of genetic hardcoding of the amount and direction of movement for each component (Vandenberg, Adams, and Levin 2012; Pinet and McLaughlin 2019; Pinet et al. 2019). When "Picasso tadpoles" are created, with eyes, jaws, and nostrils in aberrant locations (scrambled), largely normal frogs result because all of these organs move through novel, un-natural paths, until a proper frog face results. This reveals that what the evolution of the frog genome discovered is not a machine that performs rote steps to emergently produce a frog face, but rather one that executes an error minimization scheme toward a specific setpoint (the basis of teleonomic activity).

All of these examples illustrate, per James (James 1890), the ability of this unconventional agent to achieve the same goals (a specific functional anatomy) by different means – taking novel paths through morphospace despite external and internal perturbations. Indeed, the remarkable robustness and plasticity of these teleonomic processes are the envy of workers in robotics and AI. The fundamental origins of these goals will be discussed below, but it is instructive to consider how these anatomical setpoints are physically encoded (being a precursor to representation of goals within advanced brain-mind systems). The computational medium in which the collective intelligence of cells operates to so competently navigate morphospace is the same as that of the brain: bioelectric networks. This design principle, which evolution discovered long before human engineers used it for reprogrammable computers (Levin 2014; Sullivan, Emmons-Bell, and Levin 2016), enables a software-hardware distinction that allows genomes to encode biophysical hardware, not final anatomical outcomes, while the software dynamics of this hardware holds the goal states and enables measurement and action of the anatomical homeostatic loop (Pezzulo and Levin 2016, 2015).

Bioelectricity as a medium for teleonomic control of growth and form

Evolution exploits three main modalities to coordinate morphogenesis: biochemical signals, biomechanical forces, and bioelectric communication (Newman 2019; Levin 2014). It is likely that all of these can be used to illustrate the ubiquity of teleonomy in anatomical control, but the bioelectric layer of the software of life makes the most direct connection to goal-directed behavior of brains. Importantly, control of morphogenesis and that of behavior are not only functionally isomorphic, but also share molecular mechanisms. This is not an accident, because nervous systems evolved by speed-optimizing ancient bioelectric circuits that evolved first to navigate morphospace and were then pivoted by evolution to navigate 3D space when nerves and muscles evolved. All of the key components of nervous systems – ion channels, electrical synapses (gap junctions), and neurotransmitter signaling are much older than brains (C. Fields, Bischof, and Levin 2020; Levin, Buznikov, and Lauder 2006). Indeed, bioelectronics

are already seen in the behavior at the single cell level (Eckert and Naitoh 1970; Eckert, Naitoh, and Friedman 1972; Naitoh and Eckert 1969b, 1969a; Naitoh, Eckert, and Friedman 1972). The ion channels and gap junctions in a plasma membrane together form a powerful interface provided by cells which enables their collective programming by ontogenetic- and phylogenetic-scale processes both within and outside of the nervous system (Figure 4).

Recent work suggests a unification of neural and non-neural physiology because all of the techniques of neuroscience are now being used outside the brain to understand development, regeneration and cancer (Adams et al. 2014): the extreme portability of the tools, concepts, and reagents (ion channel constructs, optogenetics, and computational models) suggests that the distinction between neurons and other somatic cell types is artificial. These techniques do not distinguish neural from non-neural tissues, revealing the opportunity to expand “neuroscience” well beyond neurons (Pezzulo and Levin 2015). Modulation of native bioelectric signaling (by targeting ion channels, gap junctions, and downstream neurotransmitter machinery) has enabled the modular induction of organs such as eyes (Pai et al. 2012), the rational repair of birth defects of complex organs such as the brain induced by mutation or teratogenesis (Pai et al. 2020; Pai et al. 2018), the induction of regeneration of appendages in non-regenerative contexts (Tseng et al. 2010; Adams, Masi, and Levin 2007), and the reversal or duplication of major body axes (Durant et al. 2019; Levin et al. 2002).

A brief experience of a particular voltage state can change cellular decision-making from “tail” to “head”, from “gut” to “eye”, and from “scar” to “limb” (McLaughlin and Levin 2018) - not micromanagement but large-scale setting of goals. Indeed, the target morphology – the shape to which cells regenerate after damage – can be permanently modified by transient changes of global bioelectric patterns. Genetically wild-type planaria can be induced to form two heads instead of a head and tail, and this pattern is then permanently propagated in the animals regenerating from subsequent cuts in plain water with no further manipulation (Oviedo et al. 2010). Planarian fragments can also be induced to form heads appropriate to other species, with no genomic editing (Emmons-Bell et al. 2015). Voltage-sensitive fluorescent dyes now allow the visualization of these pattern memories, for example showing a 2-headed bioelectric prepattern induced in a transcriptionally and anatomically normal 1-head worm: the memory is latent until injury causes it to be recalled by the cellular collective (Durant et al. 2017).

The parallels with cognitive neuroscience are strong, including the abilities to: do “neural decoding” to extract the semantics (in this case, in morphospace) of the electric states (Wendy S. Beane et al. 2011; Durant et al. 2019; Durant et al. 2017; Vandenberg, Morrie, and Adams 2011), incept false pattern memories (Levin 2021a) without having to edit the genome, and detect and manipulate perceptual bistability – create planaria that randomly regenerate as 1- or 2-headed animals because the circuit cannot quite decide between two memories (Pezzulo et al. 2021; Durant et al. 2017) – all by using the same tools and conceptual framework as used in manipulation of goal-directed agents with brains. A key concept emphasized by this work is the storage and manipulation of rewritable information in bioelectric state; this control of modular decision-making in software via experiences, rather than by hardware rewiring, offers precisely the same enormous advantages that evolution exploited in nervous systems (learning) and that we exploit in our computers (reprogrammability). These attempts to view morphogenesis as

not merely an emergent physical process but a goal-directed control loop have led to many new discoveries and novel capabilities in the prediction and control of anatomical outcomes that had not been discovered from prior bottom-up approaches, and which offer numerous advantages for regenerative medicine (Mathews and Levin 2018; Levin 2021a).

