Title: The multiscale wisdom of the body: collective intelligence as a tractable interface for next-generation biomedicine

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Abstract

The dominant paradigm in biomedicine focuses on the genetically-specified components of cells, and their biochemical dynamics. This perspective emphasizes bottom-up emergence of complexity, which constrains interventional approaches to micromanaging the living hardware. Here, I explore the implications for the applied life sciences of a complementary emerging field: diverse intelligence, which studies the capacity of a wide range of systems to reach specific goals in various problem spaces. Using tools from behavioral science and multiscale neuroscience, it is possible to address development, regenerative repair, and cancer as behaviors of a collective intelligence of cells as it navigates the space of possible morphologies and transcriptional and physiological states. This view emphasizes the competencies of living material – from the molecular to the organismal scales – that can be targeted by interventions. Top-down approaches take advantage of memories and homeodynamic goal-seeking behavior, offering the same massive advantages in biomedicine and bioengineering as the emphasis on reprogrammable hardware has had for information technologies. The bioelectric networks that bind individual cells toward large-scale anatomical goals are an especially tractable interface to organ-level plasticity. This suggests a research program to understand and tame the software of life by understanding the many examples of basal cognition that operate throughout living bodies. Tools are now in place to unify the organicist and mechanist perspectives on living systems toward a much-improved therapeutic landscape.

Introduction

The current biomedical/pharmacological paradigm faces important limitations. While we are becoming increasingly effective at controlling molecular-level events with drugs, true regenerative medicine still eludes us. We are unable to predict and repair most classes of birth defects. We cannot restore damaged or missing organs and appendages following injury or degenerative disease. We resort to toxic chemotherapies in the face of cancer [1]. We are unable to build complex organs or new biobots to desired specifications. We age and die, powerless to stop senescence and the degradation of our functionality over mere decades.

Added to the limitations of anatomical control are those of physiological interventions: drug discovery is difficult and time-consuming because the use of pharmacological therapeutics is plagued with differential utility across patients, diverse and often unpredictable adverse events, and cessation of efficacy with time (habituation). Interestingly, the most successful current biomedical interventions, such as antibiotics/antivirals and surgery, target invaders in the body: microbes and parasites. For modulating the function of the host organism itself – repairing instead of killing – few treatments definitively and reliably induce permanent repair. Most existing drug interventions address symptoms, which often return once the drug is stopped (or even worsen over time despite treatment). Often the problem comes back (or exacerbates) when treatment is stopped. How do we get to definitive repair - true anatomical and physiological health?

I see the end-game of this field as represented by the idea of an Anatomical Compiler. Someday, we will be able to sit in front of a system and draw the plant, animal, replacement organ, or novel biobot that we want – at the level of functional anatomy. We will be able to specify its geometric structure, and the system will output a set of stimuli to be given to cells to coax them to build the desired structures. It will also output a communications protocol manual, which says what kinds of further stimuli will control its physiological functions and enable permanent restoration of health states after disease or damage; these same protocols will be usable to maintain and restore the health of native organs *in situ*. In this vision, the anatomical compiler is not a 3D printer or genomic editing system that seeks to micromanage the construction of a living form by specifying molecular or cell-level rules: it is a translator – a communication device that enables us to offload the complexity onto the cells[1], communicating and collaborating with the material by specifying target states for the native machinery whose fundamental nature is to seek allostatic goals [2-5]. Birth defects, traumatic injury, cancer, and degenerative disease would cease their dominance over human potential if we had a way of communicating our structural and functional goals to groups of cells.

Molecular biology and genetics have been thriving for many decades. Why do we not already have an anatomical compiler platform, or anything remotely like it? While individual successes have certainly been achieved, we are extremely far from rational control of form and function despite the deluge of molecular information and omics data. This situation is the consequence of the underlying limitations of the molecular biology paradigm which has served as the exclusive basis for traditional approaches in medicine [6,7]. Consider a few instructive examples.

Baby axolotls have forelegs (Figure 1B). Larval frogs (early tadpoles) do not have legs. Despite having sequenced genomes for both species, could we predict whether frogolotls - chimeras made of frog and axolotl cells - would have legs? And if they did, whether those legs would be made entirely of axolotl cells or of both kinds? What about planaria, made to comprise a mix of two different species' stem cells – which type of head would they regenerate (Figure 1C)? Not only are there no models in the field that would predict an outcome for such chimeric cases, we cannot even know the anatomy of a single (non-chimeric) species from its genome alone, without cheating by comparing it to the genome a species with known anatomy and predicting that it will look roughly like that. We do study developmental roles of specific genes, but we are often surprised; for example, why do cells thrive without highly conserved cell cycle and genome integrity genes and pathways [8]? We are beginning to understand the molecular hardware, but we are still very far away from a good understanding of its plasticity or how that hardware makes collective decisions in anatomical morphospace and the other spaces such as transcriptional, metabolic, and physiological, in which living things play out their struggles against entropy [9,10].

Another example is shown by the highly regenerative flatworm, planaria [11]. Due to their accumulation of somatic mutations over 400 million years (asexual reproduction driven by fission and regeneration), their cells are mixoploid – often having different numbers of chromosomes [12]. Their bodies also contain huge numbers of highly plastic and proliferative stem cells – a situation normally assumed to imply a high risk of cancer. Despite that, they are champions of regeneration, cancer resistant, and apparently do not age. The current paradigm of "genome drives function" does not predict that the animal with the messiest genome, full of undifferentiated cells in the adult stage, should be the one that has perfect regeneration, immortality, and freedom from cancer[2]. Examples like this emphasize how far we are from understanding the regulation of large-scale properties, even as we drill down into better and better molecular details. This limitation will become increasingly stark, as tools such as CRISPR exhaust applications around single-gene phenotypes and confront the problem of *which* genes to edit, to get a desired complex outcome at the level of anatomy or functional physiology.

Here, I argue that the above barriers can be overcome by augmenting today's focus on the hardware of life with a research program that seeks to exploit the inherent physiological software existing in cells and tissues. Numerous examples of non-neural memory, problem-solving capabilities, and collective decision-making [17,18] reveal that our bodies are constructed as an architecture in which each layer of organization navigates its own problem space [10]. I suggest that the tools of cybernetics, behavioral science, and neuroscience can be brought to bear on the deep problem of biological control for therapeutic and bioengineering purposes [19,20], far beyond neurons and their control of conventional "behavior" of motile animals in 3D space[3]. Specifically, I argue that the traditional modalities for engineering with passive matter face significant limitations in the life sciences. Living bodies are an agential substrate, full of competencies and agendas [25]; they demand, and offer, additional ways of engineering that are at once new (for the realm of somatic biomedicine) and also old because they have been extensively and successfully used in the behavioral sciences [26].

My position is pragmatic and naturalist (Box 1), in the sense that we must understand and exploit the mechanisms appropriate to each level, and that empirical

success in biomedicine and bioengineering are the only arbiters of frameworks – not philosophical commitments to inviolate binary categories and pre-scientific colloquial baggage of words such as "intelligence" which seeks to limit its applications to brainy organisms and navigation of 3D space. At the same time, it is a deeply organicist position[4] because the future of biomedicine and of basic biology requires us to come to grips with what is special about living materials and how they handle the scaling of intelligence (Box 2) across subsystems. However, this approach freely makes use of perspectives that have proven effective in other areas such as computer and information sciences [27].

I do not argue that living material is a computer in the sense that it uses anything like today's mainstream computer architectures, or that the typical Turing Machine model is sufficient to deal with the self-assembling, self-modifying, multiscale goal-driven living systems in which there is no barrier between data and mechanism, and no unique global perspective [28]. What I do claim is that we have too long been constrained by the implications of four dominant ideas: 1) that the genome is the software and determines final phenotypic outcomes, 2) that intelligence only applies to brainy organisms and thus conceptual tools suitable for simple mechanisms at the level of chemistry, are the only correct approach to the biomedicine of the body, 3) that goal-centered frameworks are taboo because goals are mystical features of advanced brains, and 4) that open-loop emergence of complexity, arising bottom-up from low-intelligence local rules, is the only way to understand the control of biological form and function. Below, I review some important, but under-appreciated, features of biology that represent new targets for future medicine, and conclude with a list of specific research programs enabled by this unorthodox perspective.

The central hypothesis is that the body is a collective intelligence, behaving in anatomical, physiological, and transcriptional spaces [10]. Thus, tools from behavioral science that enable efficient collaboration with complex systems should give advantages over biochemical micromanagement. Indeed, cells too are a collective intelligence of subcellular components; we must communicate not only with tissues and cells, but with the molecular networks themselves. The implication is that drugs and other interventions should be developed as messages, not low-level controls – a focus on their interpretation by a proto-cognitive system with goals and memories, and a strategy of behavior shaping, not mechanistic forcing of microstates [29]. Effective therapies must reset setpoints, effectively getting cells' buy-in to the desired outcome.

Fortunately, we already have one well-established modality for interfacing with complex goal-driven systems: the bioelectric networks that tie neurons together toward conventional cognition, and also serve as a proto-cognitive glue for the body cells as they navigate anatomical spaces [30]. Powerful tools from other fields are coming online that can be harnessed, if we are willing to soften conceptual barriers, left over from classical ages, that prevent the use of toolkits across categories. At stake are transformative advances in definitive regenerative medicine, as well as synthetic bioengineering and even truly bio-inspired AI's.

Intelligence below the cellular level

Conceptual basis for thinking about tissue intelligence

All systems can be categorized along a continuum (Figure 2A) corresponding to the degree of autonomy they implement [27]. It is often assumed that cells and tissues are at the very left of such a spectrum, as physico-chemical machines which are complicated but lack agency. This however is an empirical question, not one that can be settled by philosophical fiat. That is important, because placement on this spectrum determines the kinds of tools – conceptual and practical – that can effectively be used with a particular substrate, and the kind of outcomes that can be expected. Neuro-behavioral sciences illustrate this nicely: achieving a complex behavioral outcome in an animal does not require manipulating every neuron and muscle like a puppet. Instead, we can simply train it (the way humans have done with dogs and horses for thousands of years) because the system itself offers an interface (learning) which serves as an abstraction layer that hides underlying details in favor of a convenient way to encapsulate complex, integrated responses behind simple triggers. Could something like this be possible for morphogenesis?

Control of large-scale anatomical form and function is a central goal of the life sciences. Bioengineers and workers in regenerative medicine both seek optimal ways to coax cells to produce specific and complex outcomes [31-34]. What frameworks can be used to understand the possibilities, limitations, and optimal strategies in this field? One crucial transition that must take place is the realization that living tissue is an *agential material*. Humans have engineered with passive matter (wood, metal) for a long time, and more recently, active matter [35,36] and even computational materials [37] have come on-line. But in working with cells and other biological components, we find ourselves at a new frontier: material with agendas, competencies, and goals in physiological, transcriptional, and anatomical spaces. This is because we are made of building blocks which were once independent organisms themselves; the story of our origin is one of evolution finding behavior-shaping signals and signaling policies that scale up the information-processing and homeodynamic goal states of single cells into those of large collectives [38]. Controlling such systems requires a new approach, with tools drawn from other disciplines appropriate for multi-scale decision-making agents.

The inner life of active matter

A critical parameter for the continuum of agency is the degree to which an external observer has to take into account the system's internal representation of the option space and its autonomous decision-making. To know what a bowling ball is going to do on a bumpy landscape, an observer's external, 3rd-person view of the landscape, and calculations about energy minimization, tell the whole story. The same approach doesn't work for a mouse on that landscape – what's salient there is *its* view (internal model) of the landscape and free energy minimization with respect to its priors and goals, not the observer's [39,40]. Many simpler systems, such as homeostats and autonomous vehicles, fit somewhere between those extremes. Where do cells fit on this continuum?

Single cells, from microbes to somatic cells, have been shown to have numerous proto-cognitive capacities, including memory (learning), decision-making, and anticipation [17,41-43]. Especially relevant to future biomedicine are the examples showing that cells of multicellular organisms have not lost the basal features of adaptive information processing, including phenomena such as cardiac memory [44,45] and active cell perception and signal processing with respect to stimuli [46-53]. A diverse range of

cell types exhibit learning via molecular signaling networks and bioelectric circuits [54-58] and context-dependent decision-making [50,59,60]. This means that treating them as low-order (even if complicated) machines, amenable only to rewiring, leaves much on the table in terms of efficacious control.

As will be seen below, the competencies of cell groups during morphogenesis arise from the scaling up of the single-cell agentic repertoire. What underlies the competencies of cells? Does agential behavior first appear in single cells – are they the smallest unit of cognition [41,61-64]? It turns out that even below the single-cell level, molecular components already have aspects that benefit from the use of tools for the study of cognitive systems, and that what cells know (and what they can know) – their senome [61,64-66] - is as important as their genomes, proteomes, and other such hardware specifications.

By applying standard approaches from behavioral theory [26], it was seen that even simple models of gene regulatory networks and molecular pathways (Figure 2B) show several different kinds of learning, including habituation, sensitization, and Pavlovian (associative) conditioning [55,56]. By treating some nodes as the Unconditioned Stimulus, other nodes as the Response, repeated presentation of the UCS with an initially Neutral node results in the network treating signals arriving on that node as a Conditioned Stimulus which can now trigger Response on its own. This is a kind of dynamical state memory and doesn't require any hardware changes to the topology of the network or the strength of the edges (promoters). This is also a kind of "molecular placebo" because due to its history of experiences, even a simple network can start responding to a neutral stimulus as if it was a much more potent one.

This shows how applying tools from other disciplines can reveal novel dynamics. The metaphor of gene networks as mechanical, low-agency, dynamical systems [67,68] is useful for many things but it did not on its own facilitate the discovery that GRNs and pathways should be able to be trained, and tools from cognitive neuroscience such as active inference are shedding light on reasons for failure of drug therapies [69,70]. Importantly, for biomedical purposes, GRNs are an abstraction layer - an interface to cells which permits training them just as brains and neural networks are an interface to animals and usable long before we knew how dogs' and horses' brains worked. The implications of this molecular intelligence layer are numerous, spanning drug habituation, resistance of cells to therapeutics, unexpected side-effects and differential efficacy across patients with different physiological histories, and the potential to use associative conditioning between drugs to induce outcomes using low-cost and well-tolerated trigger compounds [70]. Cells' learning capacity can lead to drug failure because the system resists, adjusting to what it detects as a hacking attempt by an external exploiter. For this reason, 1st order models of using conventional reagents to clamp a specific pathway state in place won't work – 2nd order models, which take into account cells' ability to maintain goal states, and facilitate re-writing those goal states, are needed.

Given this learning capacity in chemical networks within cells, all the evolutionary benefits of learning become relevant, modifying the speed and course of evolution beyond what standard cycles of random mutation + selection produce alone [15,71-73]. Indeed, several computational studies have shown that evolution works quite differently over an agential material that has competencies and plasticity beyond a fixed genotype→phenotype relation [74,75]. The more intelligent the software mapping, the

more robust and rapid the evolutionary progress. A number of studies have now identified ways in which exploratory learning and other problem-solving capacities [54,76-80] can affect evolution.

It's important to emphasize that we have only begun to scratch the surface of physiological problem-solving. For example, when flatworms are exposed to barium – a nonspecific potassium channel blocker, their heads rapidly degenerate; this is not surprising given the necessity of endogenous potassium metabolism in the neurons and other cells of the head. Remarkably, they soon regenerate new heads which are completely adapted to the presence of barium [81]. RNAseq analysis of their transcriptome reveals just a handful of genes that have been up- and down-regulated to enable cells to conduct their business in this hostile environment, and morphological and physiological homeostasis is regained. The key question is: how do cells know *which genes to regulate to resolve their physiological stressor*? It's unlikely that they have a built-in response to this unusual toxin[5]. As with the examples of polyploid newts and many other novel manipulations (Table 1, and the biobots described below), navigating a high-dimensional transcriptional space to the right solution is an impressive problem-solving capacity that we do not understand. It is essential to explore the adaptive cross-talk between subsystems that handle transcriptional and physiological navigation (as our neurons handle multimodal connections between 3D action space and linguistic space).

The collective intelligence of cell groups

Cells have the capacity to solve problems in metabolic, physiological, and transcriptional spaces. But that is just the beginning of the impact that collective intelligence has on the basic and applied life sciences. Some of life's most remarkable and impactful capacities are revealed when we turn to the goals and competencies of large groups of cells, which traverse the latent space of anatomical possibilities.

Morphogenesis as behavior in anatomical space

It has previously been argued that morphogenesis can be viewed as *behavior in anatomical morphospace* [10]; on this model, cellular collectives are systems that actively navigate from various starting states to a region corresponding to the species-specific target morphology. As with all autonomous systems, the navigation process can exhibit diverse degrees of competency, ranging from a constrained random walk to highly advanced pathfinding and problem-solving [82]. The practical benefit of entertaining this metaphor (in parallel to other equally metaphorical terns, such as "pathways" and "genes for traits") is that it encourages a specific research program: the use of tools from behavioral and cognitive sciences that offer mature and powerful frameworks for understanding, predicting, controlling, and creating agents that navigate problem spaces. We have argued that neuroscience is not about neurons, but about understanding multiscale dynamics of emergent intelligence [83,84]. If morphogenesis is decision-making and goal-directed behavior, then memories, preferences, measurements, disorders of perception, active inference, self-models, and many other dynamics become potential targets in development, regeneration, and cancer [20,85].

