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Review article

Aging as a loss of morphostatic information: A developmental bioelectricity perspective

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ABSTRACT

Maintaining order at the tissue level is crucial throughout the lifespan, as failure can lead to cancer and an accumulation of molecular and cellular disorders. Perhaps, the most consistent and pervasive result of these failures is aging, which is characterized by the progressive loss of function and decline in the ability to maintain anatomical homeostasis and reproduce. This leads to organ malfunction, diseases, and ultimately death. The traditional understanding of aging is that it is caused by the accumulation of molecular and cellular damage. In this article, we propose a complementary view of aging from the perspective of endogenous bioelectricity which has not yet been integrated into aging research. We propose a view of aging as a morphostasis defect, a loss of biophysical prepattern information, encoding anatomical setpoints used for dynamic tissue and organ homeostasis. We hypothesize that this is specifically driven by abrogation of the endogenous bioelectric signaling that normally harnesses individual cell behaviors toward the creation and upkeep of complex multicellular structures in vivo. Herein, we first describe bioelectricity as the physiological software of life, and then identify and discuss the links between bioelectricity and life extension strategies and age-related diseases. We develop a bridge between aging and regeneration via bioelectric signaling that suggests a research program for healthful longevity via morphoceuticals. Finally, we discuss the broader implications of the homologies between development, aging, cancer and regeneration and how morphoceuticals can be developed for aging.

1. Introduction

1.1. The challenges of next-generation aging biomedicine

Aging is a nearly ubiquitous process that involves morphological and functional changes in cellular and extracellular components leading to a progressive decline in most biological functions de Magalhães (2011). The process of aging is influenced by a variety of factors, including genetics, lifestyle, and aspects of the environment Partridge et al. (2018). The decline of cellular function due to aging causes a gradual loss of physiological functions and increased susceptibility to a host of diseases, including cardiovascular diseases, cancer, neurodegenerative disorders, type II diabetes, and many infectious diseases, all of which negatively affect the quality of human life Partridge et al. (2018); Hayflick (2007).

Several theories have been proposed to explain the process of aging, including damage-based and programmatic theories de Magalhães (2011); Kirkwood and Melov (2011); de Magalhães (2023), of which the former is more widely studied López-Otín et al. (2023); de Magalhães (2011); Hayflick (2007); Gladyshev et al. (2021). According to this theory, inefficient repair mechanisms cause the accumulation of molecular damage, which affects crucial cellular components like the genome, telomeres, mitochondria, and proteins López-Otín et al. (2023); Kennedy et al. (2014); Gladyshev et al. (2021). Such damage is thought to drive the aging process. In contrast, programmatic theories argue that aging is predetermined by mechanisms encoded in the genome, rather than by stochastic damage accumulation de Magalhães and Church (2005); Gems (2022); Skulachev and Skulachev (2014). Recently, two groups proposed that aging is instead dependent on changes in information processing and analogized it as being dependent on the software of life de Magalhães (2023); Yang et al. (2023a), shifting the focus from aging as cellular and molecular damage to aging as a progressive failure of biological information processing. Both of these groups located this software in the epigenome as implemented by chromatin modifications de Magalhães (2023); Yang et al. (2023a). Indeed, in recent years, epigenetic clocks have emerged as a powerful tool to predict chronological age Horvath (2013); Galkin et al. (2020) and mortality risk in

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humans Horvath and Raj (2018); Chen et al. (2016), as well as the age of individuals from different mammalian species Levine et al. (2018). These clocks rely on a relatively small number of methylation sites that become either hypermethylated or hypomethylated with age. Interestingly, epigenetic clocks tick throughout the lifespan, beginning at conception and continuing in normal body cells in vitro. However, they do not tick in embryonic or pluripotent cells Horvath (2013); Kabacik et al. (2022), and reprogramming with Yamanaka factors can reset them to zero Simpson et al. (2021).

Overall, while significant progress has been made in manipulating aging in model organisms through genetic, dietary, and pharmacological interventions Partridge et al. (2018); Moskalev et al. (2022); Kenyon (2010) the underlying cause of aging in human beings remains unclear and is a subject of intense debate. Existing life extension approaches still have limited effects Mahmoudi et al. (2019). Most approaches have been bottom-up, with a focus on the cellular hardware: the genes, molecular pathways and more recently the epigenome. But micromanaging the maintenance process at the smallest scale during aging may not be feasible for structures as complex as a human anatomy Pezzulo and Levin (2016); Pio-Lopez and Levin (2023); Levin (2011). The maintenance and repair of such highly intricate and complex structures likely involves a dynamic, multi-component orchestration of events and it would be impractical to try to oversee every detail of the process. As one example, although a teratoma tumor may contain various differentiated cell types such as hair, teeth, and muscle, it does not have proper three-dimensional organization. Thus, having well-differentiated cells alone is not enough to create a functional and complex structure.

Aging can be seen as the decline of the exquisite order that is first established during embryogenesis and early growth and remodeling. In effect, cellular collectives must navigate anatomical morphospace (the option space of possible geometric configurations) to get from the a fertilized egg cell to a region of that complex space corresponding to the normal anatomy of a given species. Crucially, because cells have a finite lifespan and are bombarded with numerous stresses, a given anatomy cannot remain static. Even after the regulative processes of embryogenesis pull the anatomy from stage to stage, maintening a final adult form is a highly active process. Highly dynamic activity is necessary just to stay in one place in morphospace, resisting the natural tendency to disorder. We believe it is likely that the secret to longevity is in understanding the computational (not only molecular) processes that allow cellular collectives to achieve, and maintain, specific order at many length scales. Here we focus on biophysical interfaces that could be exploited to reinforce the morphogenetic information that produced the complex healthy organs we all wish to keep indefinitely.

Thus, to make significant advances in life extension and aging bioengineering, we must understand and learn to activate resilient endogenous morphogenetic construction and repair mechanisms Mathews et al. (2023); indeed, even the normal process of moving along developmental stages can be seen as a kind of repair toward a more adaptive form, suggesting that regeneration, broadly understood, is a fundamental and constant need for organisms from the time of conception. Fortunately, the field of developmental and regenerative biology offers numerous examples of control circuits that allow for effective self-repair and the dynamic management of multicellular shapes and large-scale anatomy Levin (2021a). By understanding the communication and computational modalities that harness individual cell behaviors toward the creation and repair of complex tissues and organs (the physiological software of life), it may be possible to stop or reverse their progressive disrepair Levin (2021a). Here, we focus on one important modality for coordinating cells into multicellular collectives that navigate anatomical, transcriptional, and physiological spaces: endogenous developmental bioelectricity. The aim of this perspective is to stimulate research in the bioelectricity of aging, a field that has been neglected until now.