Importantly, bioelectric signaling is not just another piece of biophysics. First, it is a medium for representing morphogenetic goals – the memories of the collective intelligence of morphogenesis (Pezzulo and Levin 2015, 2016). Stable distributions of resting potential in tissues encode the target morphology - the setpoint for anatomical homeostasis – toward which cells work to repair and maintain. For example, the number of heads in a “correct” planarian body (defined as that number of heads which, once complete, causes further regeneration to cease) is not set genetically but rather is determined by the memory of a bioelectric circuit, which can be re-set externally (Oviedo et al. 2010; Durant et al. 2019). By manipulating the ion channels and gap junctions to induce states encoding “2 heads” instead of the default 1-head state, planaria were produced that continue to regenerate as 2-headed *permanently*, across future rounds of regeneration in plain water with no more manipulation. A different state of the bioelectric circuit, enabling counterfactual memories that do not (yet) correspond to the current anatomy, and exhibiting the kind of perceptual bistability found in visual processing, can also be induced (Pezzulo et al. 2021). This reveals not only the stable yet re-writable memory of the morphogenetic process but also the fact that techniques of developmental bioelectricity now allow us to directly *read and write the teleonomic goals* of a complex system. These goal states are ontologically real in the most important sense of all: they serve as the target of powerful experimental perturbations (Durant et al. 2016) and enable novel capabilities, results, and research progress.

Memory (implemented by bioelectric networks or other mechanisms) is central to teleonomy as a mechanism for encoding future goal states. More generally, however, bioelectric states are a medium that binds individual cells toward large-scale goals – it underlies scale-up (Figure 5) and emergence of higher-level teleonomic individuals (Levin 2019), much as it does to create brains with emergent unified mental content out of a collection of individual neuronal cells. This is why disruptions of bioelectric communication, in the absence of genetic alterations or carcinogens, can initiate cancer *in vivo* - a shrinking of the size of goals from morphogenetic activity of normal maintenance to unicellular goals of maximum proliferation and migration (metastasis) (Levin 2021b); conversely, forcing appropriate bioelectric communication can normalize cells despite strong expression of oncogenes that otherwise induce tumors (Chernet and Levin 2014, 2013). The framework focused on inflating or shrinking the scale of the teleonomic activity leads directly to novel capabilities, in this case in the context of the cancer problem (Levin 2021b; Moore, Walker, and Levin 2017).

By implementing long-range integration of signal processing, bioelectric dynamics within cell networks enables these collectives to measure states that are larger than single cells, to encapsulate complex activities as modules that can be triggered by simple physiological experiences or stimuli, and to store patterns that serve as representations of very large-scale goal states toward which morphogenesis can work (Levin 2021a). Bioelectric networks facilitate evolution’s ability to potentiate agency by scaling up the components of tiny homeostatic loops: measured states, setpoint memory, and actuator

commands are all increased by controllable electrical connections, thus allowing for ever more grandiose goals, improved robust plasticity (Paolo and Ezequiel 2000), and the expansion of the cognitive horizon (Levin 2019).

Increased progress on bioelectric controls of large-scale decision-making of the collective intelligence of morphogenesis enables the powerful ideas of connectionist machine learning to be applied to the scaling of goals in biology. Mathematical tools for understanding generalization and memory in artificial neural networks offer great promise in mechanistically explaining how collectives of cells, neural or otherwise, can represent goal states and work to minimize error. Bioelectric networks help increase the cognitive “light cone” – the spatiotemporal scale of goals toward which any system can possibly work (Levin 2019) – and are a powerful mechanism by which evolution scales basal intelligence from the tiny, local loops of metabolic homeostasis in single cells to the anatomical homeostasis of large bodies navigating novel circumstances to achieve their objectives in anatomical morphospace.

Teleonomy drives a research program

A view of morphogenesis as teleonomic behavior of a collective intelligence in morphospace has already given rise to a number of new discoveries and capabilities (Levin 2021a; Mathews and Levin 2018; Pezzulo and Levin 2016). The emerging field at the intersection of synthetic developmental biology, computer science, and cognitive science implies numerous opportunities for next steps and further progress driven by a focus on recognizing, quantifying, and learning to exploit goal directedness of diverse biological levels. From the perspective of theory/conceptual advances and specific research directions, the following questions need to be developed:

- What is an effective Eigenspace for modeling agency – what would be the minimal axes for the space of all possible teleonomic agents? And how do we recognize, quantify, and compare teleonomic agents in radially diverse embodiments? Even gene-regulatory networks, a paradigmatic case of deterministic genetic hardware, appear to have learning capacity (Biswas et al. 2021; Szabó, Vattay, and Kondor 2012; Herrera-Delgado et al. 2018; Gabalda-Sagarra, Carey, and Garcia-Ojalvo 2018; Watson et al. 2010); it is imperative that we abandon the tendency for armchair pronouncements of what can and cannot be seen as cognitive, and develop toolkits for generating and testing teleonomic models of arbitrary systems.
- If evolution is blind and always prefers immediate fitness payoffs, how is it that it not only gives rise to creatures highly adapted for specific environments, but also evolves hardware that can problem-solve in numerous novel configurations never seen before? How does evolution capitalize on the laws of physics and computation to generalize so well from specific examples to highly diverse possible instantiations?
- How do we formulate and test specific teleonomic models of scaling from metabolic homeostatic loops to large-scale morphogenetic goals via a balance of local dynamics and global stress loops?
- Can the same models be used to understand the role of the changing environment in plasticity and adaptability and the contribution of changing internal structure and function? Can the notion of external environment be extended to a multi-scale concept in which adjacent cells, tissues, etc. are each other’s environment? Can

molecular pathways and biophysical dynamics be thought of as affordances for systems to compete and cooperate within and across levels in the organism (Queller and Strassmann 2009; Gawne, McKenna, and Levin 2020)?