The specific hypothesis explored herein is that the mechanisms guiding cell functions result not merely in emergent complexity that results in a fixed outcome as an

open-loop controller (Figure 3A), but that it exhibits a kind of intelligence that offers a powerful and tractable target for biomedicine and bioengineering (Box 2). Here, intelligence is defined in William James' [86] sense as the ability to reach the same goal by different means: it focuses on problem-solving competency which in this case is the ability to construct and repair a specific morphology (target in anatomical space). This definition of intelligence is functional and generic, enabling its study in substrates much different than typical brainy animals navigating conventional 3D space. It is supported by an emerging body of work on basal cognition and diverse intelligence which finds applications of behavioral science tools to a wide range of systems along the evolutionary path from simple biochemical systems to the kinds of animals in which it is easy for us to recognize in full bloom. Delimiting the kind and degree of intelligence that cell collectives can deploy is an active empirical research program, but already some remarkable examples are beginning to reveal the shape of the competency of living material as seen during development, regeneration, and metamorphosis.

The competencies of anatomical homeostasis

Conventional intelligence results when brains exhibit problem-solving by a collection of neurons bound together into a network which has memories, goals, and preferences far beyond those of the individual cells. In this sense, the brain is a collective intelligence too. The evolutionary precursor of this remarkable capacity is the ability of all cell networks, not just neurons, to solve problems by navigating anatomical morphospace in a way that goes beyond a hardwired path from egg to adult: perturbative experiments in this space, like those done to probe the intelligence of conventional behavior in 3D space, reveal the ability of cell collectives to solve problems as a collective – to achieve their anatomical goals despite novel scenarios and interventions that deviate them form their normal path. These types of experiments are essential because normal development is deceptive: it suggests a minimal model in which cells follow hardwired rules which mechanically take them on a predetermined path with a fixed start and a fixed outcome.

A few instructive cases of morphogenetic problem-solving are shown in Table 1. They have several fascinating aspects in common. First, the general notion of anatomical homeostasis: the ability of systems to reach and maintain a specific region of anatomical morphospace despite deviations (Figure 3B-D). This modifies the current paradigm by pushing beyond the ubiquitous teleophobia that obscures setpoints and competency mechanisms to the use of tools from cybernetics and control theory – non-magical sciences of physical systems with true goals. The recent decades' emphasis on bottom-up (open-loop) emergence of complexity from simple rules [87,88] is augmented with a realization that large-scale feedback loops exist that measure distance from a given target state and execute diverse molecular steps to implement those goals (reduce error). Second, it expands the well-known examples of homeostasis in which the setpoint is a simple scalar (hunger level, blood pH, etc.) to the realization that networks can store setpoints that serve as complex data structures (like rough morphogenetic specifications). A remarkable fact about homeostatic loops is that they implement valence (desirable outcomes) and preferences [89,90]. Chemistry does not make mistakes – every chemical reaction is equally correct in following the rules of chemistry. But developmental biology, while consistent with the rules of chemistry underneath, brings in the notion of a birth

defect – an outcome in which the system could not reach its target morphology despite efforts to do so.

A kind of creative problem solving enables life to handle novel scenarios by using the tools at cells' disposal in new ways (a classic definition of intelligence) (Figure 4). For example, polyploid newts can be made with multiple copies of the genome which forces the cells to be larger [13,14]. The resulting animals are of normal size however, because structures such as kidney tubules use fewer of them to make the same overall shape. Most remarkably, when the cells are made to be truly gigantic, a single cell may wrap around itself leaving the needed lumen in the middle. This can be analyzed as a kind of downward causation, in which distinct mechanisms (cell:cell communication and tubulogenesis vs. cytoskeletal bending) are triggered toward a specific large-scale outcome. It arises because evolution does not just make specific solutions to specific problems, it makes problem-solving systems that do not over-train on prior history, knowing that both environment and genetics will change over time [16,71]. A newt embryo coming into the world can't assume a specific amount of genetic material, a normal cell size, or normal cell number. Not only does it face an uncertain environment, but it can't even count on the stability of its own parts, which are guaranteed to mutate over evolutionary time. The multiscale competency architecture (MCA) of biology leans into this dilemma via components that (in most organisms) to not simply roll forward as cellular automata, but optimize for goals via very basal elements of intelligent problem-solving. This enables incredible robustness and noise-tolerance for development [71] and has fascinating implications for how we think about both evolution and applied biomedicine.

Evolutionary aspects of morphogenetic intelligence

In working with an agential material, evolution is searching not through the space of phenotypic states, but though the very different space of behavior-shaping signals and policies that scale up homeostatic states from molecular to physiological to anatomical ones. The multiscale competency architecture of living beings ensures the existence of modular top-down controls (subroutine triggers) and the existence of setpoints that can be re-written. In committing to persisting through inevitable change [16], biological systems can be highly reprogrammable by physiological events (both internally- and externally-initiated). Rewriting setpoints and triggering complex outcomes with a simple stimulus is an extremely powerful intervention strategy, to which some systems on the rightward side of the spectrum (Figure 2A) are amenable. Thus, one way to look at engineering with MCA systems (agential materials) is as a kind of hacking – in the sense that systems have allegiance to in-the-moment adaptive success, not prior or other systems' intent of how their controls and outputs are to be used [91]. All biological systems and subsystems can interpret events around them in different ways (a concept known as polycomputing [92]) and are constantly using the many interfaces in their environment to hack other subsystems for beneficial outcomes.

Evolution exploits this routinely, through the use of developmental modules, triggers, and setpoint-modifying signals [71,93-95]. This is how biological systems control their own parts, but this strategy has not gone un-noticed by parasites that exploit the competencies of their target material. We would have never known that the oak genome can form remarkable red and yellow spiky balls instead of the default flat green leaves (Figure 4D-D') if a non-human bioengineer (a wasp) had not shown us how chemical

prompts can hack the leaf cells to build such a thing. The resulting galls are a chimeric collective intelligence, whose morphogenetic goals have been partly hijacked. The wasp does not need to micromanage each gene and each cell in the leaf, to get an outcome very far from the normal oak leaf target morphology – it's taking advantage of the versatility (reprogrammability, at a software level) of the agential material in its target species by providing appropriate prompts. As will be argued below, biomedicine must take the same approach. The evolutionary origin of this arms race between hackers ensures a degree of cryptography within the MCA (each system wants its parts to be controllable, but not *too* controllable lest it be overrun with exploiters) [96], which makes the job of the bioengineer more interesting. Interestingly, the sophistication of the galls produced matches the overall complexity level of the parasite – on a spectrum from virus to nematode to insect, the most advanced prompter is able to induce the most complex galls [97]; this bodes well for human bioengineers, if we can commit to the task of improving our bioprompting abilities.

The difficulty with the conventional bottom-up engineering approach is that the mapping between genomic specification of the hardware and the phenotypic outcomes (which result from flexible, problem-solving software) is very indirect. It is not just that development makes the mapping more complex and nonlinear [98], but that the morphogenetic layer in the middle solves problems [99], which means that it hides information form selection. The better the mechanisms of regulative development, the more difficult it is for selection to reward the best structural genomes (because the outcome is not a simple function of the structural genes [15,74,100-102]) – well-formed, functional bodies could be due to a great genome or to mediocre structural genetics but efficient self-repair capability. Evolution is then forced to spend much of its time improving the competency – a positive feedback loop which implements a kind of intelligence ratchet. Different taxa occupy different positions along a continuum with respect to how seriously the system takes the genetic information. These range from the hardwired and mosaic *C. elegans* to the more plastic early mammalian embryos and adult amphibia which can handle some very novel scenarios in anatomical morphospace (Figure 4). The right side of this spectrum is represented by planarian flatworms [103], which are resistant to physical damage (highly regenerative), cancer, and aging (the asexual forms are immortal). All this is because of, not in spite of, their incredibly chaotic genome [15,104]. In planaria, evolution went all-in to the assumption that the genome is going to be full of errors and put all of the work into an algorithm that can build and maintain a perfect worm even when the underlying hardware is unreliable. One interesting consequence of this "don't take the genes too seriously" strategy is that planaria are also quite resistant to experimental transgenesis – there are no permanent lines of abnormal planaria made by editing the genome as there are for all other model systems (there are two abnormal lines, but they are not genetic, as described below).

This kind of robust reconfigurability goes well beyond the cellular and even the morphological level. For example, tadpoles with eyes placed on their tails can see [105] without new rounds of mutation and selection, and life is robustly interoperable in the context of artificial materials, chimeras, hybrots, etc. [106,107]. All of the examples of Table 1 point to fascinating competencies and plasticity of the living material which serve as attractive targets to exploit in biomedical approaches. In the next section, I discuss a

fascinating category of mechanisms that underlies a tractable interface to the interpretation, homeostasis, and context-sensitive behavior of the material: bioelectricity.

Bioelectricity as the interface to multicellularity

Bioelectric networks: a cognitive glue

Conventional cognitive systems operate in problem spaces, and with goals, unknown to their parts. When a rat learns to press a lever to receive a reward, no individual cell had both experiences of interacting with the lever or getting the treat. The associative memory linking lever to food belongs to the collective, which is more than the sum of the millions of cells that comprise it. What enables our large-scale memories, plans, and preferences is an electrochemical network that binds the functions of cells such as neurons into an emergent whole with novel capacities and common goals in new problem spaces. These networks are comprised of cells running electrical circuits (Figure 5) determined by ion channel proteins (which set resting potential of each cell) and electrochemical synapses such as gap junctions (which determine how changes in those potentials propagate across the network).

One of the key properties of such networks is the storage of memory (as exploited also in our computer technology) because voltage-gated ion channels provide a kind of historicity[6] in which transient physiological stimuli can induce long-term changes in the bioelectrical property of the circuit [108]. Memories are ideal as the keepers of setpoint information used by homeostatic behavior. Another key feature is top-down control, which enables stimuli to kickstart complex downstream autonomous cascades. The most widespread application in bioelectricity – the cardiac defibrillator - works because it is possible to provide a stimulus and then depend on the organ to take it from there. In terms of behavior, it is essential that simple stimuli are able to trigger multi-step behavioral responses, including autonomous homeostatic loops that perform actions until specific conditions are met. Bioelectric networks are ideal for representing (storing) the setpoints for homeostatic processes as memories [109-111].

The final crucial thing about such networks is that they allow information to cross levels of organization and be remapped across problem spaces, for example between linguistic space and the 3D motion space of active behavior. A human being's top-level career and interpersonal goals are effectively pursued because those abstract cognitive goals result in the movement of ions across muscle membranes that enable the organism to move. This ability of mental structures to control biochemistry is not limited to rare, exotic forms of biofeedback and placebo effects – such "mind-body medicine" is the everyday miracle of voluntary motion, made possible by the bioelectric network that transduces high-level mental patterns into the action of muscles and glands. Thus, neuroscience is not about neurons per se, but rather about understanding how minds and bodies interact and how information controls biophysics.

Thinking beyond the brain

While it is tempting to think of the cross-level transduction as a unique capability of neural hardware and the electrochemical software that brains enable, this architecture is ancient, being present in microbes [112]. Evolution discovered the immense benefits of electric networks by the time of bacterial biofilms [113,114], using them to integrate

physiological information across space and time in a colony. What did pre-neural electrical networks think about before nerves and muscles evolved, enabling conventional behavior? Networks that managed an organism's position in 3-dimensional space evolved from non-neural somatic precursors whose job was managing the navigation of the organism through anatomical morphospace [10]. Just as bioelectricity in the CNS binds neurons into a collective intelligence for motile behavior, somatic bioelectricity functioning from the time of fertilization binds all cells into a collective intelligence that solves morphogenetic problems.

Thus, brains and CNS function are the result of a fascinating evolutionary pivot. What changed was the space these networks represent and naivgate, and the time scale at which they operate (from the hours and days of morphogenetic change to the milliseconds of motile behavior). What stayed constant was the molecular machinery: ion channel proteins, electrical synapses (connexins), and neurotransmitter downstream targets that eventually regulate gene expression. Also, many of the algorithms (such as active inference [85,115], perceptual multistability [109], dynamic rewritable memory [116], etc.) are highly conserved between morphogenetic and cognitive functions, enabling tools of computational cognitive science to be used in developmental biology contexts [20,84]. The symmetry between developmental biology and neuroscience is deep [23,84]. It can be seen in numerous channelopathies that result in patterning defects (see Table 1 in [117], and [118-120]), and in the applicability of the tools of neuroscience – from drugs to optogenetics to training protocols – to morphogenetic decisions. This in turn has massive implications for regenerative medicine and bioengineering because the interface that is naturally used by the organismal level to control its cellular parts can be hacked to take advantage of its many competencies.

Applications of modulation of endogenous bioelectric cues

It has been clear for over a century that endogenous bioelectric phenomena play a functional role in the control of dynamic anatomical outcomes [121,122]. But the development of molecular tools to read and write bioelectric state information in non-neural tissues has led to the identification of the native genetics underlying the circuit properties, the molecular targets of the voltage change, and the processes that exploit bioelectric networks as a self-modifying control network [123]. Focusing on spatiotemporal patterns of resting potential (complementing older work on electric fields and ion fluxes) revealed several types of effects. First is the control of stem cell differentiation decisions [124]. But, the importance of bioelectricity really shines at the organ scale, because the bioelectric code mapping patterns into anatomical outcomes is not a just cell-level code.

Beyond the control of single cell behaviors such as differentiation and proliferation lies bioelectric patterns' second role - as prepatterns, or informational scaffolds that store rough anatomical setpoints for tissue-level order [125]. One example is the electric face (Figure 6B) – an endogenous distribution of resting potentials that determines the gene expression and anatomical regionalization of the vertebrate face [126]. Manipulation of this pattern via pharmacology, optogenetics, or ion channel misexpression results in predictable changes to craniofacial development, and explains why ion channel mutations lead to such phenotypes in models ranging from frog to human [127]. Similar roles have been found in *Drosophila* wings [119,128-130], in insect ovary systems [131-134], and

numerous other body structures in humans including limbs, heart, face, brain and more [117].

Specific bioelectric patterns can induce ectopic organs; misexpression of potassium channels in the Xenopus laevis model results in the formation of ectopic eyes [135], with normal internal tissue layers, by recapitulating the voltage eye spot seen in the electric face (Figure 6C-D). This effect reveals several interesting aspects of biology. First, it underscores the fact that bioelectric patterns are *instructive* – V_{mem} change induces an entire organ, not just disrupts normal development. Second, it shows that the control system is highly modular – a very simple (low information-content) signal induces a cascade of events that builds a complex organ with many cell types in the correct overall morphology. Third, it reveals an interesting competency of the cellular medium: if too few cells are injected with the channel mRNA (Figure 6E), they recruit their neighbors to help (as other collective intelligence, such as ants, do when recruiting their nest-mates to help carry something large). We did not have to engineer the ability to recognize that there are not enough cells to do it alone, or insert synthetic biology circuits to hack the behavior of the right number of neighbors to re-specify *their* morphogenetic paths to a new goal, as a kind of secondary instruction. The material already does this, challenging us to exploit such capabilities and discover new ones.

A key point revealed by these data was that numerous regions in the posterior of the animal could be induced to form eyes, e.g. on the gut. It was always thought that the cells outside the anterior neural field in vertebrates were not competent to do so (in the standard developmental biology, narrower, sense of “competence”). But that is because in prior studies, the cells had been prompted with the so-called master eye gene Pax6 [136]. While it is true that eyes can only form in the front of the head in Xenopus using the Pax6 signal, a higher-level signal (V_{mem} change) can induce them almost anywhere in the body. The developmental constraints and limits of competency we observe are always relative to *our own* skill and competency in communicating target information to cells. Higher-level prompts (bioelectric state over a single transcription factor) can often reveal new capabilities not apparent from manipulation of the molecular levels.

A final point about the eye induction concerns the dynamic aspects of this organ-level reprogramming. In embryos injected with the potassium channel, many ectopic eye spots can be detected at early stages; but surprisingly, one new eye tends to appear at the end. What happens to the induced eye cells that do not go on to form the whole organ? This phenomenon is the consequence of a conversation between two morphogenetic agents. The channel-induced cells have been pushed toward a morphological setpoint corresponding to eye development, and try to convince their neighbors to help out, via signals yet to be identified (though likely mediated by gap junctions). However, the neighbors whose morphogenetic setpoint is still set to “gut” (or other organ), disagree and in turn try to push the other cells to keep their normal fate and ignore their new voltage-mediated plan. This bi-directional communication, and the attempts to exert influence on the microenvironment to implement physiologically-specified goals, are fundamental because they provide important biomedical targets, beginning first with the phenomenon of cancer suppression.

Taking advantage of cells’ ability to read bioelectric state information can be used to repair birth defects (Figure 7). Normal brain morphogenesis is determined by a specific bioelectric prepattern that is altered by chemical or genetic teratogens [137]. Correct brain

morphology, gene expression, and even learning capacity can be established in animals exposed to alcohol, nicotine, or even mutations of the critical neurogenesis gene Notch, by forcing a return of the correct spatial voltage distribution in the neural plate [137-139]. Thus, at least some hardware defects (such as a dominant Notch mutation) can be fixed "in software" by a brief induced bioelectric pattern. The induction of this pattern does not require individual micromanagement of voltage state at every point (cell) in the relevant region. Instead, a voltage-sensitive ion channel – HCN2 – can be activated, which causes different changes in depolarized and hyperpolarized cells. In effect, it's a "sharpen filter" for the bioelectric pattern that was blurred by the teratogens, establishing crisp lines between developmental compartments and leading to normal morphogenesis. This context-sensitive property of HCN2 is the first step toward interventions that push complexity off of the scientist and onto the system itself, using a primitive form of decision-making within the tool itself to communicate a complex goal to the target tissues.