1.2. A new approach: top-down control of anatomical homeostasis via bioelectricity

Bioelectricity has long been suspected to be an important informational layer for anatomical control in development, cancer and regeneration Cone (1971); Nuccitelli (2003); Levin et al. (2017); Levin and Martyniuk (2018). However, in recent years, molecular tools have been developed that have allowed the merging of bioelectrical mechanisms with genetics and mainstream regenerative and developmental biology (reviewed in Bates 2015; Harris 2021; Levin 2021a). Bioelectric signaling is a form of epigenetics (in the original sense of the term, as anything not encoded in the primary genetic sequences), which works in conjunction with other established regulatory pathways in the body relying on biophysical and biochemical interactions. Not merely an additional step in the already complex molecular processes of the body, bioelectricity provides unique and powerful signaling control dynamics, much like the electrical circuitry underlying dynamic and flexible functions of nervous systems. Like in brains, and in our computing devices, the true power of bioelectricity is not in the molecular mechanism but in its amenability to computation and scaling. Evolution discovered, as far back as bacterial biofilms Prindle et al. (2015); Martinez-Corral et al. (2019), the advantageous properties of bioelectrical networks for coordinating information across space and time, facilitating collective decision-making, and supporting reprogrammability and robustness Levin and Martyniuk (2018). These properties are universally acknowledged and studied in the nervous system, but they are far more ancient than brains, and enable similar dynamics (using conserved molecular mechanisms Fields et al. 2020) in other parts of the body as they navigate other problem spaces Fields and Levin (2022). Importantly, just as in the nervous system (where bioelectricity enables high-level cognitive goal states to be implemented via molecular events in muscle and gland cells), somatic bioelectricity serves as a tractable interface by which high-level information (e.g., organ-level order) passes to and from molecular pathways that underlie cell behaviors. This is familiar in the context of for example, voluntary movement (high--level executive control filtering down to the depolarization of muscle membranes), but also occurs ubiquitously as morphogenetic patterns stored in tissues guide cellular collectives along specific paths in morphospace Pai et al. (2012); Harris (2021).

Bioelectric controls, such as voltage-sensitive channels, implement feedback loops that can break both spatial symmetry and negative feedback for robustness. In addition, gap junctions (electrochemical synapses) enable bioelectric signals to be sent between cells in response to voltage and other ionic parameters Palacios-Prado and Bukauskas (2009), allowing for tissue-level feedback loops that respond to changes in large-scale patterns Pietak and Levin (2017). These characteristics facilitate the precise orientation, scaling, and shaping of organs during embryogenesis, regeneration, and remodeling, through dynamic long-range coordination and anatomical decision-making Levin (2021a). Specifically, it has been argued Pezzulo and Levin (2016); Noble (2022) that these methods work because evolution exploits bioelectrical interfaces endogenously for modular control of anatomical homeostasis and repair processes Levin (2023b). Using molecular-genetic and pharmacological techniques, researchers have been able to manipulate the distribution of voltage gradients to effect alternative anatomical structure/location during development, increase regeneration after injury, and suppress cancer. They have been able to induce the growth of entire organs from different types of tissue, change the direction of primary body axes, initiate regeneration of tails and limbs in non-regenerative conditions, alter the shape of regenerating heads in planaria to resemble those of different species, and convert oncogene-induced tumors into normal tissue Mathews and Levin (2018); Levin (2014); Levin and Martyniuk (2018); Sundelacruz et al. (2009); McLaughlin and Levin (2018). A variety of tools from behavioral and cognitive neuroscience have been harnessed for the control of tissue-level and organ-level information, which enables pushing much of

the complexity onto the system itself via simple triggers, by relying on the competencies of the system itself Pio-Lopez et al. (2022); Pezzulo and Levin (2015). This top-down methodology for controlling anatomy opens promising avenues for therapeutic approaches to life extension and the diseases of aging if we consider aging as a defect of morphostasis - a gradual drift away from effective maintenance of dynamical anatomical homeostasis.

The storage of homeostatic setpoints for development, regeneration, and cancer suppression in bioelectrical patterns in tissue has been explored extensively (see reviews Harris 2021; Bates 2015; Levin 2021a). Here, we propose a developmental bioelectricity perspective on aging viewed as a defect of morphostasis that can be approached by considering the failure modes of the pattern homeostasis process, and the ways in which target morphology setpoints can be reinforced Pai et al. (2015); Rubin (2006), (1985). Given the dynamic nature of organisms, with cells continuously turning over, it is clear that just remaining in place within the healthy region of morphological and physiological state space is an extremely active process. Long after development completes, morphological prepatterns are still necessary to guide the active remodeling process that integrates cell death and proliferation into a balanced process that maintains a stable large-scale anatomical structure despite all of the noise and activity at lower scales. This coordination requires information processing with respect to the global patterns that individual cell activity must maintain. Consistent with its role in embryogenesis and regeneration, we thus present bioelectricity as the software of life, that is crucial to the dynamic process that resists aging. We then identify and discuss the links between bioelectricity and longevity strategies and age-related diseases, and develop a bridge between aging and regeneration via bioelectric signaling that suggests a research program for addressing aging. We then discuss the broader implications of the homologies between development, aging, cancer and regeneration. Lastly, we present the morphoceuticals for aging and we conclude.

2. Bioelectricity as the software of life

2.1. Developmental bioelectricity: definitions

Developmental bioelectricity refers to signaling among non-excitable cells mediated by endogenous electric fields and differences in resting potential Levin et al. (2017); Funk and Scholkmann (2023). These electric states arise due to specific ion channels and pump proteins, which uphold voltage gradients across the cell membrane. Such gradients elicit various cellular responses, including transcriptional and epigenetic responses Levin (2012), (2014); Levin et al. (2017) (see Fig. 1B). Ion channels are selectively permeable; they differentiate between the electrical charge and size of ions, allowing movement of specific ions, such as K^+, Na^+, $Ca2^+$, or Cl^-, in one direction through