- What is the relationship or overlap between the sets demarcated by “Life” and “Cognition”? If all (most?) components in living things are teleonomic agents and are thus somewhere on the continuum of cognition (Figure 1), are all living things cognitive? What is a useful definition of “Life”, given that teleonomic agents can be produced by engineering with organic or inorganic parts? While modern life is necessarily teleonomic (in order to survive in the biosphere), could there have been very early life forms that were not teleonomic? Could current efforts at truly minimal synthetic life (Cejkova et al. 2017; Hanczyc, Caschera, and Rasmussen 2011) clarify the relationship between teleonomy and physics?
- Can we find new ways to control system-level goals via the tools of behavioral neuroscience (Pezzulo and Levin 2015), rather than by trying to solve the inverse problem? Reading genomes is now easy, and clean genomic editing will surely be solved in a few years, but this technology reveals the hard problem of Lamarckism facing workers in regenerative medicine - knowing what to edit at the genetic level to achieve desired morphology and behavior outcomes in cellular collectives. We now have the opportunity to adopt tools of neuroscience (Pezzulo and Levin 2015) to learn to distort the perception and action spaces for cells and tissues via modulation of bioelectric and neurotransmitter dynamics, using computer models to help guide their behaviors by approaches focused on their teleonomic control loops. Existing data (Levin and Martyniuk 2018) have begun to show how pattern memories are encoded, but the other parts of the loop – how tissues monitor current anatomical state and perform computations to measure error relative to the remembered setpoint – are almost entirely unknown and remain to be probed. Applications of finding ways to control morphogenesis top-down, avoiding the complexity barrier of engineering at the protein hardware level, include repair of birth defects, normalizing cancer, and inducing growth of healthy organs after injury or degenerative disease.

Conclusion: the future of teleonomy

The increasingly reductive (single-cell, single-molecule focus) advances of big-data biology risk significantly delaying deep insight as they focus on contingent details of specific mechanism. How long would we have had to wait for the discovery of thermodynamics principles, if the physicists of the time had had the possibility of actually tracking every single molecule in a gas (as modern biologists now have), and didn’t feel the need to develop meso-scale laws? Teleonomy is an excellent candidate for scale-free fundamental principles driving the unique capabilities of life, enabling a study of the software of life, in complement to the molecular biology and medicine which dive ever deeper into the hardware. A key aspect is to recognize the need for pragmatic, observer-centered formalisms (Torday and Miller 2016; C. Fields, Glazebrook, and Levin 2021; Chris Fields 2018) avoiding the pseudo-question of whether systems “really” have teleologic goals in favor of empirical research focused on understanding and exploiting the robust control provided by a teleonomic perspective through which systems can model the environment and themselves. At stake are transformative advances in

regenerative medicine (to get beyond the low hanging fruit reachable by conventional stem cell biology and genomic editing approaches), robotics, and general AI.

Teleonomy is also central to developing deeper definitions of intelligence, selves, organisms, stress, robustness, etc. that can survive the coming advances in biological and software engineering, which will produce novel living forms that bear little relationship to any touchstone within the tree of life on Earth – biobots, cyborgs, hybots, etc. (Kamm and Bashir 2014). What are the classic “model systems” (from yeast to mouse) used in biological research models of? Teleonomy is a conceptual tool that allows us to move beyond the history of frozen accidents of evolutionary lineages and explore the truly general laws of biology instantiated by existing and novel beings (Rosen 1985; Maturana and Varela 1980a). The sciences of cybernetics, and the deep lessons of neuroscience that extend well beyond neurons (C. Fields and Levin 2020a, 2020b; C. Fields, Bischof, and Levin 2020; Friston, Sengupta, and Auletta 2014; Ramstead et al. 2019) to address the scaling of goals in biological collectives, will be key components of this future.

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Figure Legends

Figure 1: Goal directedness is an invariant for a continuous spectrum of cognition

Biological systems are not only structurally hierarchical, but also functionally hierarchical: each layer solves unique problems in its own relevant problem space, exhibiting teleonomy (**A**). The degree of competency and complexity that can be handled by a system in its pursuit of goal states defines an order parameter for major transitions along a continuum of cognition ranging from passive matter to advanced self-reflective minds (**B**), which can be used to compare highly diverse intelligences (Rosenblueth, Wiener, and Bigelow 1943). An empirically-useful way to exploit teleonomy across systems is as a guide to the most efficient prediction and control strategy: an “axis of persuadability” (**C**), in effect seeking to determine the optimal level of control (ranging from brute force micromanagement to persuasion by rational argument). Here are shown only a few representative waypoints. On the far left (**C1**) are the simplest physical systems, e.g. mechanical clocks. These cannot be persuaded, argued with, or even rewarded/punished – only physical hardware-level “rewiring” is possible if one wants to change their behavior. On the far right (**C4**) are human beings (and others to be discovered (Bostrom 2003; Kurzweil 2005)) whose behavior can be radically changed by a communication that encodes a rational argument that changes the motivation, planning, values, and commitment of the agent receiving this. Between these extremes lies a rich panoply of intermediate agents, such as simple homeostatic circuits (**C2**) which have setpoints encoding goal states, and more complex systems such as animals which can be controlled by training using stimuli which communicate to the system how it can achieve its goal of receiving a reward (**C3**). This continuum is not meant to be a linear *scala naturae* that aligns with any kind of “direction” of evolutionary progress – evolution is free to move in any direction in this option space of cognitive capacity. The goal of the scientist is to find the optimal position for a given system. Too far to the right, and one ends up attributing hopes and dreams to thermostats or simple AIs in a way that does not advance prediction and control. Too far to the left, and one loses the benefits of top-down control in favor of intractable micromanagement. Note also that this forms a continuum with respect to how much knowledge one has to have about the system’s details in order to manipulate its function: for systems in class C1, one has to know a lot about their workings to modify them. For class C2, one has to know how to read-write the setpoint information, but does not need to know anything about how the system will implement those goals. For class C3, one doesn’t have to know how the system modifies its goal encodings in light of experience, because the system does all of this on its own – one only has to provide suitable rewards and punishments. Ascertaining the optimal level of teleonomy in the objects around us is a key task for scientists interested in understanding and managing novel complex systems, and a built-in cognitive module for animals navigating complex environments, conspecifics, prey, etc. Images in panels A,C by Jeremy Guay of Peregrine Creative.