The third mode of bioelectric networks' function is to encapsulate complex organ-building cascades and bind them to specific voltage state triggers. One example is the use of a very simple sodium flux to trigger regeneration of a tail or limb in scenarios where they would not normally regenerate [140]. Another is the prepattern that determines the polarity of the planarian head-tail axis [141]. Altering the bioelectric pattern for just a few hours is sufficient to convert planaria into a 2-headed form [142,143] (Figure 8). Remarkably, the bioelectric circuit is a true memory because once flipped into a 2-head state, it is permanent: pieces cut from such 2-headed worms will continue to regenerate with 2 heads in perpetuity (without any further manipulation) [144]. This permanent line of animals with a drastically altered body architecture was not induced by any editing of the genome – the change cannot be seen at the genetic level and is an example of non-genetic inheritance of morphology (which has previously only been shown in the cytoskeletally-mediated transgenerational inheritance of morphology in single-cell organisms [145,146] although mammalian versions of this phenomenon also exist, such as trophic memory of deer antler regeneration [98,147]). This is an example of re-writing the memory information that encodes the target morphology, and of top-down modular control, because bioelectrically-induced heads are correctly proportioned (unlike those induced with Wnt pathway modulation [143]), illustrating how a simple voltage state triggers numerous downstream events needed to build a head, scale it to the rest of the tissue, etc. without the need for the bioengineer to micromanage the myriad of cell and molecular events needed to actually build an entire head.

Having seen how bioelectricity functions as a "cognitive glue" mechanism, binding individual cells toward specific targets in anatomical morphospace [30], we now turn to a failure mode of this system in which cells defect from the organ-level network.

Cancer and the scaling of the Self

Cancer is a highly complex, heterogeneous systemic disorder [148-151]. Current approaches focus on genetic damage – a perspective in which irrevocably broken must be killed by toxic chemotherapies (or immunotherapeutics) [1]. This focus on cell cycle checkpoints and dysregulated molecular pathways predicts that animals with ready access to large numbers of plastic, undifferentiated, proliferative cells should be

especially prone to cancer. In fact, it is often speculated that human bodies' limited regenerative potential are an evolutionary tradeoff to limit the cancer burden in such a relatively long-lived animal. But if so, what to make of the fact that animals such as planaria (which have huge numbers of undifferentiated stem cells throughout their adult lifespan, and enormous genetic heterogeneity among cells) and salamanders, are both highly regenerative and cancer resistant? An important clue is provided by the striking observation that regenerative [152,153], but also embryonic [154,155], environments can reprogram cancer.

Perhaps a better question would be not why cancer occurs, but why is there ever anything other than cancer – why do cells cooperate to build complex structures in the first place? Focusing on the initial state of all cells as highly proliferative unicellular organisms leads to a view of cancer as a breakdown of the mechanisms of multicellularity [156-159]. But it is more than simply growth inhibition by neighbors. A recent theory of cancer [160-162] focuses on the concept of the cognitive light cone: the size of homeodynamic goal states that any active system can pursue (Figure 9). Consider an amoeba: all of its physiological, transcriptional, and metabolic goal states are limited to a very small spatial diameter, with very limited memory and predictive capacity (time horizons). Everything this cell does is in service to tiny goal states, and everything outside of this horizon is considered external environment, at the expense of which the cell may survive. What happens during evolution and developmental morphogenesis is an enormous scaling of this cognitive light cone (Figure 9). The cells belonging to a salamander limb are working on grandiose goals – they are minimizing distance (in anatomical morphospace) to a state comprising complex structure of a certain size and number of fingers. It is a goal in the sense that when deviated from this attractor, the cells will rapidly work hard to get back to it (by rebuilding) and then stop when it is achieved. The cellular collective's goal is a grandiose construction project with a much larger spatiotemporal horizon.

Thus, one way to view cancer (from the perspective of basal cognition) is as a pathological rolling back to the smaller cognitive light cones of the deep past. This has already been conformed for transcriptional profiles, as proposed in the atavistic theory of cancer [163-165], and has been extensively discussed in the literature addressing the inadequacies of the mutation theory of cancer [166-170]. But more specifically, the cognitive light cone model suggests that cancer cells are not more selfish, they just have smaller selves. They begin using action loops with much smaller local goals, in effect shrinking the boundary between self and world, and fragmenting in a kind of dissociative identity disorder where the rest of the body (and their neighboring cells) are treated as external environment and outside the set of variables that must be maintained in desired ranges.

Many things, including but not limited to mutations, can kickstart the transformation process in which cells physiologically disconnect from the tissue-level network that can store and process complex prepattern states used for organ maintenance and repair. For example, a long period of danger signals (stress) can cause cells to close off gap junctions to prevent bystander toxicity effects. Each reduction in physiological connectivity makes it easier for cells to perform computations at the local level – ones that were impossible during the efficient mind-meld of the highly connected tissue, because the shared memories and signals dominate individual cell control loops and deform their action space

toward adaptive outcomes for the collective (e.g., large-scale tissue maintenance). This makes it easier for cells to close off gap junctions even more, and this drives a positive feedback loop – a cycle of dissociation and isolation which makes it ever harder to do the things that a large-scale cell collective knows how to do which its individual parts do not (maintain complex anatomical structure). This picture is consistent with the known early steps of transformation involving gap junction closure [171,172], and the seemingly paradoxical tumors induced by geometric barriers between tissues made of materials that themselves are not carcinogenic [173-175].

This "changing boundary of the Self" model reinforces the theme of divergence between the DNA-specified hardware and the physiological software that drives outcomes, and makes strong predictions for a research agenda. If cancer is a failure of cognitive glue mechanisms that normally bind cells to common paths through morphospace, then targeting these mechanisms should enable: a) detecting incipient cancer by monitoring cell physiological connectivity, b) induction of cancer in genetically-normal cells by physiological stimuli, and c) normalization of cancer despite genetic defects. One crucial component of these mechanisms is bioelectricity [30,119], which functions in the body as the cognitive glue that scales up the cognitive light cone for navigation in anatomical space by cell collectives just as it does for neurons in brains for navigation toward complex goals in 3D space. Ion channel genes are increasingly recognized as oncogenes and ion channel drugs as potential electroceuticals [176-184], with increasing recognition that bioelectrical parameters are important in cancer initiation and metastasis [185,186]. It has now been shown that a) cancer induced by human oncogenes in vivo can be detected early by bioelectrical imaging [187], b) a melanoma-like phenotype can be induced in the absence of carcinogens, oncogenes, or DNA damage – by transient perturbation of bioelectrical and serotonergic signaling among cells [188-190], and c) tumors induced by powerful human oncogenes can be prevented and normalized (not killed) by managing their bioelectric state [187,191-193]. This ability to reinflate the cognitive light cone of cells shows that the physiological information processing, not the genetic hardware, dominates outcomes, and suggests a clinical roadmap quite different from the chemotherapy that dominates the field today [177,180,194].

Applications and a roadmap toward a radical regenerative medicine

It is now clear that living bodies are comprised of many subsystems which have various degrees of competency to achieve and maintain desired states in physiological, anatomical, and transcriptional spaces, despite novel circumstances. The homeodynamic, problem-solving aspects of molecular pathways and cell groups present challenges to traditional bottom-up approaches such as drugs that seek to manage specific symptoms. Fortunately, the concepts and experimental tools of behavioral neuroscience offer a roadmap for exploiting the intelligence of the agential material of life in biomedical and bioengineering contexts (Figure 10). The first step is to take seriously the symmetries between brainy intelligence in 3D space and a much more ancient, diverse intelligence reaching back into our distant evolutionary past, using these symmetries to help design novel approaches to system-level health and disease.

Biomedicine becomes more of a communication and a collaboration with an unconventional agent, and less about rewiring the molecular hardware to force specific phenotypic states. Crucially, this path aims to dissolve the categorical distinction between molecular pathways (as "real" hardware targets) and cognitive content (memories, world models) [16,70]; in this, the ancient questions on the relationship of mind and matter are not philosophical but of immense practical urgency. Below are listed just a few examples of specific research programs that extend and distinguish future medicine from the status quo.

Top-down control exploits agential materials by pushing complexity from the engineer onto the system itself

One feature of integrated large-scale Selves is that control signals are not local; the benefit of information networks, from bacterial biofilms [114,195] to brains [196-199] is that they integrate across space and time and enable collectives to have concerns and competencies in problem spaces inaccessible to their parts. Beyond the brain, the causal structure of multi-scale order in biology often means that diagnostics and interventions can be deployed far from the cells in question. Long-range influences are seen in planarian regeneration [200], the rapid change of state in the voltage profile of a frog leg when the *contralateral* leg is amputated at that location (Figure 6E, [201]), and the ability to control brain patterning [202,203] and tumor incidence [192,193] by modulating the bioelectric pattern of cells on the opposite side of the body.

Importantly, integrated control systems go beyond the typical examples of cells integrated into tissues. For example, the hypothesis of scale-free biology [204] has led to the discovery that individual embryos in large groups form a kind of "hyperembryo" with its own unique transcriptome and an ability to solve teratogenic challenges far better than individual embryos (or small groups) exhibit [205]. Other recent work has identified social metabolic control of immune cells [206]. Short-term opportunities targeting these kinds of phenomena, for example by learning to fake the cross-embryo morphogenetic assistance effect within one organism and deploying it in biomedical settings, are just a part of a much bigger effort of learning to communicate with, and thus control, larger levels of organization that are not apparent from molecular-biology perspectives [19,20].

Another aspect of biological MCAs is their context-sensitivity. For example, tail regeneration (and not generic outgrowth all over the body) is induced in tadpoles by bathing the entire animal in the bioelectric modifying drug, because only the wound cells are paying attention to the signal [140]. Similarly, only ectopic optic nerve (and not the endogenous nerves in the head) respond to drug-based signals present systemically [207]. Even more remarkably, the exact same electroceutical – monensin – triggers tails in tail wounds and legs at leg wounds: the specificity of response in all of these cases is in the cell collective that responds to the stimulus [140,208]. Thus, the intervention does not need to micromanage the spatial properties of the resulting structure, if we understand the circumstances under which the cells know what to do.

This is especially promising because, as seen in the case of eye [135] or tail [140] induction, a very simple (and brief) stimulus can kickstart a complex cascade of gene expression, cell behavior and tissue biomechanics changes. This is an ideal property for biomedical interventions because we can then trigger tissue outcomes that handle size control and all of the molecular details that we cannot (and may never be able to)

micromanage. More broadly, the ability of cell groups to navigate anatomical and transcriptional space toward specific, encoded goals suggests that one powerful way to achieve complex goals is to re-write the setpoints, as can be done in planarian regeneration [104]. One benefit is that this method avoids the intractable problem of computing what genetic changes would have to be made to induce a complex outcome – cells are already very good at harnessing their hardware toward specific goal states. Another is that modifying setpoints as opposed to forcing specific states avoids compensatory regulation (push-back by the cells). This approach gets the system's "buy-in" as to the correct state, and does not trigger resistive responses (which can lead to unexpected side effects elsewhere in the system) because it makes the intervention appear as if it originated *within* the system itself, not as a potential hacking signal from outside, which triggers evolutionarily critical defense behaviors.

Prepatterns of resting membrane potential are very convenient control knobs for complex downstream modules [125], but bioelectricity is not the only modality. Proto-cognitive competencies exist below the cell level, in the learning and optimization capabilities of molecular networks; thus, precisely timed stimuli (a.k.a., dynamiceuticals [209]) offer the possibility of benefitting from, or shutting down, cellular memories of past physiological events [55,56]. Thus, the roadmap of the future includes not merely drug discovery, but *behavioral* discovery – like evolution, we must learn to search the space of behavior-shaping signals that motivate cells to adopt desired phenotypes. Many drugs fail because the system finds a way around the intervention that seemed efficacious in 1st order modeling [210]. Second-order interventions include: patterns of stimuli designed via behavioral control strategies (drug conditioning, training molecular and cellular components for desired outcomes using reward and punishment) [26], drugs that target homeostatic control loops, such as perhaps semaglutide [211-213], and anti-cancer strategies that seek to reinforce cellular connections to the collective (not establish a particular molecular state) [161,214]. Third-order interventions could include psychedelics or plastogens to directly control the self-models (and their plasticity) in tissue contexts [215,216] and nootropics to help cells find better solutions to stressors.

Beyond finding new ways for bioengineers and regenerative medicine clinicians to use drugs to communicate with cells lie more complex agential interventions: reagents that are themselves context-sensitive. One example is the HCN2 channel, whose activator can be deployed systemically because the channel itself distinguishes cells in different physiological states and thus can sharpen voltage prepatterns (leading to a repair of birth defects) by selectively acting on depolarized vs. hyperpolarized cells [138,139]. The next level of agential interventions are cellular constructs such as biobots, which can move autonomously and dynamically interact with their living or abiotic microenvironment, with context-sensitive and tissue-hacking competencies remaining to be discovered. These have been shown to induce repair of neural cells in vitro [217] and bile ducts [218]. The use of bespoke, personalized, patient-derived biobots to exert repair within the body without need for genetic editing or immunosuppression is a major opportunity for biomedicine, as these share many priors with body in terms of inflammation, damage, cancer, microbiome, and health and contain a myriad of sensors and decision-making machinery accumulated during a billion years of evolution and far beyond anything our nanotechnology can produce today.

A better understanding of disease: from molecular markers to physiological patterns

One thing that needs to be expanded is the notion of "disease" beyond specific molecular states to an understanding of undesired systemic states as learned attractors and dynamic patterns within physiological and other spaces [219,220]. For example, the apparent inability of limbs to regenerate without neurons is *learned* – it is not an innate limitation but rather a kind of "nerve addiction" [221-223]. What other disease states and limitations of healthy functioning is a direct result of learned priors by cells and molecular networks, which could be re-trained? Likewise, beyond today's methods to ascertain the current static *state* of a cell or pathway, lie efforts to understand and modify the *algotype* [224] of cells and molecular networks – their behavioral tendencies and the ways they would respond to specific scenarios.

The next stage of advances will go beyond conventional dynamical systems theory approaches to systems medicine, by including not just a view of states as passive features of a complex landscape, but as *patterns within a proto-cognitive system* which might themselves have minimal decision-making and computational competency to facilitate their own persistence (in the same way that depressive and repetitive thoughts enact niche construction on the neural hardware of the brain to make it easier for such thoughts to exist and amplify [225]).

Given the many kinds of persistent, coherent, self-reinforcing patterns of energy and information seen in dynamical systems theory and physics (solitons, autowaves, etc. [226-229]), could some disease states be those kinds of persistent quasi-objects – states in transcriptional, physiological, or anatomical space that exist and exert causal power despite the fact that they are not classical *objects*? These have been found in physiological media for example as domain walls [230] – bioelectrical patterns propagating through homogenous tissue, and the bioelectric prepatterns discussed above are examples of these in vivo, as are "mirror foci" in the brain – epilepsy-triggering physiological states that exist in a brain hemisphere opposite from the one that actually sustained damage [231-237] – a pernicious natural process that is the opposite of bioengineers' attempts to repair bioelectric state from remote regions [192,193,202,203]. Packets of stress, setpoints, self-models, and estimates of safety may be not just memory data for cells, but minimal agents in our body that live in physiological, metabolic, and transcriptional state space, actively impacting health and disease as do their mental counterparts in the area of mental health.

Could some of these patterns within the cellular collective intelligence be addressed in the same way as harmful, persistent thoughts are treated within the neural cognitive system of patients [69,238-240] Some diseases may be due to perceptual illusions, sensory or attention deficits, mistaken beliefs, excessive insecurity, or harmful self-models formed in tissue as a result of prior experiences and could be addressed by the powerful emerging tools of computational psychiatry and cognitive behavioral therapies, but aimed at the non-neural intelligence in tissues and implemented in physiological and transcriptional spaces. As we too are temporary dissipative systems from the perspective of thermodynamics [226-228], it is also possible to consider that some of these dynamical patterns are not in fact at the left-most side of the spectrum of persuadability (Figure 2A), but could have cybernetic, self-reinforcing, and problem-solving features that require behavioral approaches to defeat their ability to resist and

morph in the face of therapeutics that target only the molecular hardware and not the cognitive disorder [70,241].

Conversely, not all disease may be caused by the addition of unwanted information patterns; we have previously proposed that aging is due to the degradation of important endogenous (bioelectric) pattern memories that are required throughout the lifespan to maintain tissue order [158,159]. It is known that removing instructive signals, for example by denervation, can cause disorganization of mature tissues such as tongue papillae and in general render tissues much more susceptible to disorders of morphostasis such as cancer [242-245]. Morphogenesis does not end when the body is complete – the Ship of Theseus is a good analogy for the body, consisting of the replacement policies in the somatic intelligence of the body that needs to make context-sensitive repairs to a tight target specification. It is likely that solutions to the aging problem need to not only include rejuvenating signals at the cell level (e.g., Yamanaka factors) but also target the information scaffold needed to know what the new cells should do and where [246]. Some of that information could be imposed directly (by optogenetic or pharmacological stimuli), but some of it may be best implemented by facilitating the communication between the right kind of modules - letting cells talk to other cells, biobots, or next-generation living "bandages". In the case of cancer, 1st order treatments would be bioelectrical stimuli that force a hyperpolarized state [187,193]; 2nd order treatments would facilitate gap junctional connections among cells or exposure to active morphogenetic cues (including non-bioelectric ones) that are known to induce normalization: [247-249]. Third-order treatments may target the stress perception machinery in cells [250] to counteract the eventual shrinkage of the border between self and world that occurs in agents with continuous exposure to danger signals in their social milieu [162].