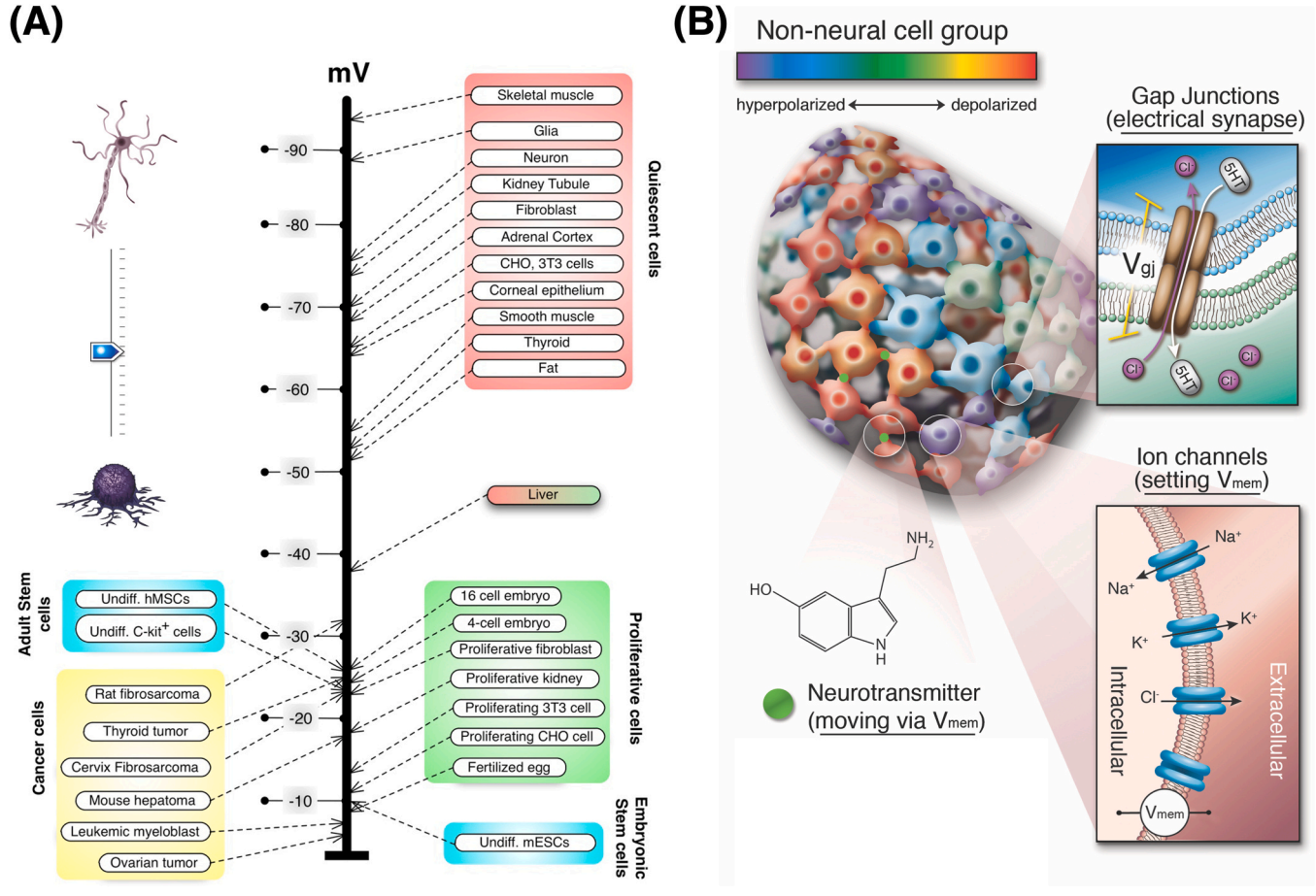

Fig. 1. Bioelectricity in cells and non-neural cell groups. **(A)** Highly adaptable cells such as embryonic, stem, and cancer cells tend to have a relatively depolarized state, whereas mature and fully differentiated cells are hyperpolarized (data from Binggeli and Weinstein 1986). **(B)** The process of developmental bioelectricity involves ion channel proteins on cell surfaces, which control the movement of ions and establish a resting potential (V_{mem}) across the membrane. This cell V_{mem} can also be communicated to other cells through electric synapses, or gap junctions. The resulting interactions between cell voltages lead to stable distributions of V_{mem} across tissues, as seen in the frog embryo face, where they determine the placement and number of craniofacial organs like eyes and mouth. These gradients can be manipulated using interventions that target ion channels, gap junctions, and small molecular signals like neurotransmitters. Panel A and B reproduced with permission respectively from Levin et al. (2019b) and Pio-Lopez and Levin (2023).

their pore. The flow of ions across membranes and the resulting changes in the bioelectrical pattern play a crucial role in many cellular processes, including muscle contraction, nerve signaling, secretion, tissue growth, cell proliferation and apoptosis Levin (2021a). Ion channels play a critical role in the control systems of embryonic development and have been linked to several channelopathies of embryonic embryogenesis Srivastava et al. (2021); Sun et al. (2019); Smith et al. (2018); Bauer et al. (2018); Masotti et al. (2015); Kortüm et al. (2015), which are disorders caused by mutations in ion channel genes. These conditions have been well-studied in various animal models such as fruit flies, zebrafish, mice, frogs, and human patients, implicating several ion channels, such as the potassium channel $K_{ir}2.1$, and gap junctions (connexins). Research on these disorders has helped to better understand the underlying mechanisms and the role of ion channels in normal embryonic development. In addition, dysregulation of ionic gradients can contribute to age-related declines in physiological function and dysfunction of ion channels is often linked to organ failure during aging Kass (2005). Because of their central role, bioelectric signals are an emerging target for induction of organ formation and regeneration (reviewed in Davidian and Levin 2022; Bates 2015; Harris 2021; Ferreira et al. 2016; Oliveira et al. 2019).

Together, the voltage states induced by the action of channels, pumps, and gap junctions create a network of bioelectrical activity throughout the tissue, which ultimately triggers changes in gene expression Pai et al. (2016) and cell behavior (migration, differentiation, shape change, proliferation, apoptosis, etc.) that lead to specific morphogenetic outcomes. This bioelectric code translates patterns of voltage into information about organ size, shape, and positioning through mechanisms such as neurotransmitter gating, calcium signaling, and voltage-sensitive phosphatases. Analogous to the way electrical neural networks of the brain control muscle movement to reach behavioral goals, the ancient bioelectric networks of the body control cell activities to achieve morphogenetic outcomes, by storing and guiding cell collectives toward implementing specific anatomical patterns Mathews and Levin (2018); Levin (2014); Levin and Martyniuk (2018); Sundelacruz et al. (2009); McLaughlin and Levin (2018).

2.1.1. Bioelectric control of single-cell function and differentiation

The state of V_{mem} (the resting potantial across the membrane) in a cell and its neighbors is crucial in regulating cell behavior Sundelacruz et al. (2009), along with other, more canonical, modes of signaling (see Fig. 1A). Usually, quiescent and differentiated cells exhibit strong polarization, while embryonic, stem, and tumor cells tend to be depolarized Binggeli and Weinstein (1986). Changes in V_{mem} are involved in controlling differentiation and proliferation in various cell types, including human mesenchymal stem cells Sundelacruz et al. (2013a); You et al. (2013), cardiomyocytes Lan et al. (2014), iPSCs Jiang et al. (2010), vascular muscle Jia et al. (2013), embryonic stem cells Ng et al. (2010), and myoblasts Hinard et al. (2008), as well as in neurotransmitter specification Root et al. (2008) in the developing nervous system and heart. While V_{mem} regulation is being employed in bioengineering to control cell connectivity Ozkucur et al. (2015), differentiation Sundelacruz et al. (2013b), 2009, and wound healing Sundelacruz et al. (2013a), the true power and significance of bioelectric networks lies in multicellular patterns and their ability to harness cells toward specific anatomical outcomes - crucial for control of large-scale order in regeneration, developmental defects, and disorders such as cancer Levin and Martyniuk (2018); Levin (2021b).

2.1.2. Bioelectric control of large-scale anatomy

The dynamics of bioelectric signaling within the body play a crucial role in regulating diverse processes including wound healing, the formation of neural circuits, eye development, facial patterning, brain and tail size, and the determination of left-right and anterior-posterior body axis (reviewed in Levin et al. 2017).

Manipulation of bioelectrical patterns has emerged as a promising approach for controlling morphogenesis and advancing regenerative medicine Levin (2021a); Levin et al. (2017); Pio-Lopez and Levin (2023), especially because it offers the potential of using a high-level interface where simple signals can serve as triggers of complex, downstream self-limiting cascades that do not have to be micromanaged by the bioengineer. These interventions can be implemented at various levels, such as using electrotaxis to control cell movement in wound healing Feng et al. (2017); Zajdel et al. (2020) or by manipulating ion channels using different types of drugs known as morphoceuticals Pio-Lopez and Levin (2023) to establish specific bioelectric prepatterns for organogenesis or appendage induction. Studies have demonstrated that malformations caused by mutations and teratogens can be reversed by enforcing the correct voltage maps using drugs, optogenetics, or channel misexpression Chernet et al. (2016); Pai and Levin (2022); Pai et al. (2015), 2020. Additionally, profound defects in brain structure and function caused by teratogens can be reversed by restoring normal endogenous voltage prepatterns in Xenopus Pai et al. (2018). Furthermore, research has shown that developmental defects in the brain caused by mutations in key neurogenesis genes, such as Notch, can be rescued by the overexpression or activation of native HCN2 (hyperpolarization-activated cyclic nucleotide-gated) channels Pai et al. (2015). As voltage-regulated ion channels, HCN2 channels are sensitive to their context; they increase hyperpolarization in slightly polarized cells but have no effect on depolarized cells, thus functioning as "contrast enhancers" that sharpen weakened differences in V_{mem} across compartment boundaries, similar to how a sharpen filter emphasizes order in a fuzzy image. Importantly, application of HCN2 opener drugs was systemic, eliminating the need to precisely control the spatial properties of delivery.