Figure 2: Robustness and plasticity: morphogenesis as a problem-solving agent

A mammalian embryo split in half (**A**) gives rise not to two half-embryos but to normal monozygotic twins (**A'**) because development is not hardwired in most species

but rather is remarkably context-sensitive and plastic. One way of seeing development is as a continuous process of regenerative repair, in which each embryonic stage (**B**, shown here as embryos of the frog *Xenopus laevis*) is a defect from the perspective of the next stage and must be repaired by developmental remodeling and morphogenesis. At each point, the error between the current state and the target morphology is estimated (**B''**) with reference to an information structure encoded in biophysical parameters (in this case, schematized as a bioelectric pattern memory, **B'**, see Figure 4 and its discussion). Some animals retain this capacity in adulthood; shown in **C** is a typical salamander limb amputation experiment, where the correct amount of perfectly-formed tissue is restored regardless of the level of amputation: the process halts when the correct target morphology is achieved. This suggests a model of anatomical homeostasis (**D**) in which bodies exhibit not only feed-forward emergent morphogenesis (complexity derived from parallel execution of simpler microscale rules) but also feedback loops that trigger cell movement, gene expression changes, etc. in order to progressively reduce the error between a current state and a coarse-grained anatomical setpoint that specifies the goal of the morphogenetic process stop condition. This loop is homologous to similar structures regulating drives and behaviors of complex animals, because it reflects the teleonomic behavior of an agent: a cellular collective working in morphospace. Importantly, this agent exhibits a degree of intelligence (competency in navigating this space) because it can handle novel scenarios. For example (**E**), tails grafted onto the flanks of salamanders slowly remodel into limbs – the more appropriate large-scale structure, including re-specification of tail-tip tissue (labeled in red) whose local environment is correct but which nevertheless gets remodeled by the emergent large-scale anatomical goals of the system (Farinella-Ferruzza 1956, 1953). An even more remarkable example of problem-solving is observed when cells making up kidney tubules are increased in size (**F**, cross-sections). When cells get larger, fewer of them cooperate to make the same required large-scale lumen; when the cells are made too big, one single cell can wrap around itself to do the job, showing how diverse lower-level mechanisms (cell:cell communication vs. cytoskeletal bending) can be triggered by the needs of a higher-level teleonomic process. This kind of capability is still far beyond the artificial intelligence of today's robot swarms. Not only can morphogenetic agents reach the correct region of morphospace despite significant perturbations of environment and self-structure, but they can take different paths to reach those same goals. The normal stages of frog limb development (**G**) are not the same intermediate stages observed in induced frog leg regeneration (**H**), which creates a normal limb but does it in a central “stalk” with side branches for toes, instead of a paddle sculpted by programmed cell death. The paths through morphospace are sometimes associated with actual movements, such as the remodeling of tadpole to frog (**I**) which creates largely normal frog faces even when starting with scrambled tadpole faces with all the organs in the wrong position: the primordia move around in novel paths until a correct frog face is reached, showing that genetics specifies not a machine with hardwired motions in specific directions but rather one that can minimize error from a target morphology and thus handle novelty. Panel sources are as follows: A' is reproduced with permission from Wikimedia Commons (Oudeschool; <https://commons.wikimedia.org/wiki/File:Power20302.jpg>; licensed under the Creative Commons Attribution 3.0 Unported license), B is courtesy of Brenda de

Groot, C and F are by Jeremy Guay of Peregrine Creative Inc., E is from (Farinella-Ferruzza 1956), G is from Xenbase at <http://www.xenbase.org>.

Figure 3: Knowledge gaps for predictions of morphogenesis: genetics and teleonomy

A key goal is to be able to predict the behavior of morphogenetic agents: what shape will result under specific circumstances? Important knowledge gaps in this area exist because our knowledge of the genomically-specified hardware is much greater than our understanding of the teleonomic activity that this hardware implements. For example, some species of planaria reproduce by fission and regeneration (**A**). This implements somatic inheritance – for hundreds of millions of years, they accumulate mutations as each change to the genome which doesn't kill the stem cell ends up amplifying as that cell restores a portion of the next generation's body. As a result of this, their genomes are very messy and animals are mixoploid - the cells within a given animal have different numbers of chromosomes (reviewed in (Levin, Pietak, and Bischof 2018)). And yet, they are champion regenerators (Saló et al. 2009), restoring perfect little worms from any type of cut fragment (**B**); how can the morphology be so reliable when the genomic information is so fungible? Our inability to predict outcomes is clearly revealed by the following experiment. Consider two species of planaria, one which has cells that make a round head and then stop morphogenesis, and one whose cells make a flat head and then stop; what will happen if half of the neoblasts in one species are destroyed by irradiation and replaced by those from another species (**C'**): when the head is removed, what shape will result? Despite all the progress in molecular biology of stem cell differentiation in planaria, the field has no models that make a prediction about outcomes – one dominant shape, an intermediate shape, or a continuous remodeling which never ceases because neither set of cells is ever satisfied with the current shape of the head (**C''**). We lack computational models that link molecular details about the cellular hardware with large-scale decisions that cell collectives make in navigating morphospace. Similarly (**D**), despite being able to read both axolotl and frog genomes, we don't know how to predict whether chimeric larvae will have legs (like axolotls) or not (like tadpoles), and if so, whether those legs will be made of frog cells whose behaviors have been altered toward a novel anatomical task. Panels A-C" by Jeremy Guay of Peregrine Creative. Panels in D courtesy of John Clare at <https://www.axolotl.org/biology.htm>.

Figure 4: Bioelectric circuits encode teleonomic goals as pattern memories

The most familiar goal-driven system, the brain, operates via a network of electrically-active cells, whose resting potential is set by the activity of ion channels and can be propagated to their neighbors via gap junctions (**A**). Consistent with the fact that this architecture evolved from much more ancient cell types already using bioelectric signaling, all cells in the body (**B**) do the same thing (but on slower timescales than neural spiking). Patterns of resting potential thus arise in tissues (**C**), and are a complex, nonlinear property of large numbers of cells driving coupled electric circuits. Such patterns are often instructive scaffolds for gene expression and anatomy, such as the "electric face" observed in frog embryos (**D**) which guides the position of the eyes, mouth, and other organs (shown by the depolarization in light colored-cells, revealed by a voltage-sensitive fluorescent reporter dye). The functional role of these bioelectric patterns is revealed by experiments in which ion channels are introduced or opened in ways that