Of course, this goes well beyond biomedicine in vivo, and applies likewise to bioengineering efforts to re-create organs and other needed living structures for transplantation or other purposes. Currently, synthetic biology is difficult because we treat cells as a puppet and then have to fight their tendencies; cells often resist synthetic circuits by turning them off or compensating in ways that create undesirable dynamics. We have previously argued [25] that a collaborative mode - top-down reprogramming of agential material – is essential for fulfilling the promise of an arbitrary anatomical compiler. As part of that effort, automated robot scientist platforms will use AI tools to test hypotheses about the best communication methods with cells and tissues.

Eavesdropping on the wisdom of the body

Complementing the efforts to influence higher levels of biology (writing information into the system), the field must develop methods to query the insights that these higher levels have about their own function (reading information, at levels across the neuroscience spectrum ranging from physiological recording, behavioral analysis, and conversation).

Exploiting the problem-solving capacities of cells and tissues is essential to unlock the promise of other, conventional technologies. For example, even when CRISPR becomes 100% reliable and specific, genomic editing will still be facing a ceiling of applications beyond single-gene diseases: which genes to edit, to get the desired complex anatomical change? Planaria rapidly discern which of their tens of thousands of genes hold the answer to a novel stressor (barium) [81]. While it is not yet known how

they do it, it is clear that there exist native mechanisms for identifying the molecular affordances which can be activated to solve even unforeseen stressors [81]. Likewise, salamander cells call upon the right molecular mechanism to make a kidney tubule out of many or just one cell [13,14]. It should be possible to use imaging and computational interpretation filters to get cells (in situ, or in bioengineered avatars) to *tell us* what steps they would take for a given situation and use it to guide gene therapy and pharmacological interventions. The technology that must be developed for this is simply the neural decoding [251-254] system applied to non-neural tissues.

More broadly, tools (such as AI applied to non-invasive, multi-modal physiological profiling) can provide a communications channel to biological sensors. In top-down diagnostics, we might not try to read the status of specific molecules (and try to interpret their meaning) but to ask cells and tissues what their perception is of their neighbors. Not just surrogate site diagnostics at a distance [201], but using living components as the final layer of a classifier neural network to help interpret complex biological states as inputs. We could track stress levels and other aspects of behavior of cells, organoids, and biobots as they are exposed to patient tissues to benefit from their built-in ability to coarse-grain and react to the myriad of physiological and biochemical parameters of their microenvironment. The combination of language models, living information filters, and physiomic profiling raises an intriguing possibility. If molecular states can be controlled through the linguistic interface in psychodermatology [255-257] (and indeed through the more familiar example of voluntary motion), perhaps similar techniques can be used to extract insight into health and disease processes. Spontaneous cases of novel, undiagnosed disease states being brought to clinician's attention via language [258], suggesting that it may be possible to create tools that penetrate the normally tight virtualization (abstraction layers) used in biology and communicate bi-directionally with organs, tissues, and cells.

Conclusion

"Words and drugs have the same mechanism of action." – Fabrizio Benedetti

A fundamental question about information in biology, especially setpoints (target morphology specification), is "where is it encoded?". Physically, bodies consist of a functional heterarchy in which genes and the laws of chemistry determine the properties of molecular interaction, which in turn, with the laws of computation, determine the resulting behavior of cells, tissues, and organs as they self-construct and repair toward complex anatomical outcomes. Philosophically, one can hold that the final result is encoded anywhere along that range of scales – from the basic laws of physics underlying everything that happens in the universe to the pattern memories that serve as navigational goals in morphospace and finally indicate a specific shape for a given organ. Practically, what matters is the *distance* between a given level of organization and the actionable information specifying outcomes one seeks to control. The distance between dynamic anatomy and the genetic sequence of proteins is enormous, due to the many active processes of morphogenesis that lie between them. The distance between the

prepatterns encoded for example in bioelectric states and the anatomy is smaller. Crossing levels via interventions is very difficult, which is why we typically do not program our computers with by tweaking the properties of silicon and copper. It is critical to identify the most proximal layer of description to the phenotypes one wishes to control, and discover a set of tools which optimally manipulates the system at that level.

The major hypothesis discussed herein is a fundamental symmetry between mind and body, in terms of mechanisms and the functional causal architecture they implement. The implication of this perspective is that tools from behavioral neuroscience – ranging from electrophysiology to psychiatry – could be applicable outside the brain and its control of conventional behavior. Some of these tools have already been used to implement novel capabilities in birth defects, regeneration, and cancer. Others remain speculative proposals whose value will be tested by forthcoming experimental approaches.

The key issue in any application in biomedicine, bioengineering, and physiological health/disease is: what is the optimal level of interaction (Figure 2A)? Training animals is more efficient than micromanaging nerve and muscles because it exploits the native top-down control system that the body itself uses to manage low-level molecular events toward whole-body adaptive goals. Learning writes information into the medium much more efficiently than our clumsy interventions, and it behooves us to understand which layers offer what affordances to read and write information toward desired outcomes. In some cases, the most efficient targets will be molecular components. In others, it will be the higher-order memories, goals, and self-models of the cells and tissues. A crucial component of this strategy is an organicist perspective that treats the biology not as a simple machine, and not just as a source of emergent complexity, but as a multi-scale society of agents with agendas. It is known that in psychiatry, the best predictor of success is the belief-congruent approach in which the patient respects and feels aligned with the therapist. The somatic version of this is interventions that are perceived by cells and tissues as something they wanted to do in the first place – not micromanagement of symptom states (which are easily detected by cells as an external hacking attempt) but by targeting deep control structures that represent the system's own goal states and memories, resulting in an effective "therapeutic alliance" [259]. The path to effective regenerative medicine is to take seriously the teleonomy that pervades living systems and harness it.

Albert Mason developed a remarkable practice of hypnodermatology [255,260], using commands filtered through the language interface to modify cellular behavior (now known as mind-body medicine [261]). He eventually changed course and became a psychotherapist because he noted that his patients' skin conditions would clear up, but they would develop problems elsewhere in their life because, albeit at a higher level, he was still treating the manifestation of disease, not the underlying cause. Perhaps a similar path will play out in this field. Re-writing bioelectric patterns [123] and exploiting drug conditioning [70,262-264] are higher-level interventions than direct modulation of transcription factors and signaling proteins, but it may still be just a temporary crutch for an even higher-level semantic interface. Top-level executive mental constructs can cause ion flows in muscle (voluntary motion in the pursuit of career goals for example). If bioelectricity transduces mental content into changes in biochemical events, and bioelectrical signals can induce regeneration [120,265] and cancer normalization [160], is it possible that eventually, we will be able to go directly from mental states to anatomical

outcomes, skipping the intermediate components described above? This of course has been suggested by alternative health practitioners for a very long time, in terms of their emphasis on the power of the mind for healing. But moving beyond theoretical claims and the occasional anomalous remission toward reliable universal regenerative effects requires a lot of rigorous research that fleshes out the connection across therapeutic levels via available technologies. Future medicine may look a lot more like psychiatry than it does like chemistry because in the end, the real mind-body medicine may have to target the many minds operating within the body, not just the mind of the “patient” that normally commandeers our attention via the irresistible linguistic prowess of the left brain hemisphere. At stake are truly transformative applications ranging from the repair of birth defects and injury, to cancer reprogramming, bioengineered organs, and the freedom of embodiment offered by effective rational control over growth and form.

Tables

Table 1: examples of morphogenetic problem-solving competencies

System:	Competency:	Reference:
Frog metamorphosis	Highly abnormal tadpole faces (scrambled craniofacial organs) remodel to normal frog faces as structures move through novel paths and stop when the correct pattern is reached	[266]
Mammalian early embryos	Early embryos can be split, fused, or even injected with carcinoma cells, resulting in normal embryos	[154,267,268]
Frog, zebrafish, newt	Structures such as kidney tubules, nervous system, somites, and overall body reach normal shape and size despite induced changes in ploidy, cell size, and cell number	[13,269-271]
Axolotl	Normal number of dorsal root ganglia form despite induced gains or losses of neural crest cells	[272]
Axolotl	Tails grafted to flank positions remodel into limbs, showing how local shape is governed by large-scale bodyplan information adjusting to unexpected configurations as needed	[273,274]
Cnidarian, simple chordate, and vertebrate embryos	Embryos find alternative developmental trajectories to a gastrulated embryo when the patterning and the topology of the embryo are altered	[275-277]
Mouse embryos	Growth and cell division systemically adjust to ensure catch-up of long bone morphogenesis to compensate for induced cell cycle arrest	[278]
Vertebrate embryo limb development	Muscle bundles, tendons, and some nerves duplicate and adjust as needed to make functional fingers when ectopic bones are induced. Implanting a bead with growth factor that triggers cartilage condensation also results in ectopic joints and flexor and extensor tendons	[279-282]
Mouse embryos	Genetic mutants with misrouted axons from the dorsal lateral geniculate nucleus still find their way to the visual cortex via alternate routes and reestablish a normal pattern of thalamocortical connectivity.	[283]
Goat embryo	Goat born without forelegs established many coordinated changes in pelvic structures needed for bipedal locomotion	[284]
Planarian regeneration	Planaria re-established chemotactic sensing even after irradiation prevented creation of new cells after removal of auricles	[285]

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Box 1: beyond the mechanist/organicist dichotomy

A fundamental argument has raged across the biosciences for centuries. The mechanistic approach sees living beings as a kind of machine, focusing on data about molecular components, and research agendas that emphasize decomposition into parts, and emergence and complexity science as the key tools with which to predict and control systems [286-290]. In contrast, the organicist approach seeks evidence [287,291-297] that autopoietic living things are fundamentally different than machines, emphasizing top-down causation and control, and unique features of life that cannot be captured by algorithmic models. Which framing is more conducive to the next generation of regenerative medicine? I argue that it is neither, as both take on unnecessary baggage that constrains future discovery by limiting the toolbox that workers in the life sciences can use.

The perspective presented herein could be critiqued from both camps. One the one hand, I am arguing to introduce strong forms of teleology (goal-driven behavior) and cognitive capacities into molecular and cell biology as well as developmental and evolutionary biology. The use of tools from behavioral science to understand molecular pathways and morphogenesis is squarely against the mechanist approach, the goal of which is to reduce life phenomena to networks of unthinking components and to put as much distance as possible between modern science and the vitalist theories of the past. On this view, the best stories are told at the level of chemistry and physics. On the other hand, I liberally make use of computational tools (notions of software, reprogrammability, etc.) to understand life and uncover novel bioengineering capabilities, which is anathema to the organicist project that holds that such attempts inevitably miss what is special about life and mind, shoehorning the majesty of life into machine metaphors that are too limited to contain it. In prior work, I have suggested that “machines” and “living beings” are in fact

on the same continuum (a “spectrum of persuadability”, defining the relationship between agents, Figure 2A), but that the cognitive aspects of this continuum reach all the way down, at least to the level of molecular networks. This view does not fit comfortably in either of the major camps.

I emphasize two main concepts that dissolve the dichotomy between these positions and enable them to be compatible in a way that facilitates future research [86]: pragmatism and pluralism. We should lean embrace the idea that everything in science (including such mechanist favorites as “pathways”) is a metaphor, and that all we have is the empirical test of which metaphors enable what research programs. We cannot rely on philosophical commitments, and stale categories that were developed in pre-scientific times and constrain us from supposed “category errors” resulting from trying to import tools across disciplines. The reductionist/organicist debate [293,294,298-307] rages largely because both camps believe they are describing things *as they are*. One especially divisive question is whether living things *are* computers, Turing Machines, etc. and thus demarcated by their known limitations. The knot is untied if we understand that cognitivist, computationalist, and other claims are about our formal models, not about the system itself, and thus many could be simultaneously useful in different contexts. These terms are engineering protocol claims, signaling the intention to use a particular framework to study the system – they refer to a proposed relationship between scientist and system, not an objective unique natural kind. Nothing, especially living things, is objectively one thing – all we have are a multitude of approaches and metaphors, many of which can be appropriate (useful) depending on context. An orthopedic surgeon should see their patient as a mechanical machine. Their psychotherapist should not. Both are correct, in context. Specifically, the notion of an “observer” is central; in biology, observers are scientists but also conspecifics, parasites seeking to hack a system, and the living subsystems of the body seeking to make sense of each other’s signals [92].

It is critical to dissolve binary categories such as “machines”, in favor of a continuum hypothesis with respect to cognition and a commitment to uncover the principles of scaling of minds: not whether something is/is-not cognitive, but how much and what kind of cognitive competencies it has that can offer a useful interface. The mechanists should get over the teleophobia that has held back research, and the organicists should realize that mind is not a zero-sum game – placing constructed and hybrid physical systems on the same spectrum as naturally evolved life does not diminish life’s ineffable qualities. The future lies in telling more generative, productive stories about how cognition scales and about symmetries of deep concepts applied to novel substrates and levels of organization and size. The gate-keeping of tight categories and wrangling over what is or isn’t a goal, a memory, etc. has not served us well – it is a sterile way of dissipating effort on pseudo-problems that offer no empirical reward.

Current computational paradigms do not capture everything that is important about life: self-reference, self-construction, blurring of the data/machine distinction, allegiance to on-the-fly salience not fidelity of information, and much more. This means we must improve those paradigms for use with some kinds of systems. But other aspects – virtualization, abstraction layers, encryption, modularity, software, reprogrammability, etc. are useful and we should draw on them without the fear that using some of those tools commits us to the idea that they provide access to everything. Likewise, the utility of modeling an inner perspective (with memories, goals, preferences, and decision-making

competencies) is a perfectly rigorous approach to physical systems. The acid test of this framework, as with mechanistic and organicist approaches, is empirical testing. Specifically, not whether each viewpoint can be fitted with epicycles to explain, post-hoc, new biology that is discovered, but whether it *generates* new research agendas and leads to the experimental discovery of new capabilities – whether it facilitates questions that could not be asked before, and leads to new vistas.

Box 2: on proto-cognitive terminology applied to unconventional systems

The use of the word Intelligence and other cognitive terms applied outside of its familiar context of brainy animals is highly controversial. Are not morphogenetic systems simply following the rules of chemistry – why anthropomorphize them? The goal is not to anthropomorphize biological subsystems, it is to naturalize cognition and use that knowledge where-ever it proves useful. All cognitive systems – ourselves included – reveal chemistry, not magic, when one drills down to examine the lower levels. There simply is no special human category which one can correctly anthropomorphize as somehow being beyond the laws of physics at its base. 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 [196,308-313], in which it is unavoidable that systems both, be subject to chemistry, and also to possess additional levels of description and control whose recognition affords novel benefits. I take the lessons of evolutionary and developmental change as defining a spectrum of changing capacities (a continuity thesis developed in detail elsewhere [314]).

It should be uncontroversial that claims of intelligence (and other cognitive terms) must be based on rigorous experiment, supported or ruled out by the degree of objective benefit that a given framework provides along the dimensions of prediction and control, and future discovery (and new research programs) it facilitates. The latter is most significant, because almost any paradigm can be maintained on life support by post-hoc epicycles; after one has discovered a new effect or reached a new capability, it is easy to focus on the chemistry and – looking backwards – claim that there is no intelligence there because its mechanisms “simply follow the laws of physics”. Of course, same is true for any act of a complex human brain-body system – if one insists on a view from the level of genes or proteins (but then, why not of quarks?), it will always be there. The right question should be: does that level of perspective provide the most interesting, useful platform from which to make the next discovery or to develop the most effective control technology. The emphasis should be on novel capabilities, and new research programs facilitated (or suppressed) by a given perspective. I suggest that attempts to mine the rich toolbox of behavioral science to understand and exploit capabilities of morphogenetic systems will pay off optimally in many (though likely not all) use cases in biomedicine and bioengineering [70,315].

Crucially, traditional framings of what can and cannot be viewed in cognitive terms must be updated with the science, they cannot be known *a priori.* The less conventional, and often uncomfortable, consequence of this position is that the empirical utility of such framings needs to be applied fearlessly and followed wherever it leads: its empirical consequences must be taken seriously even when they contradict long-cherished commitments to how non-intelligent a given system must be. If a specific framework,

which uses tools normally reserved for brains, results in fruitful new research programs on bacterial biofilms [110,113,114], plant roots [316-322], the training of gene-regulatory networks [54,56,323,324], or developmental/regenerative biology [325], then the scientific approach requires that we consider those systems to be bona fide subjects of the behavioral science of a spectrum of minds.

Figure Legends

Figure 1: beyond the genetic hardware

(A) This image shows what computer programming looked like at the dawn of the information technology are: in order to change the behavior of the system, the user had to physically re-wire it. This is analogous to the state of biomedicine today, where the focus is largely on tools to address molecular states: genomic editing, protein engineering, pathway rewiring, etc.

(B) An illustration of why hardware information is just the beginning. Axolotl larvae have forelegs; frog larvae do not. Despite having sequenced the genomes of both species, and thus full information about the cellular hardware, the field currently has no models that will make predictions about whether a "frogolotl" embryo (a chimera of both kinds of cells) would have legs or not (and if so, whether those legs would be made entirely of axolotl cells or include frog cells). This is not only true for development, but also for regeneration:

(C) In planaria of different species, head shapes differ. What kind of head shape would be regenerated if a planarian was irradiated to remove half of its neoblast stem cells, and receive an injection of neoblasts from another species with a different head shape? Despite decades of study of the molecular biology of planarian stem cells, the field has no models that would reveal whether one shape would be dominant, or a combination shape would result, or the head would not stop regenerating because neither set of cells would ever reach the specific target morphology that normally triggers an end to remodeling and growth. These examples illustrate the knowledge gaps in our ability to predict the behavior of cell collectives in anatomical space, despite increasing understanding of the molecular hardware specified by the genomic information. Image courtesy of Daniel Lobo [326].