Bioelectric signaling has also been found to be a viable method for inducing the regrowth of entire body parts Leppik et al. (2015); Oliveira et al. (2019); Sisken et al. (1984); Becker and Spadaro (1972); Libbin et al. (1979). Studies on rats have demonstrated that limb regeneration can be enhanced through the use of bioelectric signals Oliveira et al. (2019). Additionally, in a frog model of tail regeneration, complete regrowth of muscle, spinal cord, blood vessels, and skin has been observed in a normally non-regenerative state, subsequent to one-hour treatment with an ionophore, which induced a pro-regenerative state in the wound. Ionophore treatment did not need to be maintained during the subsequent regeneration process Tseng et al. (2010).

These bioelectrical networks in the tissues store the target morphology and coordinate cellular activity across distances Pezzulo and Levin (2015); Fields et al. (2020). Because a cell's bioelectric state is influenced by prior experiences, extracellular signaling, and signals from neighboring cells, these post-translational events are invisible to traditional omics approaches. While complicating modeling and experimentation, this historicity property offers a unique target for biomedicine: reprogrammability.

2.1.3. Reprogramming anatomy: the software analogy

Although the mechanism of biological information processing in living systems differs from that in computer architectures, it leverages essential aspects of the "software" concept utilized in computer science: reprogrammability, the storage of malleable data that determines the subsequent behavior of the hardware, and modularity, which allows for the initiation of a complex activity by simple triggers in various spatiotemporal contexts because much of the functionality is in the interpretation of the pattern by the system. Software modularity is particularly significant because the trigger that starts a module does not have to be a specific gene that is mechanistically linked to the mechanisms it triggers. In bioelectricity, this is achieved through patterns of V_{mem}. For example, a particular V_{mem} pattern triggers eye development anywhere in the body, independent of which ion-channel protein or ion is employed to implement that state Pai et al. (2012) - the organ-level outcome is encoded by a physiological state, not the molecular details. The same was seen in studies where tail (including spinal cord)

regeneration could be induced by a yeast proton pump in vertebrates Adams et al. (2007).

Bioelectric information is not independent from DNA, in the same way that software is not independent from hardware. Adaptive physiology requires the DNA-encoded molecular hardware (ion channels and gap junctions), and cannot run without it. Many ion channels contribute to the bioelectric state which allows considerable robustness. Nevertheless, there is good evidence that ion channel genes do impact bioelectric states indicated by: 1) work in synthetic biology McNamara et al. (2020), (2018); Lou et al. (2016) using ion channels to build bioelectric patterns from scratch, 2) the many known channelopathies (see Table 1)in both human embryos and those of model species, and 3) experimental work that exploits specific channels to make desired (and experimentally confirmed) bioelectric field changes in vivo Pai et al. (2018), 2020. However, once provided, bioelectric circuits made of specific ion channels can generate, process, and store information that is not directly "in" the DNA itself similarly to how the brain processes novel information (see Fig. 2).

Moreover, bioelectric gradients also determine gene expression, of ion channels (providing a feedback loop) and of other genes such as transcription factors and signaling proteins. Thus, bioelectric controls work together with biochemical and biomechanical networks as the computational medium through which genomically-specified hardware creates, repairs, and maintains anatomical order. Here, we focus on the uniquely tractable and powerful ways in which the bioelectrical interface enables top-down control over setpoints and their implementation.

In planaria, the bioelectric prepattern that determines head number and shape (reviewed in Durant et al. 2016) can be readily re-written by brief drug exposures Durant et al. (2019), after which the cells build new heads of the right shape, size, and composition. Importantly, the planaria continue to make the new pattern (e.g., 2 heads) in all subsequent rounds of regeneration without further intervention, showing the existence of a stable but re-writable setpoint that can be modified and leads to long-lasting cooperativity of cells toward the new information. All of these examples offer the possibility that through this interface, we would be able to re-specify the setpoints for anatomical homeostasis (see Fig. 3), and/or improve cells' ability to implement those setpoints by using: low information-content triggers to help the body maintain its correct, healthy target morphology at the tissue and organ levels throughout its lifespan. Two simple hypotheses suggest themselves. Could aging be a decline in the precision of the bioelectric prepattern over time? And/or, could aging be due to a reduction in the cells' ability to sense the prepattern and implement it? Both possibilities seem tractable given the state of the field today.

3. Aging as a morphostasis defect: a developmental bioelectricity perspective

3.1. Longevity strategies and bioelectricity

Strategies to delay and potentially reverse the aging process have recently been explored including blood factors, metabolic manipulations, senolytics and cellular reprogramming Mahmoudi et al. (2019). Here, we review how these strategies are linked with bioelectricity.

3.1.1. Blood factors

Blood factors seem to play a major role in rejuvenating effects Ruckh et al. (2012); Villeda et al. (2014); Castellano et al. (2017). This has been shown using heterochronic parabiosis, in which the circulatory systems of a young mouse and an aged mouse are fused. This technique can revitalize muscle stem cells and reverse the decline in stem cell activation and number Brack et al. (2007); Conboy et al. (2005). It reduces genomic instability Sinha et al. (2014) in the aged mice and reverses age-associated gene expression signatures Villeda et al. (2014). It also has positive effects on several other organs, including the liver, heart, and brain Loffredo et al. (2013); Villeda et al. (2011); Katsimpardi et al. (2014); Smith et al. (2015).

It seems that the reverse is also true: the pro-ageing effect of aged blood is higher than the pro-rejuvenation effect of young blood on the liver, muscle and brain Rebo et al. (2016). Systemic pro-aging factors have been identified through heterochronic parabiosis and include eotaxin (also known as CCL11) and β2-microglobulin. The levels of these two factors increase with age, and it has been shown that they inhibit neurogenesis and cognition in young mice Villeda et al. (2011); Smith et al. (2015). The excessive Wnt signaling that underlies the differentiation bias of aged muscle stem cell is also reversed by heterochronic parabiosis Brack et al. (2007), (2008). Interestingly, Wnt signaling has been linked to bioelectrical changes and is aberrantly activated in several human diseases including cancer Muccioli et al. (2021); Rapetti-Mauss et al. (2020). Wnt signaling is an important pathway mainly active during embryonic development and is implicated in the control of cell proliferation. Ion channels regulate Wnt signaling in several ways. Fei et al. found a downregulation of $Ca_V1.2$ calcium ion channel in aging models characterized by an altered osteogenic differentiation caused by the inhibition of the Wnt signaling pathway Fei et al. (2019). More generally, the variation in K^+ and Ca^{2+} fluxes across cell membrane induced by changes in transmembrane potential can modulate canonical Wnt signaling Breuer et al. (2019); Rapetti-Mauss et al. (2017); Schickling et al. (2015). Other channels (i.e., K_v 7.1, CFTR for example) may also be implicated in the formation of multiprotein membrane complexes that modulate the correct cytoplasmic-nuclear localization of β-catenin by physical interaction Breuer et al. (2019); Rapetti-Mauss et al. (2017). The Wnt/β-catenin pathway is also the pathway most associated with channels regulation development and cancer progression Rapetti-Mauss et al. (2020).