alter the standing bioelectric patterns – for example, specific potassium channel misexpression can trigger a “build an eye here” pattern on the gut, resulting in the creation of an ectopic eye (**E**). Lineage marker labeling of such ectopic structures (e.g., the lens induced in a tail, **F**) reveals that after some cells (blue stain) are bioelectrically-instructed, they further instruct neighboring cells (brown cells forming the bottom half of the lens) which were not themselves altered in any way, showing that the patterning goals encoded by bioelectric states are not single-cell level properties but can trigger a teleonomic process of instruction toward a new organ-level goal. In planaria, the number and location of heads are indicated by an endogenous bioelectric pattern which can, with drugs targeting ion channels and gap junctions, be re-set to a new pattern (**G**). As befits a kind of memory, the circuit not only leads to the creation of 2-headed animals, but keeps the new pattern permanently, as these 2-headed animals continue to generate 2-headed regenerates in further rounds of cutting with no new manipulation. Teleonomic models of planarian regeneration as a goal-directed process that builds to a specific, directly represented pattern memory has led to the ability to produce permanent lines with a different anatomical bodyplan despite their wild-type genetics (no genomic editing or transgenes need to be used in this process). Remarkably, not only head number, but head shape can be altered by disruption of bioelectric communication after head amputation, resulting in the formation of head (and brain) shapes belonging to other species of planaria (**I**), as the system is pushed out of the normal region of morphospace by injury, and is confused by a general anesthetic on its way to find the correct attractor in the space of possible planarian heads (**J**, discussed in (Sullivan, Emmons-Bell, and Levin 2016)). Panels A-C by Jeremy Guay of Peregrine Creative. Panels D, E, G, and I are from (Vandenberg, Morrie, and Adams 2011), (Pai et al. 2012), (Pezzulo et al. 2021), and (Emmons-Bell et al. 2015) respectively. Panel J by Alexis Pietak.

Figure 5: Conceptual tools for understanding scaling of goals in morphogenesis

Tools from dynamical systems theory and connectionist machine learning (**A**) are examples of how to rigorously conceptualize the goal states needed for teleonomy: attractor states in specific spaces which serve as memories for processes like morphogenesis which direct lower-level systems (cells and pathways) toward higher-level goals. This facilitates hypotheses about the scaling of goals from those of single cells (**B**) such as metabolic states, which require very little memory, spatial measurements, and forward anticipation, into those of tissues and organs, which have larger goals (**B'**) because the collective is able to measure and act in a larger spatio-temporal sphere because of size and computational power. The homeostatic loops of single cells (**C**) are readily scalable as cells join into networks via gap junctions, forcing the measured states, actions, and instructive pattern memories to necessarily be larger and more complex (**D**). A model of cognition for truly diverse intelligences, focused on the scale of the goals they are able to work toward (**E**, (Levin 2019)), shows how teleonomy can serve as a central invariant – a symmetry that enables comparison and synthesis despite huge variance in diverse agents’ construction and origins. In biology, the scaling of the “cognitive light cone” (as a measure of the spatio-temporal size of the goals of a given system) shows how cells can electrically detach from the network, scaling their goals to those of an amoeba, which leads to treating the rest of the animal as external environment – exemplified by the transition to metastatic cancer (Levin 2021b), which can be observed

in their electrical properties via reporter dyes (**F**). Importantly, this model of cancer led to specific research that showed how to normalize cellular behavior and avoid tumorigenesis (**F'**), despite the strong presence of oncogenes (**F''**, red fluorescence), by artificially inflating the cells' ability to sense and participate in morphological goals, rather than by micromanaging their DNA states or gene expression.