(D) An operational definition of success in the control of growth and form can be described as an "anatomical compiler", which allows the user to specify the desired 3D anatomical structure, and compiles that description into a set of stimuli that will coax the cells to build exactly that structure. It is not intended to micromanage (e.g., 3D print) the final outcome but to serve as a communication device, converting the goals of the bioengineer into the setpoints of the homeostatic circuits guiding cells' navigation of anatomical space. Left panel courtesy of Daniel Lobo [327]; right panel courtesy of Junji Morokuma.

Figure 2: living substrate on the spectrum of persuadability

(A) Systems fall on a "spectrum of persuadability", which defines the kind of tools to which their prediction and control are amenable. Here are shown just four representative regions on that spectrum. Simple systems are only tractable to physical rewiring: changes of the hardware, which means that the engineer must understand every element and all of their emergent system-level interactions. Homeostatic circuits enable simple goal states, and can be manipulated via the tools of cybernetics and control theory: re-writing their setpoints and letting the system achieve them. What is needed for these kinds of systems is knowledge of where and how the setpoints are stored and interpreted. More complex systems can learn, enabling the tools of behavioral science (e.g., behavior-shaping) to achieve outcomes that are too

complicated to be implemented directly. In these systems, the learning interface provides an abstraction layer that hides the underlying detail (which is managed by the learning algorithm), enabling the effective training of such systems without knowledge of the mechanisms under the hood. The far right end of the spectrum belongs to advanced symbol manipulating systems with complex meta-cognitive circuits that can change their own goals, choose novel problems to solve, and otherwise exert their own self-modifying agency to various degrees. Overall, moving rightward across the spectrum, the amount of micromanagement needed (or even possible) falls, moving from bottom-up to top-down control strategies, and the ability to depend on the system for autonomous problem-solving rises. Crucially, what also rises is the importance of taking the perspective of the system itself (what does it know, what are its memories, and how does it make decisions) in order to have good predictive and control capabilities, while the need to understand every molecular component falls. Image courtesy of Jeremy Guay of Peregrine Creative.

(B) Crucially, the position of any given system (e.g., single cells) on this spectrum is not a philosophical question but an empirical one, settled only by making hypotheses and determining what level of control they afford. Here is shown an example [55,56] in which the standard approaches of behavioral science (in this case, associative learning) are applied to what seem initially to surely be low-agency, mechanical systems: gene-regulatory networks (B'). They are deterministic, small networks of molecules that up- and down-regulate each other's activity, and are currently addressed in biomedicine and synbio research exclusively via hardware rewiring e.g., gene therapy and promoter editing. But taking seriously the idea that unexpected proto-cognitive capacities (not merely complexity) can be emergent in simple systems enables an empirical test in which such networks are exposed to patterns of stimuli one would use to train an animal, revealing several kinds of learning (which does not require changes to the hardware) including Pavlovian conditioning. Image courtesy of Jeremy Guay of Peregrine Creative.

Figure 3: unconventional intelligence

(A) Cognitive capacity lies on a spectrum [82] which spans from passive matter through diverse forms of active behavior with different degrees of causal linkage to past and future events. As one moves up the ladder, systems acquire more autonomy and require more consideration of their past and their internal model of the world (i.e., seeing the world from the system's perspective) in order to effectively control them.

(B) Anatomical outcomes are a combination of two fundamental processes. The more conventional and most often emphasized is feed-forward (open-loop) emergence of complexity: gene-regulatory networks (GRNs) produce proteins which interact according to the laws of physics and eventually result in complex outcomes. However, a critically important and less often emphasized component is the ability of the system to activate effectors at the level of transcription and physiology to continuously reduce the error relative to the creature's target morphology.

(C) An example of this anatomical homeostasis is seen in salamander limb regeneration, where an amputation anywhere along the axis causes cells to rapidly proliferate and undergo morphogenesis, stopping when (and only when) a "correct salamander limb" is complete. This closed-loop process, which is context-sensitive and most effectively

described as a homeostatic loop with a specific setpoint, is fundamentally different than just emergence because it aims at a well-defined, yet complex, goal state and specifically implies questions such as the mechanism of storage of the target morphology information and the degree of competency the system would have to reach its goal in the face of various different kinds of perturbations away from that setpoint. Image courtesy of Jeremy Guay of Peregrine Creative.

(D) One powerful formalism for modeling the ability of systems to return to their setpoints, especially at higher levels along the hierarchy in (A), is through the concept of navigation of problem spaces. In this case, the anatomical morphospace is the latent space of possible shapes that can be built [9,328]. Each specific head shape of a planarian for example represents an attractor in that space, and cell collectives navigate the space to get to their correct species-specific region if deviated by damage or undergoing embryogenesis. However, as with many kinds of autonomous navigational systems, the same hardware can occupy different attractors, and a genetically wild-type planarian fragment can grow heads appropriate to different species of planaria [329,330]. Image courtesy of Alexis Pietak.

Figure 4: biological plasticity: coherent outcomes that differ from the genomic default

(A) Frog embryos in which the primary eyes were prevented from forming, but an ectopic eye was placed on their tails (red arrowhead) can see [105]. The nascent eye cells transplanted onto the tail complete normal eye development, and put out an optic nerve (A', visualized by the red fluorescent protein labeling), which can connect to their spinal cord (A") but does not reach to the brain. The animals can perform well in visual training assays without need for generations of adaptation to the radically altered sensory-motor architecture.

(B) Tadpoles remodel their face to become frogs; experimental scrambling of the craniofacial organs, which still results in fairly normal frog faces after novel movements of the components, reveals that this is not a hardwired process of rote movements but rather an error minimization process that keeps remodeling until a specific end-state is achieved regardless of starting positions [266].

(C) A schematic of the data in [13,14], showing cross-section of the kidney tubules in newts of different ploidy. By forcing the cells to be larger than normal, it was observed that this process not only adjusts the number of cells to their size, but also can trigger different molecular mechanisms (cell-cell communication in tubulogenesis vs. cytoskeletal bending of a single cell around itself). This is a remarkable example of cellular problem-solving in anatomical space: cells adjusting as needed, to an evolutionarily-novel perturbation, to attain a large-scale morphogenetic goal.

(D) Evolution, not only bioengineers, has learned to hack such goal-seeking systems to exploit their competencies and drive them into novel regions of morphospace. While acorns (and the oak genome) produce a specific flat, green leaf pattern very reliably, signals from a wasp parasite push the cells to build a completely different structure (a spiky red and yellow Hedgehog Gall form). This demonstrates that the option space available to cell collectives is not apparent from their default morphogenetic paths; such possibilities (and developmental constraints) can only be mapped out by perturbational analyses. Image courtesy of Andrew Deans.

(E) Anthrobots are motile, self-assembling constructs created from human tracheal epithelial cells [217]. Not only do the cells from adult patients form a totally new, functional shape but they also reveal interesting and unpredictable capabilities (E'), such as gathering into a super-bot cluster (green) and healing injuries in cultured human iPSC-derived neurons (red). White arrow points to the healed portion under the bots.

Figure 5: developmental bioelectricity: fundamental mechanisms

(A) Neurons form networks that can perform computations and guide behavior in 3D space because context-sensitive ion channels enable each cell to set and modify a resting potential (voltage gradient across the membrane) which it may communicate to neighbors if the (also context-sensitive) electric synapses – gap junctions – are sufficiently open. This enables the project of "neural decoding" (A') in which the physiological states are read out and decoded to read out the memories, preferences, and other aspects of the internal cognitive states of the being implemented by the neural network.

(B) This machinery is evolutionarily ancient, with all body cells having ion channels and most having gap junction connections to a tissue network. Thus, the parallel task is cracking the bioelectric code to decode the proto-cognitive content of the cellular collective intelligence, which uses precisely the same bioelectric and neurotransmitter mechanisms to navigate through anatomical space and solve problems (deal with injury and other perturbations).

(C) Tools have now been developed to read and write the bioelectric state of non-neural tissues, using molecular-genetics, pharmacology, and light (optogenetics) to open and close ion channels and gap junctions, thus regulating the topology of connections in the network and the specific bioelectrical patterns encoded in it at any specific time.

All images in A-C courtesy of Jeremy Guay of Peregrine Creative.

Figure 6: anatomical outcomes enabled by reading and writing bioelectric prepatterns

Voltage-sensitive fluorescent dye can be used to non-invasively reveal the bioelectric patterns during morphogenesis.

(A) Frog embryo cells during early development (image courtesy of Dany S. Adams).

(B) The "electric face" prepattern which reveals the location of the eyes, mouth, and other structures that determine the locations of the gene expression domains that regionalize the craniofacial ectoderm and ultimately determine the position and size of the organs [126].

(C) These patterns are functionally instructive, which is revealed by experiments such as injecting mRNA encoding potassium channels to induce a voltage spot resembling the eye field (B) in ectopic locations. This induces eyes to be formed (red arrow, C') in ectopic locations such as in the gut. These eyes have the normal structure of internal components as seen in histological section and immunostaining (C").

(D) Remarkably, when only a small number of cells are injected (blue beta-galactosidase stain reveals the cells misexpressing the K^+ channel protein), the task of making a lens in an ectopic location is still completed because these cells autonomously recruit

neighbors (brown tissue) to complete the task for which the original cells' numbers are insufficient.

(E) A froglet soaked in voltage-sensitive fluorescent dye reveals a depolarization signal (green stain above the dashed white line) in the un-touched, contralateral leg (right arrow) which indicates whether, and where, the left leg was amputated (blue arrow). Yellow arrow indicates the spinal cord. Image from [201].

Figure 7: a context-sensitive bioelectric intervention for birth defects

(A) The neurectoderm in early frog embryos bears a specific bioelectric pattern (quantified in A') prior to forming the brain [137].

(B) That pattern is required for normal brain development, because equalizing the resting potential across the midline, by bring all the cells to the same high value (red) or the same low value (green), using chloride (GlyR) or potassium (Kv1.5) channel misexpression, results in severe brain defects: it is the *difference* between the cells at the left and right edge of the nascent brain field that is crucial – not a specific voltage number but a pattern. This pattern is disrupted by numerous teratogenic influences [138,139,202], including nicotine, alcohol, and mutation of the Notch gene.

(C) The normal bilateral pattern of forebrain, midbrain, and hindbrain is severely disrupted after Notch mutation (C'): the forebrain is gone, and the midbrain and hindbrain are reduced to fluid-filled bubbles. These complex anatomical structures can be restored by reinforcing the bioelectric prepattern; this can be done for example by homogenously up-regulating HCN2 channel activity, because this channel will sharpen the "bell curve" pattern by only hyperpolarizing the cells in the correct middle region, which are somewhat but not entirely depolarized as a result of the Notch mutation (C").

Figure 8: rewriting the pattern memory in planarian regeneration

(A) Planaria in which their head and tail are amputate regenerate perfectly from the middle fragment (between the red dashed lines). While the molecular markers of anterior tissue identity (purple, indicating expression of the *Fringe* gene) are present in the correct location (anterior, green arrow, and not posterior, red arrow), the fate of the fragments (A''') can be normal (1-headed) or two-headed, depending on the bioelectric pattern state. The normal bioelectric circuit has one depolarized region indicating one head is to be created, while it can be modified by exposure to specific ionophores [142] to indicate 2 such regions (A'', orange arrow points to depolarized region). The bioelectric pattern is thus dissociable from, precedes, and controls the number of heads that will be formed if an animal is injured.

(B) Remarkably, the bioelectric circuit that holds this information has stable memory: once modified, the two-headed pattern persists in perpetuity, continuously generating 2-headed animals with no more perturbation needed [144]. As in the brain repair example (Figure 8C), it shows that at least some phenotypes can be overridden from their genomic defaults with temporary signals that target the setpoint information guiding cells' path through morphospace.

Figure 9: cancer as a dissociative identity disorder of the morphogenetic intelligence

(A) Simple homeostatic loops are ubiquitous in biology and medicine but most often studied in the context of simple scalar setpoints like pH, temperature, or hunger level.
(B) Regenerative biomedicine requires us to understand complex homeostatic processes that pursue a complex anatomical state, such as proper planarian morphology which not only repairs all organs after amputation but scales and remodels tissue to be of the correct overall size and shape. This is not just about regulating the fate of stem cells but of coordinating a path through a complex morphospace to reduce the distance between current shape and target shape.
(C) A key aspect of multicellularity, lost in cancer, is the ability of cells to join into networks which have larger computational capacities and thus can pursue much more complex setpoints. A cell collective has a larger ability to coordinate information across time and space and thus can pursue goals in anatomical space, which is critical for maintaining functional multicellular bodies, vs. the simple single-cell states that serve as goals for unicellular organisms (C'). These physiological networks, connected by gap junctions (GJ), in effect enlarge the "cognitive light cone" – the spatiotemporal size of the goals that the system can work towards, or the size of the boundary which the system measures and actively manages (the boundary between self and external world, C"). It is this boundary that shrinks during the failure of normal cognitive scaling mechanisms known as cancer. Images courtesy of Jeremy Guay of Peregrine Creative.
(D) When a human oncogene such as a dominant p53 or KRAS mutation is injected into tadpoles, a tumor will eventually appear (red arrow), and then metastasize (D', red arrow).
(E) This condition can be seen using voltage-sensitive fluorescent dyes, because cells undergoing transformation shut off their gap junctions and become electrically isolated from the network, in effect becoming independent unicellular organisms that treat the rest of the body as external environment. The bioelectric dye can be used as a detection modality to predict where cancer is going to develop before the tumors become morphologically apparent.
(F) The model of cancer as a shrinkage of goal capacity predicts that oncogene-bearing cells, forced into the appropriate bioelectrical states, can be normalized. When hyperpolarizing ion channels such as the GlyR chloride channel are injected into embryos along with the oncogene, the tumor is suppressed (i) while the oncoprotein is still very strongly expressed and the cells are normalized, not killed (ii).

Figure 10: the future of biomedicine

(A) Biomedical interventions can be grouped into two major categories. The bottom-up ones seek to directly manage hardware states though surgery, transplantation, modification/creation of transcriptional circuits, and drugs that force specific pathway states. The top-down approach, which is only now emerging in allopathic medicine, consists of attempts to signal to, communicate with, and change the internal memory states of the living material. Ways to control the agential material of the body include: shaping the behavior of pathways, cells, and tissues through training signals (rewards and punishments, deployment of interventions which are themselves not low-agency drugs or materials but biobots or smart implants with goal-directed loops and capacity to control cellular decision-making, and modalities (drugs, light, etc.) which modify the

course of complex morphogenesis by serving as triggers (for example for organ-building cascades) or other ways to impact their navigation in morphospace. A subset of these morphoceuticals are electroceuticals, which use the bioelectric interface to communicate goal state information to tissues via ion channel and gap junctional modulation.

(B) Future progress can be envisaged where AI-augmented algorithms can intervene anywhere on the continuum of the body, from high-level mental constructs in the brain to control structures within the collective intelligence of body cells. Such an AI can act as a translator of bioelectric and other information, mimicking the effects seen in “mind-body medicine” where information crosses levels from the human personality’s cognitive intent to the downstream changes of biochemical states.

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Footnotes:

[1] Viewing biomedical interventions as acts of communication enables a crucial advantage. When we produce stimuli to evince specific complex behaviors, such as training an animal, we do not have to embark on the infeasible task of micromanaging the neural states in their brain directly. We use the learning interface and allow the system itself to do the hard work of adjusting its inner components as needed. The same benefits can be reaped in biomedicine and bioengineering, by identifying and exploiting the proto-cognitive features in all cells and tissues which shape their behavior via salient triggers that induce complex desirable responses.

[2] In fact, one can define a spectrum with respect to the degree of strict interpretation vs. creative plasticity. Mosaic organisms like C. elegans are at the left end of the spectrum – lineage determination and a precise number of each kind of cell (very hardwired). Mammalian embryos have more plasticity, and amphibian embryos and adults have even more ability to adapt to radical changes of configuration [13,14]. On the far right of the spectrum are the remarkable planaria. This is discussed further in [15,16].

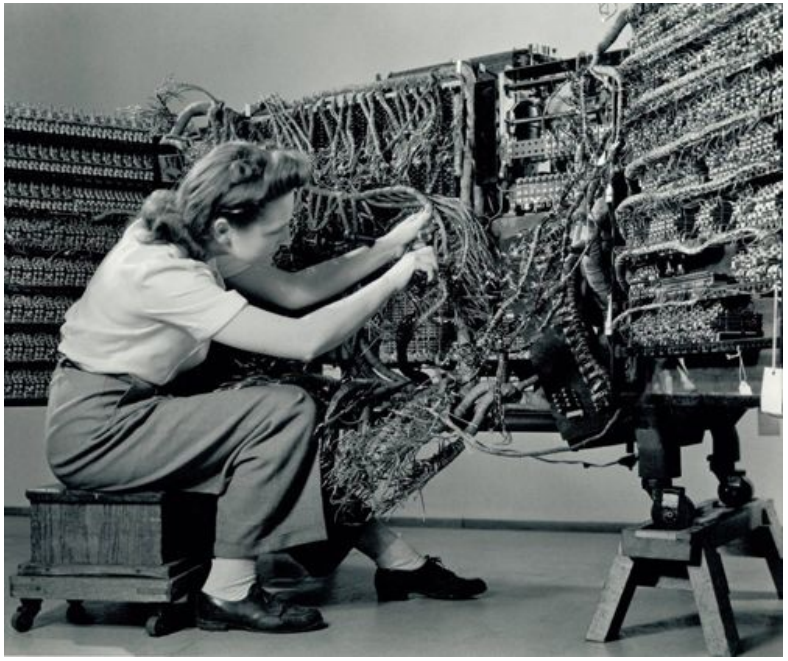
[3] A number of workers over the last few decades have pointed out the applicability of modern connectionist machine learning frameworks to an understanding of morphogenesis, and in particular, the parallels between the self-assembly of bodies and minds [20-24].