Extracellular vesicles from young animals have also been shown to rejuvenate aged cell bioenergetics and induce skeletal muscle regeneration Sahu et al. (2021). In that study, they enriched 313 genes that were altered in the presence of extracellular vesicles to investigate their regulatory role in young serum on the transcriptomic profile of injured aged skeletal muscle. Interestingly, they found that the top altered processes, are related to the regulation of ion channels, specifically Ca^{2+} and K^+ channels. Indeed, the regulation of ion gradients is critical for mitochondrial health and function Murphy and Eisner (2009); Garlid and Paucek (2003); de Cavanagh et al. (2015).

Another blood factor potentially involved in the rejuvenating effect necessary for muscle maintenance and regeneration is oxytocin Elabd et al. (2014). Oxytocin levels in the blood decrease with age and it has several roles in ion channel regulation. For example, its action as a neuromodulator Stoop (2012) is mediated via ion channels regulation of depolarization, integration and burst firing in CA2 pyramidal neurons Liu et al. (2022). Oxytocin also regulates acid-sensing ion channels Qiu et al. (2014).

3.1.2. Metabolic approaches

Long-term dietary restriction including fasting regimens are known to extend healthspan and lifespan across several species de Cabo et al. (2014); Kapahi et al. (2017). mTOR and insulin-IGF signaling could play a key role in nutrient-sensing pathways with a rejuvenating effect Kenyon (2010); Johnson et al. (2013); Imai and Guarente (2014). Rapamycin, an mTOR inhibitor, improves haematopoietic stem cell function in aged mice and extends lifespan with a short-term treatment (6 weeks) Chen et al. (2009). Autophagy, the process of cellular self-degradation, is also known to be regulated by the insulin and mTOR signaling pathways Kenyon (2010); Johnson et al. (2013); Imai and Guarente (2014). mTOR could be central in mediating the beneficial effects of dietary restrictions, raising the possibility that mTOR inhibitors could be used to rejuvenate ageing tissues.

Rapamycin and the mTOR signaling pathway have several impacts on bioelectricity. Rapamycin inhibits voltage-gated K^+ channels in dendritic cells Tyan et al. (2010) and the reciprocal relationship between ion channels and pumps in autophagy has been shown to be

Table 1
Table of known human channelopathies (extracted partly from Srivastava et al. 2021) and the links between bioelectricity and age-related diseases.

	Protein (gene)	Channel type	Mutant phenotype	Reference
Developmental defects	V-ATPase TCIRG1, VATB1	Vacuolar proton pump	Facial dysmorphism, dense bones	Borthwick et al. (2003); Tamirisa et al. (2018)
	$K_{ir}3.2$ (kcnj6)	Voltage-gated K^+ channel	Keppen-Lubinsky syndrome Craniofacial defects and microcephaly	Masotti et al. (2015)
	$K_v10.1$ (kcnh1) VATB2	K^+ channel and vacuolar proton pump	Zimmermann-Laband and Temple-Baraitser syndrome Craniofacial and brain defects, dysplasia/aplasia of nails of thumb and great toe	Kortüm et al. (2015); Simons et al. (2015)
	GLRa4	Ligand-gated Cl^- channel	Craniofacial defects	Labonne et al. (2016)
	$K_{ir}6.1$ (kcnj8)	K^+ inwardly rectifying channel	Cantu syndrome—face, heart, skeleton, brain defects	Hiraki et al. (2014); Cooper et al. (2014); Brownstein et al. (2013)
	NALCN	Na^+ leak channel	Freeman-Sheldon syndrome Congenital contractures of face and limbs Cerebral and cerebellar atrophy, small pituitary	Chong et al. (2015)
	CFTR	Cl- channel transmembrane conductance regulator	Bilateral absence of vas deferens	Uzun et al. (2005); Wilschanski et al. (2006)
	SCN3A	Voltage-gated Na^+ channel	Polymicrogyria	Smith et al. (2018)
	TRPV1 TRPV4	Transient receptor potential cation channels	Temperature-induced face, heart defects	Hutson et al. (2017)
	$K_v3.1$ (kcnc1)	Voltage-gated K^+ channel	Head/face dysmorphias	Poirier et al. (2017)
	$K_T3.2$ (kcnk9)	K^+ two-pore domain channel	Birk-Barel dysmorphism syndrome Craniofacial defects, cortical patterning defects	Veale et al. (2014); Barel et al. (2008); Bando et al. (2014)
	$K_{ir}6.2$ (kcnj 11)	Inwardly rectifying K^+ channel	Craniofacial defects, neural differentiation	Gloyn et al. (2004)
	$K_v1.9$ (kcnq1) (via epigenetic regulation)	Voltage-gated K^+ channel	Hypertrophy of tongue, liver, spleen, pancreas, kidneys, adrenals, genitalia	Lee et al. (2000); Weksberg et al. (2001); Moore et al. (2000); Wen et al. (2005)
	$K_v1.9$ (kcnq1)	Voltage-gated K^+ channel	Jervell and Lange-Nielsen syndrome Dysmorphism of inner ear	Rivas and Francis (2005); Casimiro et al. (2004); Chouabe et al. (1997)
	$K_v3.3$ (kcnc3)	Voltage-gated K^+ channel	Cerebellar dysplasia	Khare et al. (2017)
	$K_{ir}2.1$ (kcnj2)	Inwardly rectifying K^+ channel	Andersen-Tawil syndrome Craniofacial defects, abnormal limb patterning, gracile ribs, and long bones	Bendahhou et al. (2003); Dahal et al. (2012); Yoon et al. (2006)
	$Na_V1.2$ (scn2a)	Voltage-gated Na^+ channel	Laterality defects	Fakhro et al. (2011)
	$Ca_V1.2$ (cac1c)	Voltage-gated Ca^{2+} channel	Timothy syndrome-webbed fingers, dysmorphic facial features, heart development defects, small teeth	Splawski et al. (2004)
	Cx43 (gja1)	Gap junction	Heart defects (outflow tract and conotruncal), ODDD, visceroatrial heterotaxia	Britz-Cunningham et al. (1995); Debeer et al. (2005); Pizzuti et al. (2004)
Cardiovascular	MaxiK	Ca^{2+} activated K^+ channels	Coronary smooth muscle	Marijic et al. (2001)
	KCNMA1	BK_{Ca} alpha subunit	Coronary smooth muscle	Toro et al. (2002)
		Na^+, Ca^{2+}, and K^+ channels	Dysfunction of the sinoatrial node (SAN)	Rao et al. (2016)
	KCNMA1 and TRP	BK_{Ca} and TRP channels	Dysfunction of the cardiovascular system	Behringer and Hakim (2019)
Brain		Calcium, sodium and potassium channels	Dyskinesia, seizures, epilepsy, and ataxia	Behringer and Hakim (2019)
	$Ca_V3.1$ T-type	Calcium channel	Alzheimer	Rice et al. (2014)
		Potassimum channels	Hyperexcitability, inflammation, and neuronal loss	Patel and Sesti (2016)
	Ca^{2+} family	Calcium channels	Cognitive decline	Yamada et al. (1996)
	Ca^{2+} family	Calcium channels	Neuronal loss	Ciovannelli and Pepeu (1989)
	TRP1	TRP channels	Neuroinflammation	Matta et al. (2008)
	$K_v1.5$	Potassium channels	Pakinson's disease beta amyloid	Chung et al. (2001)
Cancer	$K_v1.1$, $K_v1.3$, $K_v1.5$	Shaker-like K^+ channels	Proliferation in glioma, breast cancer, lung cancer, pancreas cancer, prostate cancer, lymphoma	Preussat et al. (2003); Comes et al. (2013)
	$K_v11.1$ (HERG)	EAG-related K^+ channels	Proliferation in melanoma, neuroblastoma, breast cancer	Chung et al. (2001)
	TRP (TRPC6, TRPV6, TRPM7, TRPM8)	TRP channels	Proliferation in breast cancer, prostate cancer, head and neck cancer, human glioblastoma cell line	Ding et al. (2010); Lehen'Kyi et al. (2007); Guilbert et al. (2009); Jiang et al. (2007); Tsavaler et al. (2001)
	$K_v10.1$ (EAG1)	EAG K^+ channels	Migration of breast cancer cells	Hammadi et al. (2012)
	SOCs (ORAI1/STIM1)	Store-operated Ca^{2+} entry	Cell migration and metastasis in breast cancer, cervical cancer, hepatocarcinoma, glioblastoma	Yang et al. (2009), (2013); Chen et al. (2011); Motiani et al. (2013)
	EAG1	EAG K^+ channels	Tumor angiogenesis in breast cancer and other solid tumors	Pardo and Stu-hmer (2008); Downie et al. (2008)
	$K_v1.3$	Shaker-like K^+ channels	Apoptosis resistance in large B-cell lymphoma and glioma	Preussat et al. (2003)
Inflammaging		Potassium, chlorine and calcium channels	Inflammasome	Preussat et al. (2003)
	$Ca_V1.3$	Calcium channels	Neuroinflammation	Swart and Hurley (2016)