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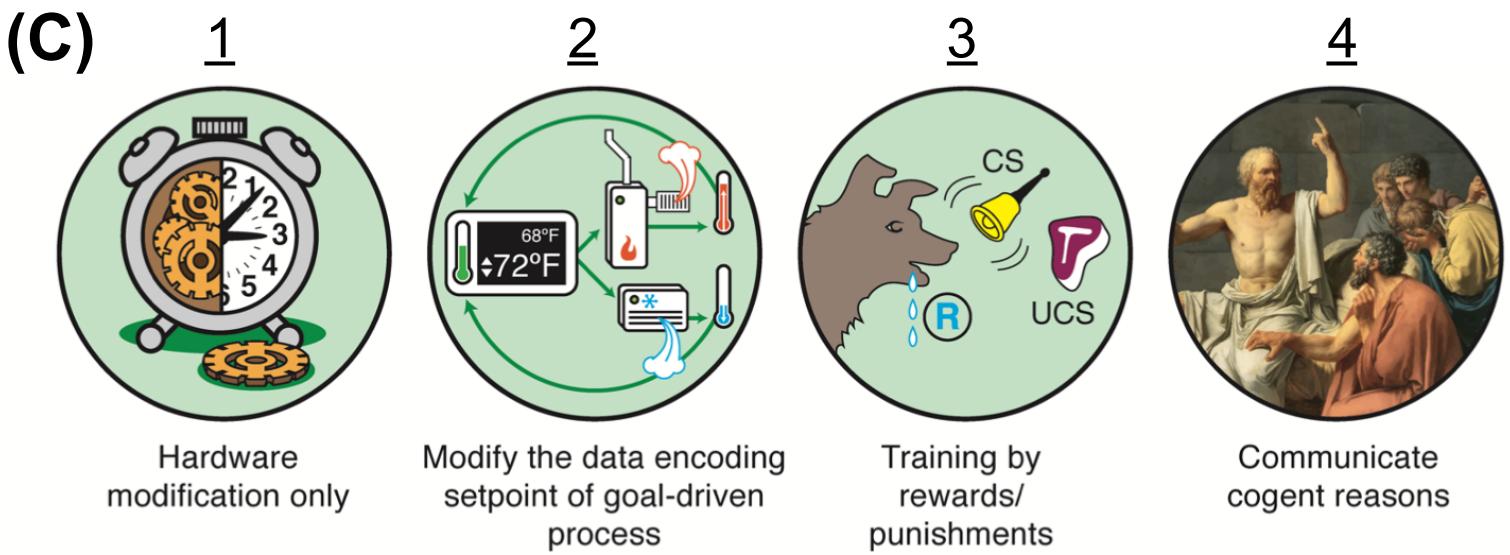
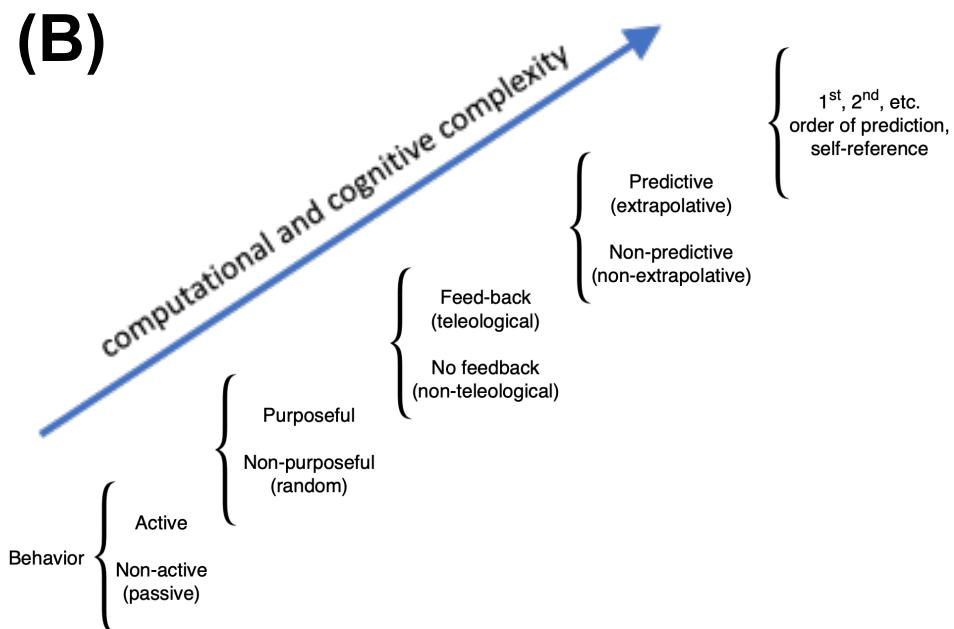
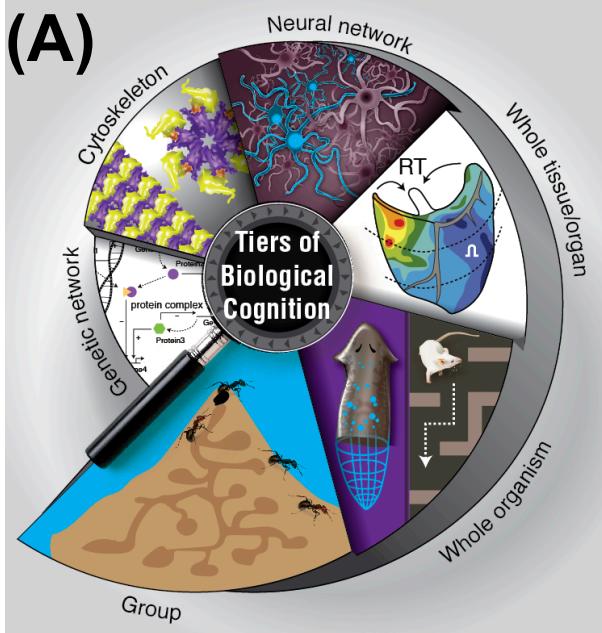
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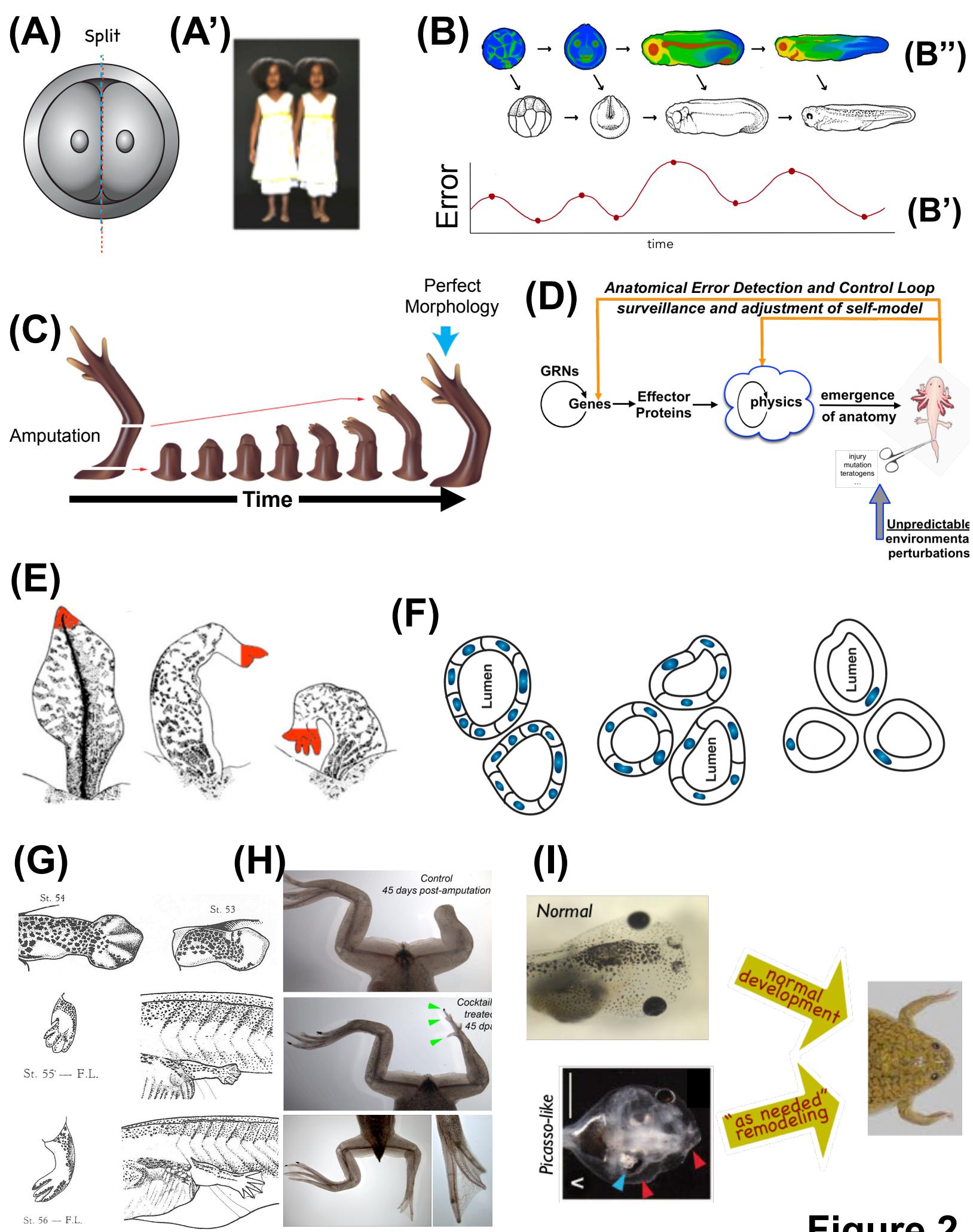