[4] However, I part ways with many organicists who believe in firm distinctions between “machines” and “living beings”. I think that by understanding how cognition (not just complexity) emerges from the dynamics of matter, we discover the true majesty of embodied intelligence which is unlikely to be constrained to those systems where we can easily imagine it. By finding and exploiting basal components of cognition in chemico-physical systems (such as cells and even subcellular networks, as well as potential synthetic or chimeric constructs), we do not cheapen or deflate the majesty of life – we extend it and demonstrate its central importance to the evolutionary and health sciences.

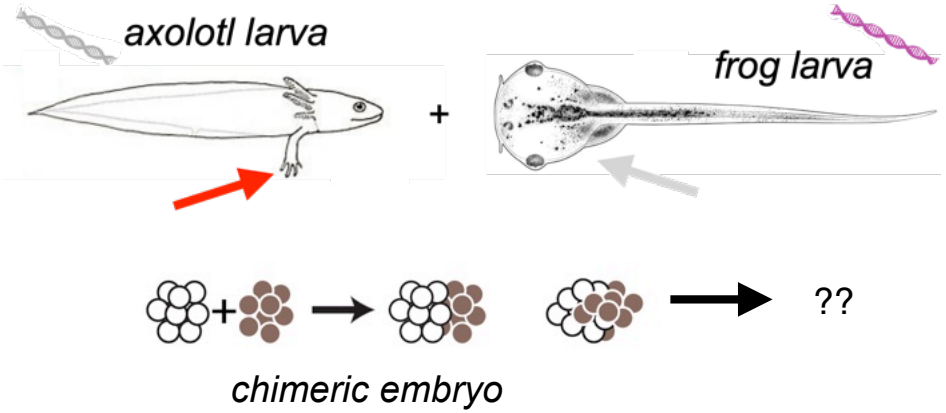
[5] Though they probably do have a response to epileptic seizures, which is similar in some way (with respect to excessive depolarization for example), suggesting that this kind of problem-solving may involve the ability to generalize – grouping specific new scenarios into a class, for which responses may be available.

[6] Because at any given time, their ability to pass ions is a function of previous events which impacted the membrane potential. This provides a kind of context-sensitive decision-making and a sense of temporality in the physiological circuit that operates post-translationally.

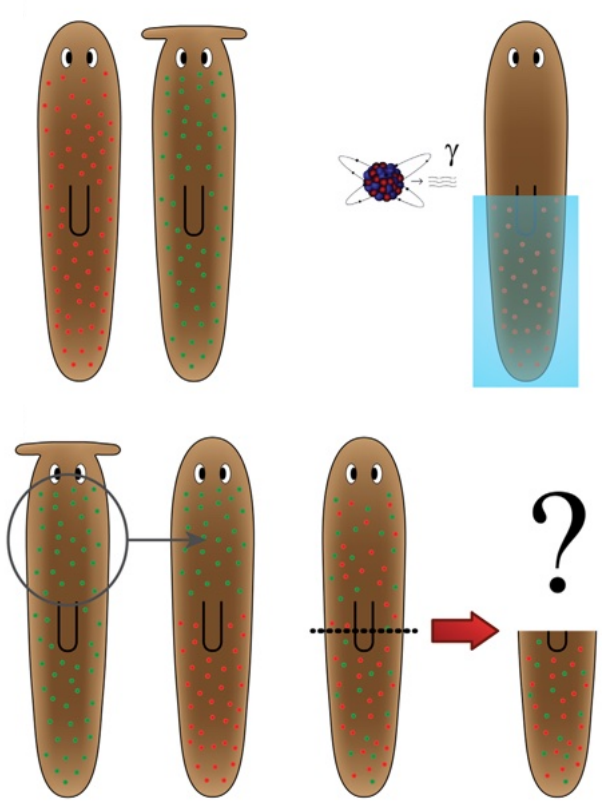
(A)



(B)



(C)



(D)

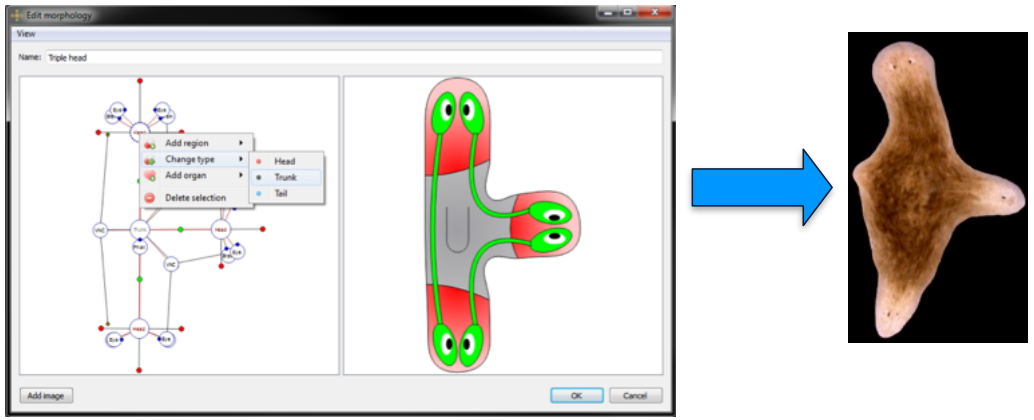


Figure 1

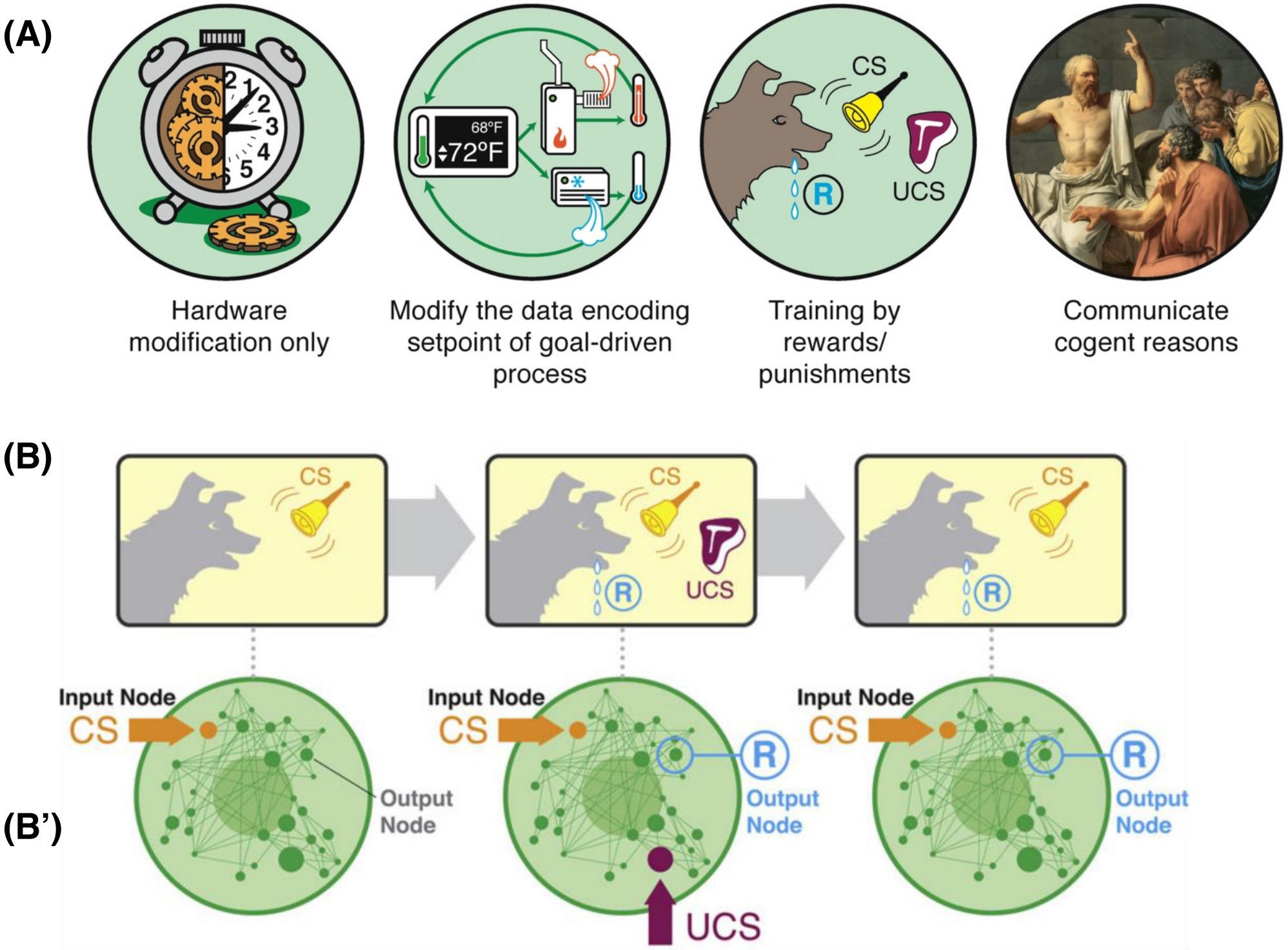
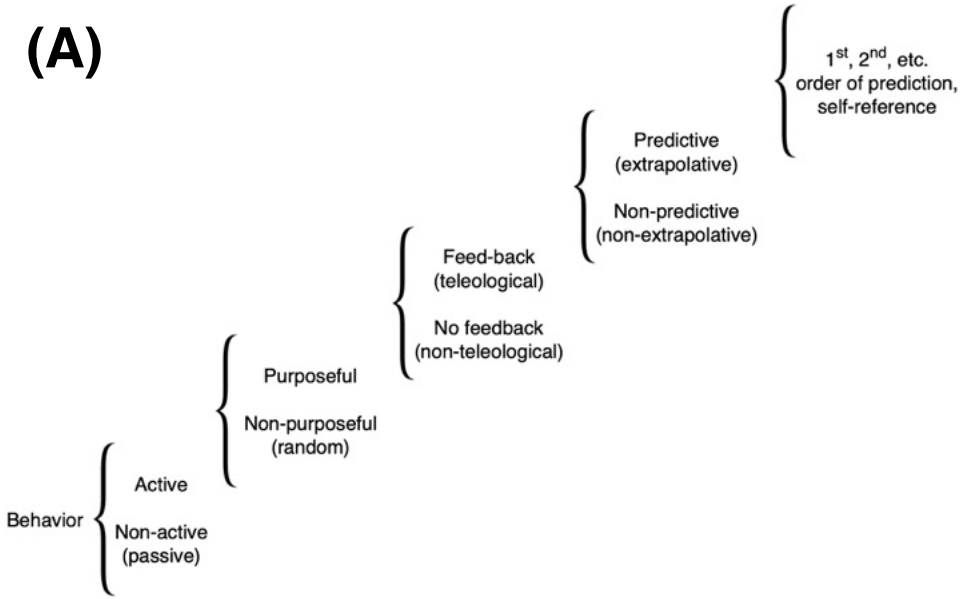
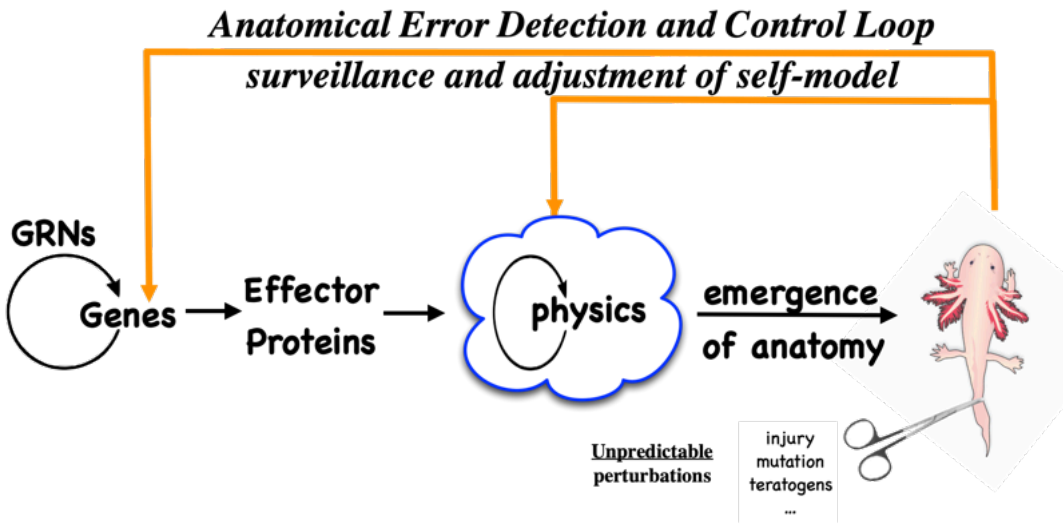
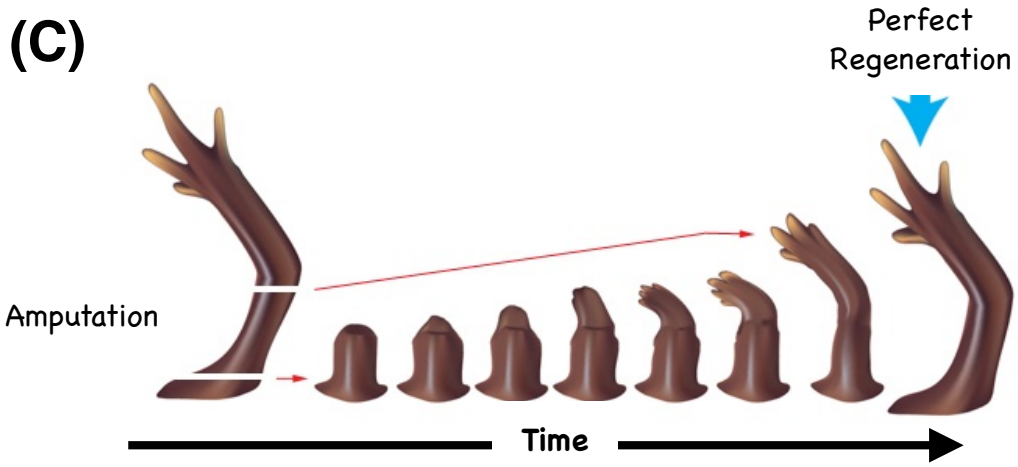

(A)
Hardware modification only
68°F
72°F
Modify the data encoding setpoint of goal-driven process
CS
UCS
R
Training by rewards/ punishments
Communicate cogent reasons
(B)
CS
R
UCS
Input Node
Output Node
(B')
UCS

Figure 2


(A)
Behavior
Active
Non-active (passive)
Purposeful
Non-purposeful (random)
Feed-back (teleological)
No feedback (non-teleological)
Predictive (extrapolative)
Non-predictive (non-extrapolative)
1st, 2nd, etc. order of prediction, self-reference


(B)
Anatomical Error Detection and Control Loop
surveillance and adjustment of self-model
GRNs
Genes
Effector Proteins
physics
emergence of anatomy
Unpredictable perturbations
injury
mutation
teratogens
...