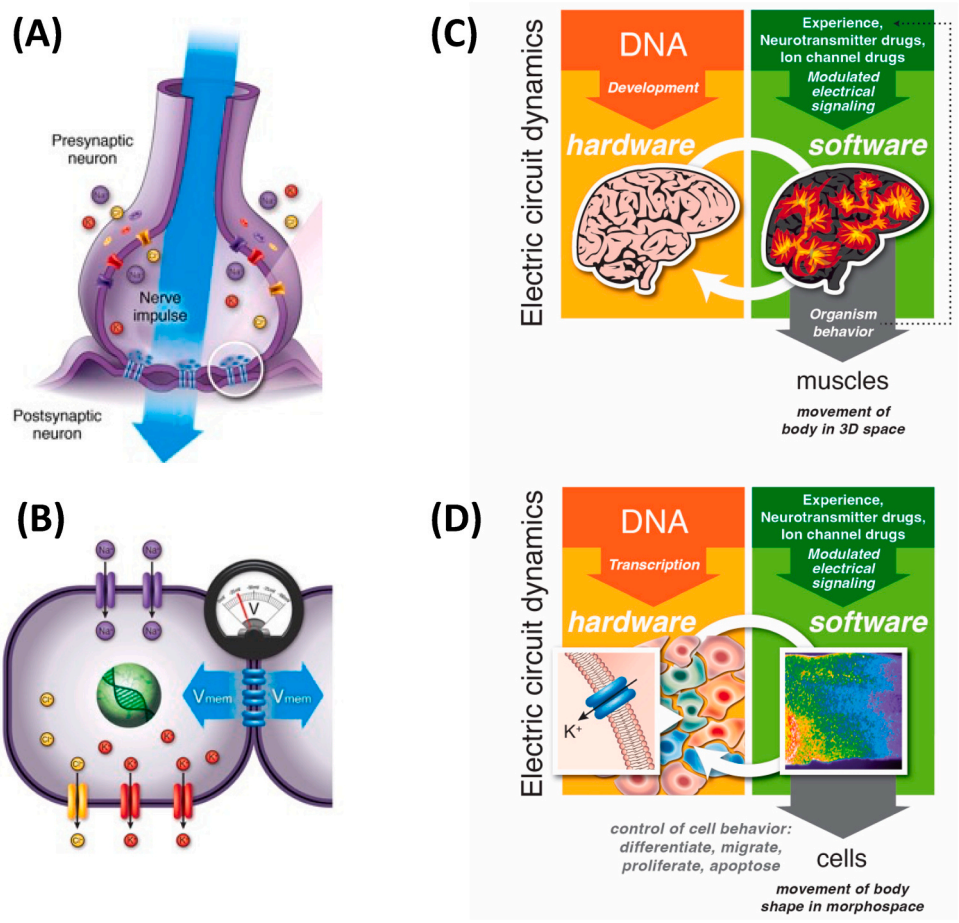

Fig. 2. Bioelectricity as the software of life, comparison with brain information processing. **(A)** Neural cells compute by forming networks in which each cell can use ion channels to establish a specific resting potential and selectively communicate it to connected neighbors through electrical synapses known as gap junctions. **(B)** Neural dynamics represent an optimized version of an older system that is present in all cells, where ion channels are utilized, and most cells form electrical connections with neighboring cells. **(C)** DNA-specified ion channel hardware present in neurons in the brain facilitates bioelectric computation, which represents the software that can be influenced by stimuli or experiences. The synapses illustrated in (A) allow for quick communication over long distances, which helps the brain regulate muscle cell physiological dynamics and achieve three-dimensional movement of the body. **(D)** Before the emergence of specialized, high-speed neurons, preneural bioelectric networks utilized the same physiological software architecture and ion channel hardware. Bioelectrical networks' memory and information-processing features were used to regulate cell behaviors and control the body configuration's movement through morphospace Fields et al. (2020); Levin (2021a). The figure is reproduced with permission from Fields and Levin (2022). Images by Jeremy Guay of Peregrine Creative.

mediated via mTOR pathways Abuammar et al. (2021). Importantly, autophagic progression is regulated by calcium signaling produced by TRPML1, which induces biogenesis of autophagic-lysosomal organelles, activation of mTORC1 (mechanistic target of rapamycin complex 1) and degradation of autophagic cargo. Two critical components of the autophagic network regulate TRPML1 function: LC3 (microtubule-associated protein light chain 3) and mTORC1. Autophagy is intrinsically linked to the degradative function of the lysosome. Lysosome-associated ion channels implicated in autophagy such as TRPML1, TPCN and TMEM175 have been linked to neurodegenerative and age-related diseases, including Parkinson's disease and Alzheimer's disease Jinn et al. (2017); Senft and Ze'ev (2015); Wie et al. (2021). Rapamycin also has anti-cancer effects and has been shown to inhibit both oncogenic intestinal ion channels and neoplasia in APCMin/+ mice Koehl et al. (2010).