Persuadability

Effort Needed to Exert Influence

Mechanism Knowledge Needed to Exert Influence

Figure 1



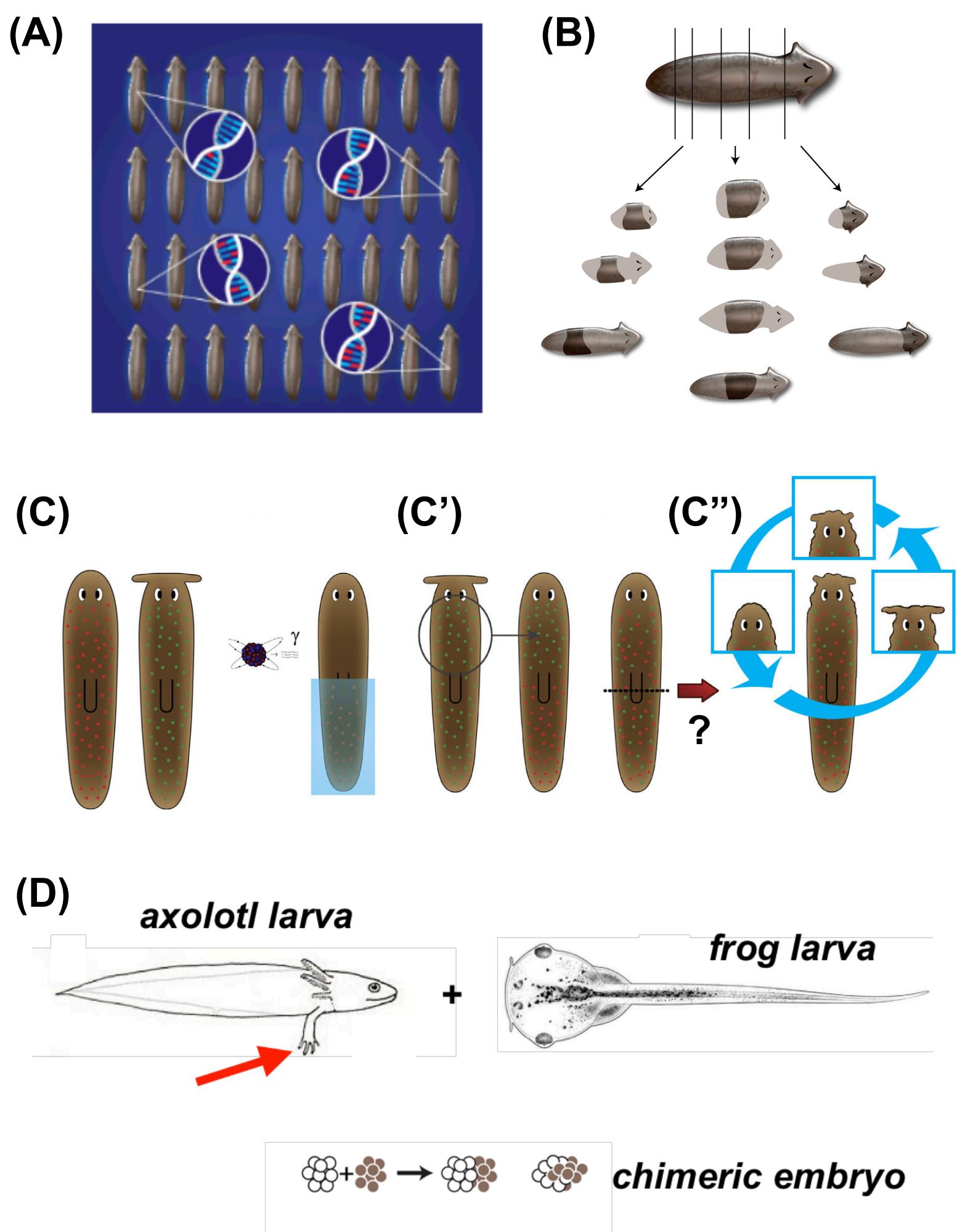