(C)
Perfect Regeneration
Amputation
Time

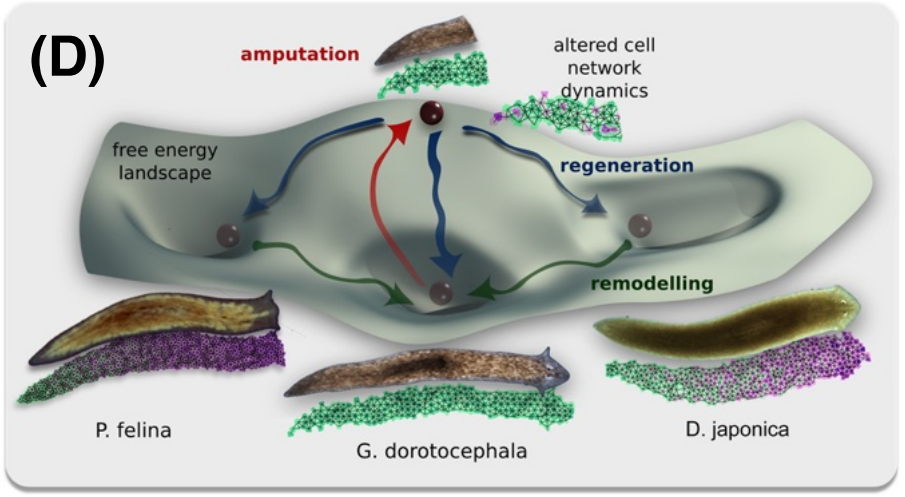

(D)
amputation
altered cell network dynamics
free energy landscape
regeneration
remodelling
P. felina
G. dorotocephala
D. japonica

Figure 3

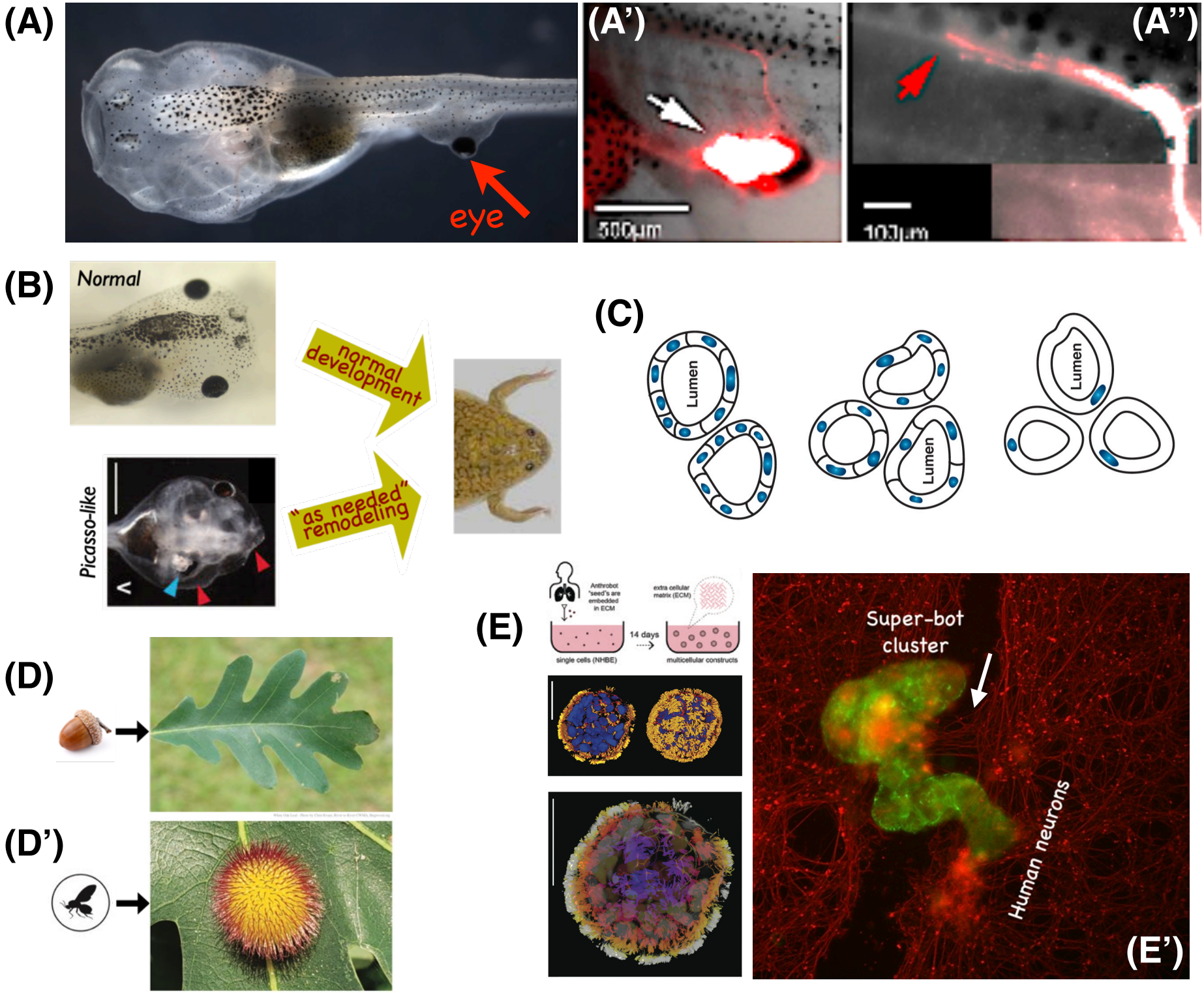
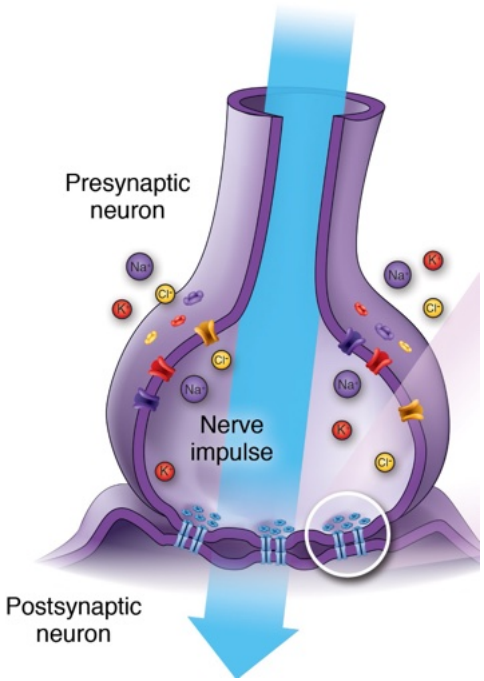

(A)
eye
(A')
500μm
(A'')
100μm
(B)
Normal
normal development
"as needed" remodeling
Picasso-like
(C)
Lumen
Lumen
Lumen
(D)
(D')
(E)
Anthrobot "seed's are embedded in ECM
extra cellular matrix (ECM)
14 days
single cells (NHBE)
multicellular constructs
Super-bot cluster
Human neurons
(E')

Figure 4

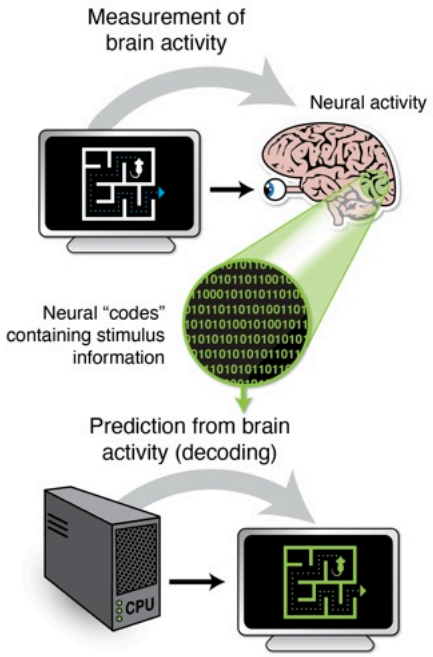
(A) **Hardware** **Software**

gene products -> electric circuits electrical dynamics -> goal-directed behavior

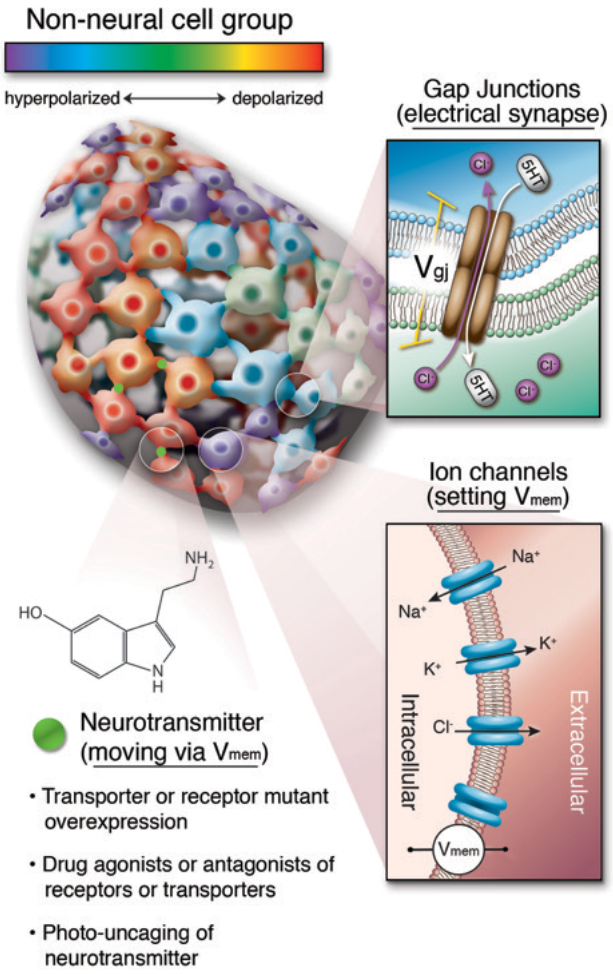


neural (3D space)

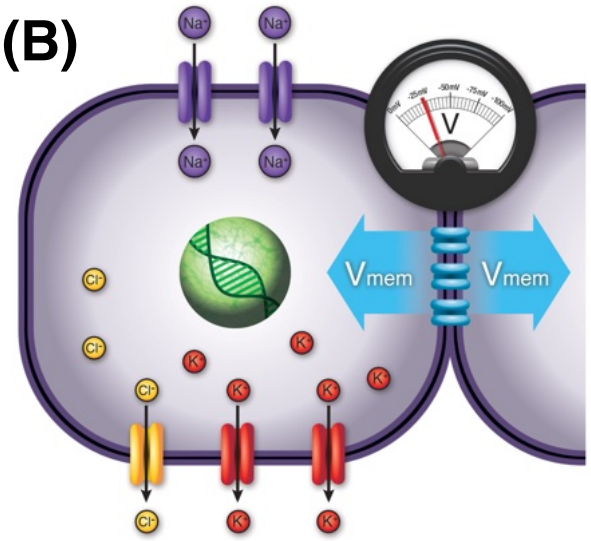
(A')



(C)



(B)



developmental (Morphospace)

(B')

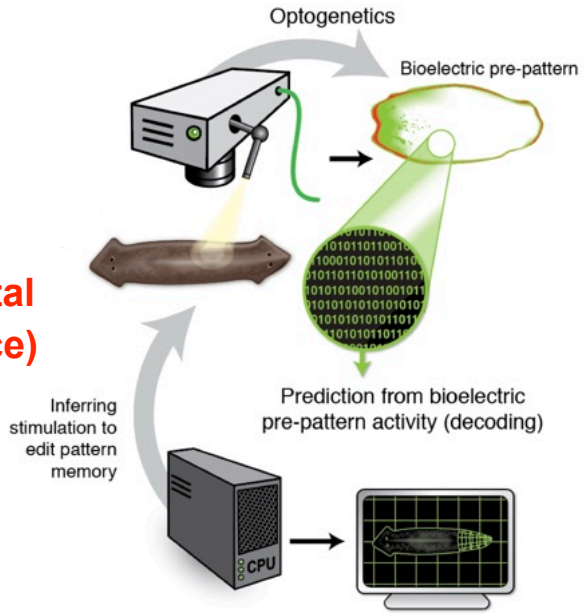
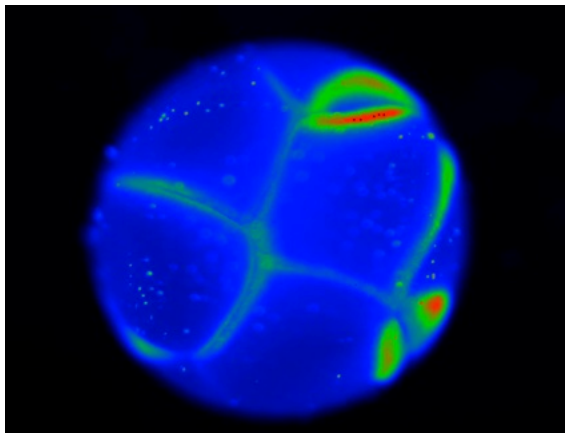


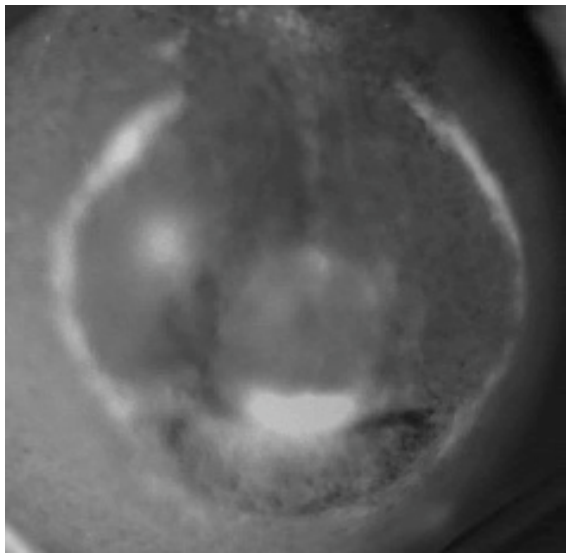
Figure 5

(A)



hyperpolarized depolarized

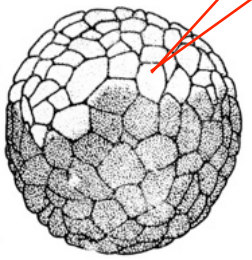
(B)



hyperpolarized depolarized

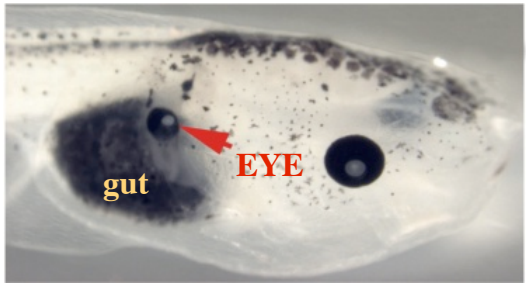
(C)

ion channel mRNA targeted to ventral or posterior regions

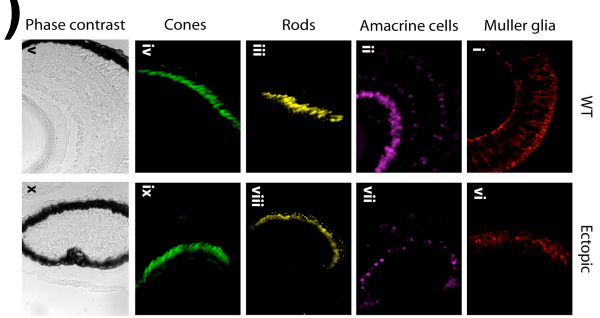


can reprogram many regions, even outside "competency zone", into complete ectopic eye!

(C')

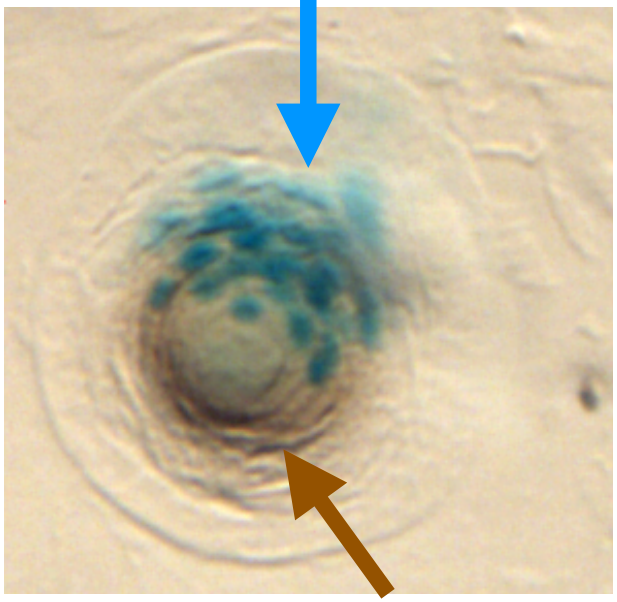


(C")



(D)

voltage-modified cells



wild-type cells hacked secondarily by injected cells

(E)