Other nutrient-sensing pathways could also be involved in the life extension effects of dietary regimens including metformin and resveratrol Mahmoudi et al. (2019). Metformin is known to increase AMPK activity Bonkowski and Sinclair (2016); Imai and Guarente (2014) which preserves mitochondrial function and decreases inflammation when administered starting at middle age Martin-Montalvo et al. (2013). Metformin has several effects on bioelectricity. It restores electrophysiology of small conductance calcium-activated potassium channels in the atrium of Goto-Kakizaki diabetic rats Fu et al. (2018). CLIC1 channels regulate the antineoplastic effects of metformin in gallbladder cancer cells Liu et al. (2017). This drug also may increase cardioprotection in diabetic patients. Indeed, in adult rat myocytes, metformin has been shown to normalize aberrant intracellular Ca^{2+} clearing induced by high glucose Ren et al. (1999). Resveratrol, a red wine antioxidant, can activate sirtuins and other nutrient-responsive pathways. It reduces inflammation and improves cognitive and renal functions in rodents when initiated at mid-to-late life Gocmez et al. (2016); Kim et al. (2018); Pearson et al. (2008). Resveratrol derivatives modulate voltage-gated potassium channels Orsini et al. (2004). It also regulates intracellular calcium signaling via ion channels McCalley et al. (2014).

3.1.3. *Senolytics*

Cellular senescence is a process characterized by the cessation of cell division. It is induced by stress and prevents the development of damaged cells Hernandez-Segura et al. (2018); Campisi (2013). Senescence is known to be involved in the prevention of tumor development Campisi (2013), tissue remodeling during embryogenesis Muñoz-Espín et al. (2013); Storer et al. (2013), wound healing Demaria et al. (2014)

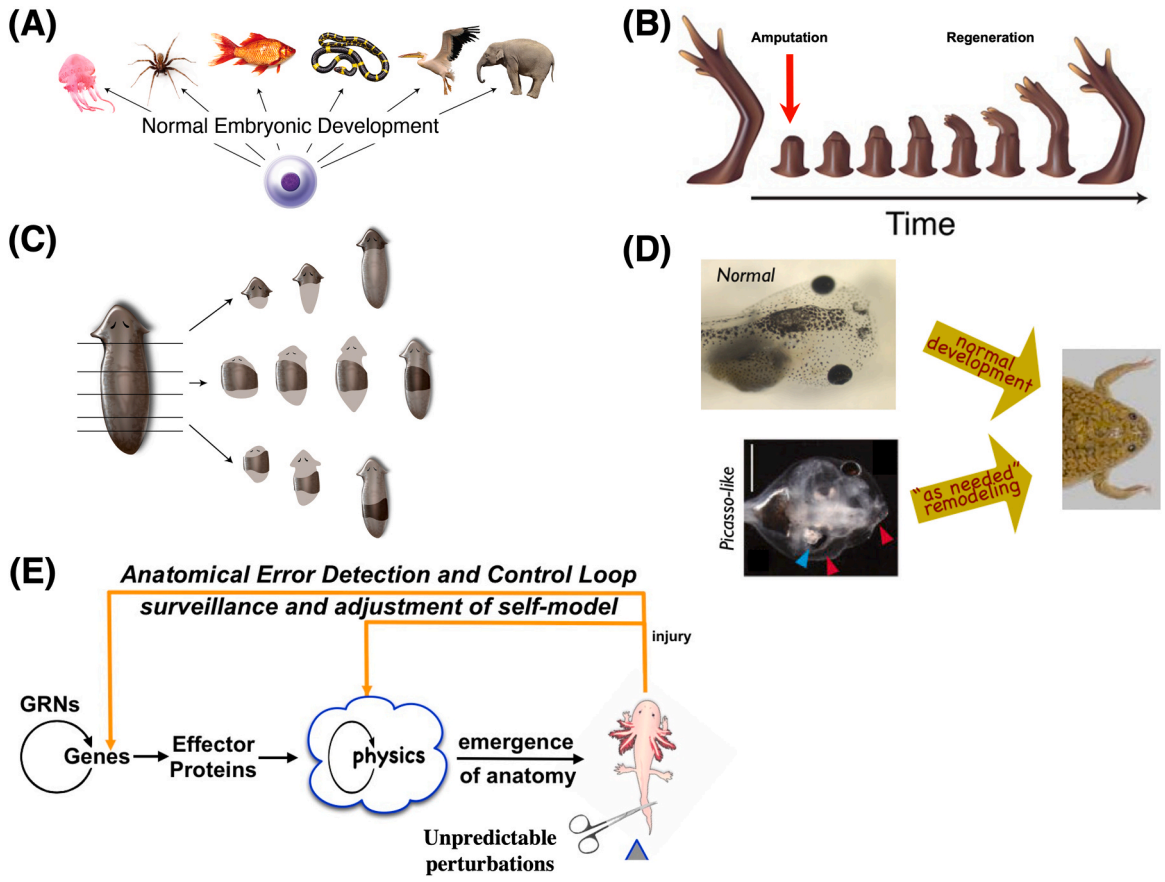

Fig. 3. Anatomical homeostasis or the ability to reach the target morphology from different starting points. (A) The normal development of an embryo results in complex structures originating from a single egg cell, essentially reconstructing an entire body from one cell. This process consistently follows a complex path in morphospace to achieve the correct final form. (B) Regeneration of a limb after amputation. (C) Fragments of planaria have the ability to regenerate and reconstruct the complete organism, adjusting their size as necessary to maintain proportional dimensions. (D) During the transition from tadpole to frog, the head undergoes significant remodeling. Even when tadpoles have highly abnormal facial features, the various anatomical components migrate and rearrange until they reach the desired normal head morphology in frogs. (E) Anatomical homeostasis is reached through an error-minimization scheme. Panel A-B is reproduced with permission from Pio-Lopez and Levin (2023), panel C-D-E respectively from Levin (2022), Vandenberg et al. (2011), and Levin (2023b). The illustrations in panels A-C were created by Jeremy Guay of Peregrine Creative.

and aging Baar et al. (2017); Ogrodnik et al. (2017); Zhu et al. (2015). Cellular senescence has long been thought to be a marker of organismal aging Campisi (2013), although whether it is a cause or consequence is only now beginning to be resolved. Indeed, elimination of senescent cell in vitro using compounds or via specific mouse models have revealed that it can reverse or delay aspects of the ageing process Baar et al. (2017); Ogrodnik et al. (2017); Zhu et al. (2015); Baker et al. (2016); Chang et al. (2016); Jeon et al. (2017); Xu et al. (2018).

The cell-cycle inhibitors p16INK4a and p21CIP1 are markers of cellular senescence, as are many secreted inflammatory factors (collectively referred to as the senescence-associated secretory phenotype (SASP)) Hernandez-Segura et al. (2018); Campisi (2013). The mRNA levels of p16INK4A were elevated by 1.4-fold in TRPM7-deficient BxPC-3 cells (human pancreatic cancer cell line) suggesting a direct link between the bioelectrical pattern and senescence Yee et al. (2012b). TRPM8 ion channel is also aberrantly expressed and required for preventing replicative senescence in pancreatic adenocarcinoma Yee et al. (2012a).