Figure 3

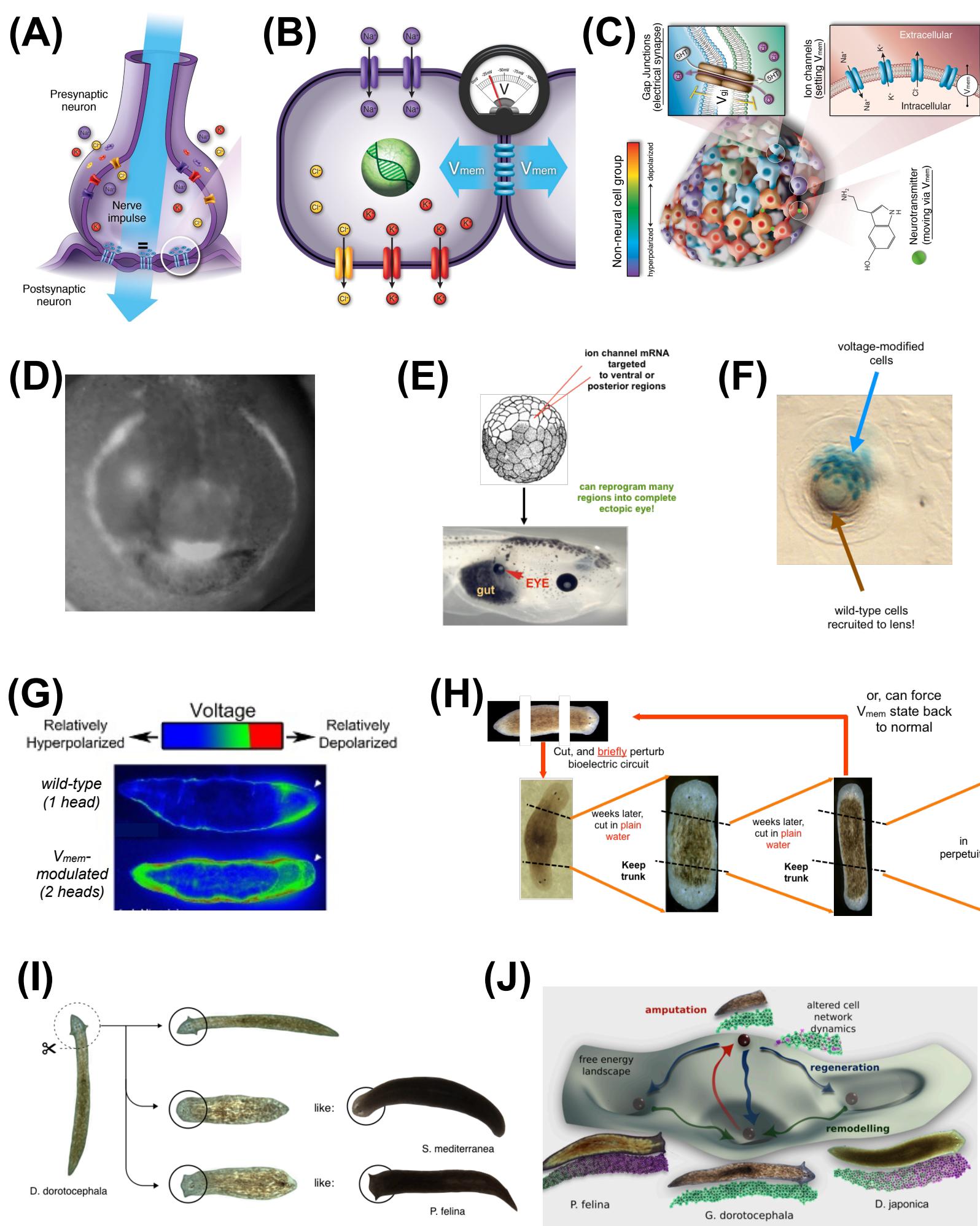


Figure 4

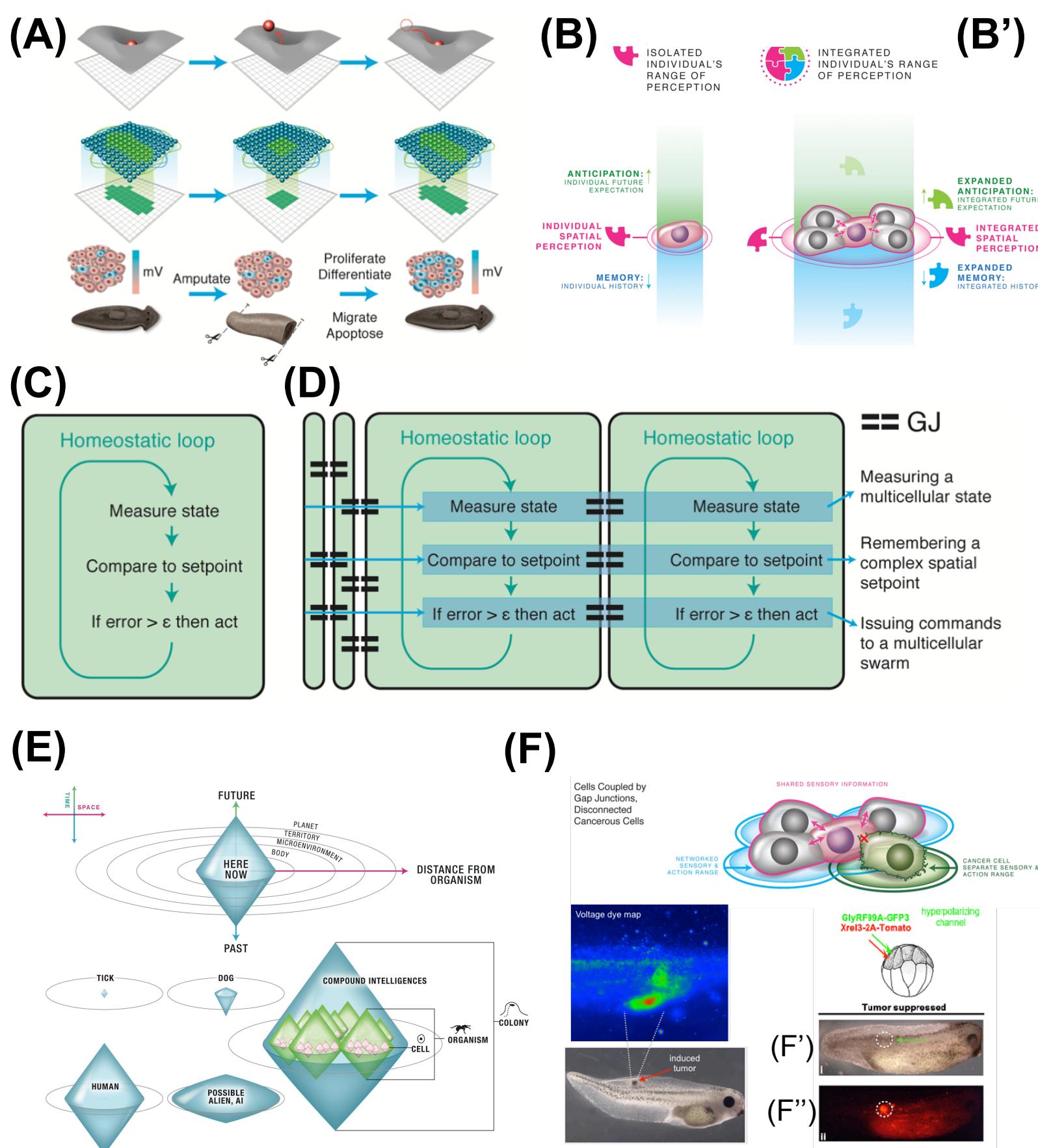


Figure 5