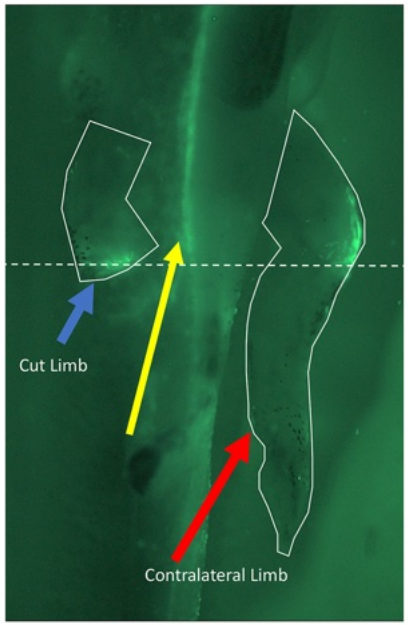


Figure 6

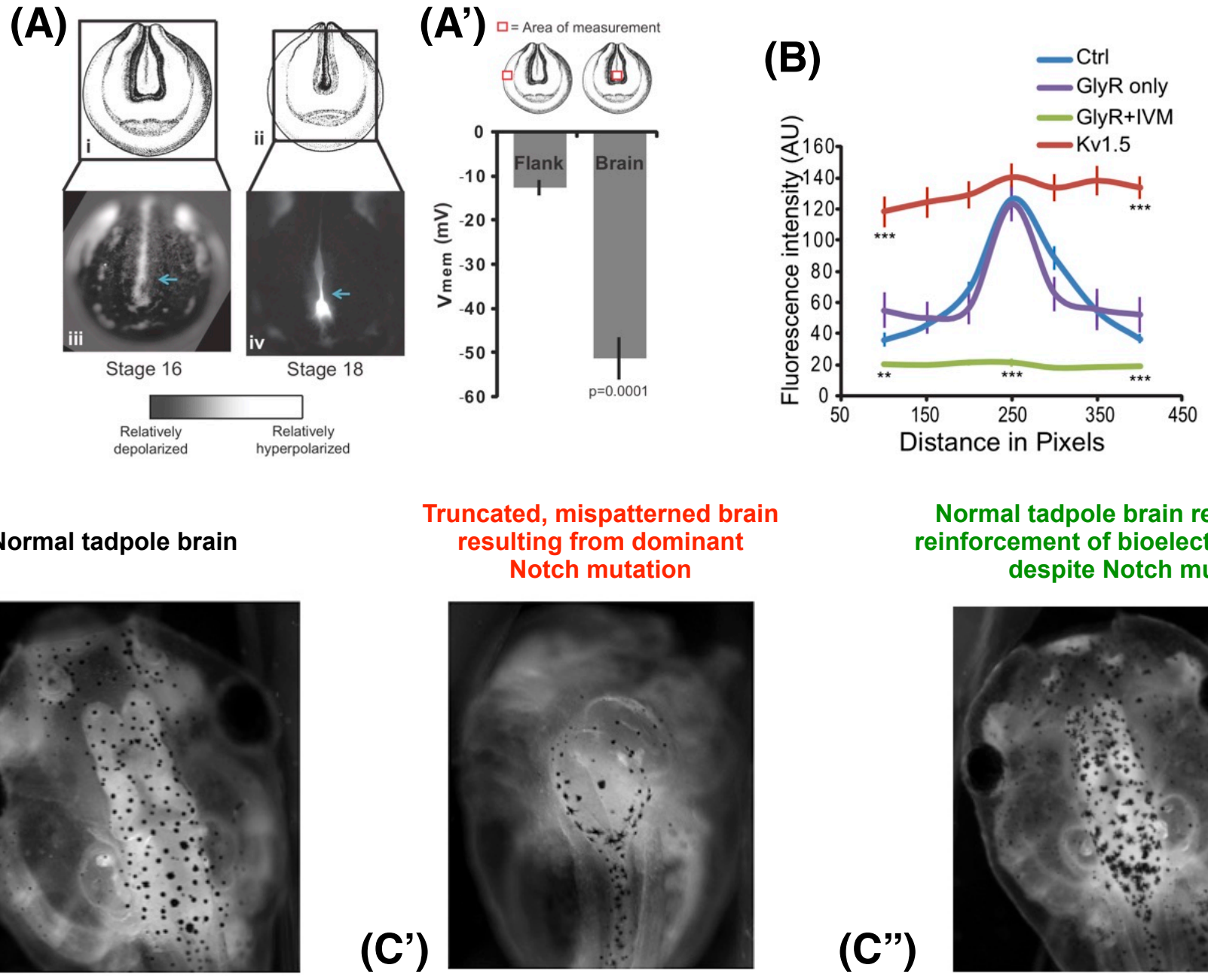

(A)
i
ii
iii
iv
Stage 16
Stage 18
Relatively depolarized
Relatively hyperpolarized
(A')
= Area of measurement
Flank
Brain
p=0.0001
Vmem (mV)
0
-10
-20
-30
-40
-50
-60
(B)
Ctrl
GlyR only
GlyR+IVM
Kv1.5
Fluorescence intensity (AU)
Distance in Pixels
Normal tadpole brain
Truncated, mispatterned brain resulting from dominant Notch mutation
Normal tadpole brain resulting from reinforcement of bioelectric prepattern, despite Notch mutation
(C)
(C')
(C'')

Figure 7

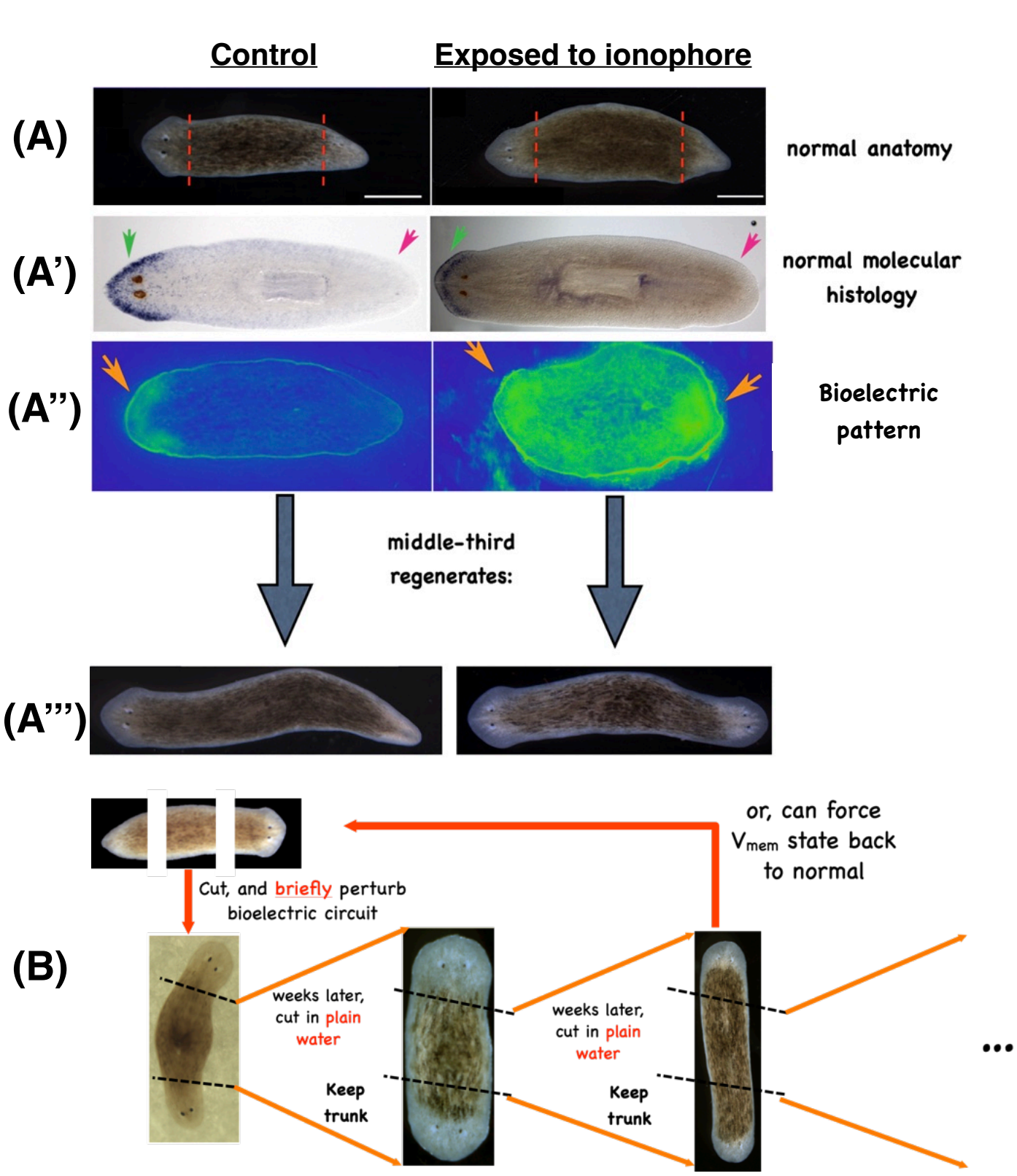

Control
Exposed to ionophore
(A)
normal anatomy
(A')
normal molecular histology
(A'')
Bioelectric pattern
middle-third regenerates:
(A''')
(B)
Cut, and briefly perturb bioelectric circuit
or, can force V_{mem} state back to normal
weeks later, cut in plain water
Keep trunk
weeks later, cut in plain water
Keep trunk
...

Figure 8

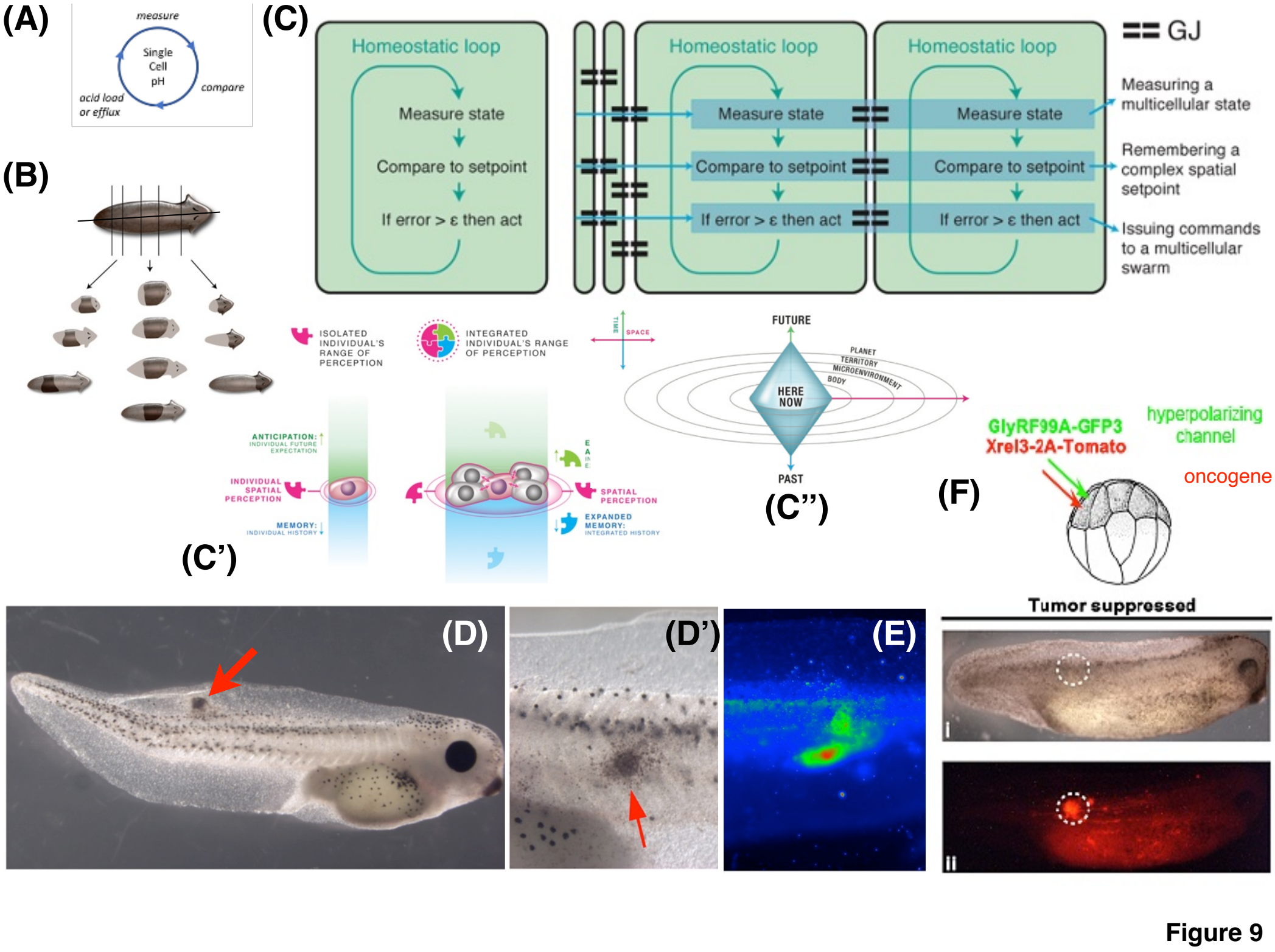
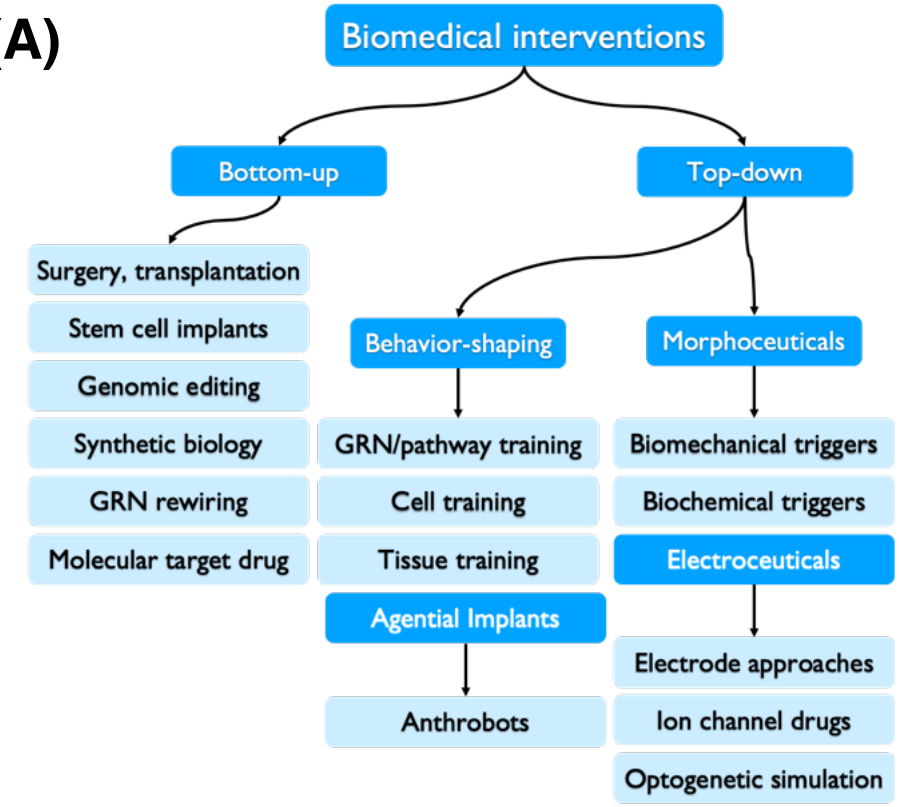

(A)
measure
Single Cell pH
compare
acid load or efflux
(B)
(C)
Homeostatic loop
Measure state
Compare to setpoint
If error > ε then act
GJ
Measuring a multicellular state
Remembering a complex spatial setpoint
Issuing commands to a multicellular swarm
(C')
ISOLATED INDIVIDUAL'S RANGE OF PERCEPTION
INTEGRATED INDIVIDUAL'S RANGE OF PERCEPTION
ANTICIPATION:
INDIVIDUAL SPATIAL PERCEPTION
MEMORY:
INDIVIDUAL HISTORY
SPATIAL PERCEPTION
EXPANDED MEMORY:
INTEGRATED HISTORY
(C'')
FUTURE
PAST
HERE NOW
PLANET
TERRITORY
MICROENVIRONMENT
BODY
(F)
GlyRF99A-GFP3
Xrel3-2A-Tomato
hyperpolarizing channel
oncogene
(D)
(D')
(E)
Tumor suppressed
i
ii

Figure 9

(A)


Biomedical interventions
Bottom-up
Top-down
Surgery, transplantation
Stem cell implants
Genomic editing
Synthetic biology
GRN rewiring
Molecular target drug
Behavior-shaping
GRN/pathway training
Cell training
Tissue training
Agential Implants
Anthrobots
Morphoceuticals
Biomechanical triggers
Biochemical triggers
Electroceuticals
Electrode approaches
Ion channel drugs
Optogenetic simulation

(B)

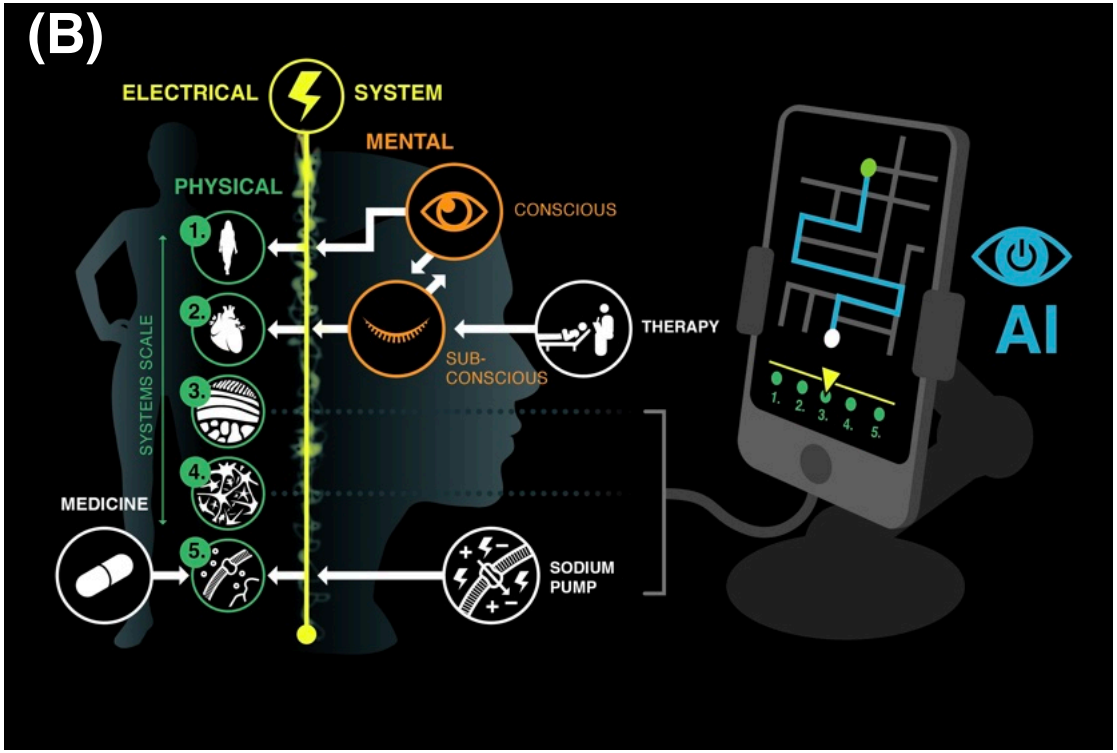

ELECTRICAL
SYSTEM
MENTAL
PHYSICAL
CONSCIOUS
SUB-
CONSCIOUS
THERAPY
SYSTEMS SCALE
MEDICINE
SODIUM
PUMP
AI

Figure 10