Several senolytic drugs have been developed: for example, inhibitors of the Bcl protein family (for example, Navitoclax, also known as ABT263) Chang et al. (2016), of kinases (like dasatinib and quercetin) Zhu et al. (2015), and of heat shock protein 90 (HSP-90) Fuhrmann--Stroissnigg et al. (2017). Interestingly, Bcl-2 protein family has been seen as ion channels Schendel et al. (1998). Navitoclax inhibits these Bcl-2 proteins Zhu et al. (2016) and therefore directly affects the bioelectric pattern. Quercetin is also known to regulate ion channel function Redford and Abbott (2020), potentiating KCNQ1/KCNE1, KCNQ2/3 and KCNQ4 currents Redford and Abbott (2020) and regulating ligand-gated ion channels Lee et al. (2008). Several studies have also demonstrated the potential role of quercetin action on voltage-gated ion channels Yao et al. (2010); Lu et al. (2013); Jin et al. (2017). HSP-90 has a role in intracellular calcium homeostasis Li et al. (2014). HSP-90 also promotes HERG potassic channel maturation Ficker et al. (2003).

3.1.4. *Cellular reprogramming*

Cellular reprogramming allows the conversion of terminally differentiated somatic cells into pluripotent cells (iPSCs) via somatic cell nuclear transfer (SCNT) (the transfer of the nucleus of an adult somatic cell into an enucleated oocytes), or forced expression of Yamanaka factors (Oct4, Sox2, Klf4, and c-Myc) Takahashi and Yamanaka (2006). Ion channels have also been shown to be regulators of cell differentiation. Bioelectric signaling has been shown to regulate a range of cellular characteristics, such as differentiation in mesenchymal stem cells Sundelacruz et al. (2019), (2015), (2013a), (2008). Ion channels and transporters can also influence skeletal muscle myoblast differentiation, as well as vascular smooth muscle cell differentiation and cardiac differentiation from pluripotent stem cells Chen et al. (2021). The TRPV4 ion channel has been shown to be a novel regulator of dermal myofibroblast differentiation Sharma et al. (2017). In addition,

mechanosensitive ion channels and stem cell differentiation are intrinsically linked Djamgoz and Pchelintseva (2021).

3.2. Aging-related diseases as channelopathies?

Recent research is starting to uncover the connections between aging, aging-related diseases, and bioelectricity primarily by recognizing the central role of ion channels Rao et al. (2016); Strickland et al. (2019); Venkatachalam (2022); Santulli and R Marks (2015). Ion channels play a key role in maintaining physiological homeostasis by regulating membrane potential, signal transduction pathways and tissue information processing. Further, it is believed that abnormal changes in ionic gradients may be responsible for the decline of physiological functions as we age. Santulli and R Marks (2015); Rao et al. (2016). Studies have shown that ion channels can regulate rates of cellular or organismal aging, and that ion channels are involved in aging-related diseases such as heart disease, brain disease, cancer, and eye disease Rao et al. (2016), as well as in aging-related inflammation via mitochondrial functions Strickland et al. (2019). Could it be possible that age-related diseases are a kind of channelopathy, the result of ion channel dysfunction?

3.2.1. Developmental defects

Mounting genetic and cell-biological evidence suggests that channel dysfunction indeed impairs morphogenesis in human bodies (Table 1). Srivastava et al. meta-analysis identfied a diverse range of affected organs in mammals, with notable prevalence in craniofacial defects (14.7%), neural defects (16%), skeletal defects (12%), limb defects (10%), and heart defects (10%) Srivastava et al. (2021). These results emphasize the critical role of gene products regulating bioelectricity in shaping various aspects of pattern formation, particularly in the skeletal, neural, craniofacial, and cardiac systems. However, Srivastava et al. also note that the list presented in the table 1 likely underestimate the actual extent of bioelectrical controls in development because single-gene knockouts or mutants often go unnoticed due to compensation mechanisms and functional redundancy among channel family members or even entirely different types of conductances Koni et al. (2003); Kim et al. (2017); Srivastava et al. (2021). Human channelopathies affect all organ systems, and if aging is a loss of morphostatic information, they should also be involved in age-related diseases.

3.2.2. Cardiovascular diseases

Vascular dysfunction, which is characterized by changes in the structure and function of blood vessels, is a leading factor in the development of aging-related diseases such as cardiovascular and cerebrovascular conditions. Ion channels play a crucial role in this process by modulating blood vessel dilation through activation of potassium channels or inactivation of calcium channels. Studies in aging coronary smooth muscle have shown a decrease in voltage-gated calcium-activated potassium channels Marijic et al. (2001). Altered regulation of ion channels due to aging-related decreases in testosterone and estrogen may also play a role in cardiovascular disease of aging. Testosterone has an inhibitory effect on vasodilation Scragg et al. (2004) and hormones such as testosterone and estrogen participate in vasorelaxation by modulating ion channels and activating signaling pathways, such as the phosphoinositide 3-kinase (PI3K)/Akt-dependent pathways, in vascular endothelial cells Hisamoto et al. (2001). Both hormone receptors and calcium voltage-gated channels are found on the plasma membrane, suggesting that similar signaling pathways may be involved Núñez et al. (2019). Toro et al. also reported an aging-related decrease in the density of the voltage- and calcium-gated potassium channel BKCa alpha subunit in coronary smooth muscle, associated with a reduction in the release of nitric oxide (NO) Toro et al. (2002). Similarly, dysfunction of the sinoatrial node (SAN) has been linked to alterations in the activity of ion channels that regulate the directionality of ionic fluxes in the SAN and cardiac muscle Rao et al. (2016). In addition, functional interaction among calcium-activated potassium KCa and TRP channels, important for normal cardiovascular physiology, is altered during aging Behringer and Hakim (2019). As a result, ion channels are becoming a focus of cardiovascular drug development, with ion channel modulators being considered as promising therapeutics for reducing age-related physiological changes Testai et al. (2015); Bhattacharya and Biber (2016); O'Conor et al. (2016).

3.2.3. Brain diseases

Dysfunction of certain types of sodium, potassium, and calcium channels has been linked to conditions such as dyskinesia, seizures, epilepsy, and ataxia Simms and Zamponi (2014). A variety of neurological disorders are associated with dysfunction or genetic mutations in ion channels, including Alzheimer's, Parkinson's, and Huntington's diseases, and multiple sclerosis Kumar et al. (2016). In particular, changes in calcium ion channels cause dysregulation of intracellular calcium homeostasis, which plays an important role in age-related neurological disorders Navakkode et al. (2018). Studies have also demonstrated that $Ca_V3.1$ T-type calcium channel is downregulated in cell and mouse models of Alzheimer's disease Rice et al. (2014).

Another contributor to aging-related dysfunction in the brain is the dysregulation of calcium and potassium homeostasis caused primarily by oxidation of thiol groups by the reactive oxygen species produced in cells during aging. Changes in calcium levels have a significant impact on cellular properties such as phosphorylation and excitability, both directly and indirectly through alterations in the threshold for activation of KCa channels. Additionally, direct oxidation of voltage-gated potassium channels disrupts potassium homeostasis, resulting in hyperexcitability, inflammation, and neuronal loss. All of these effects contribute to the cognitive decline seen in both normal aging in neurogenerative disease Patel and Sesti (2016).

Changes in calcium homeostasis have been linked to the decline in neuronal activity that occurs with aging Thibault et al. (2007); Feng and Zhang (2000). However, the specific mechanisms underlying this relationship are not yet fully understood. Some studies have suggested that a decrease in the number or function of calcium channels may contribute to cognitive decline, while others have proposed that an increase in intracellular calcium may be harmful to neurons Yamada et al. (1996); Ciovannelli and Pepeu (1989). Furthermore, research in the field has shown that changes in the expression and function of specific calcium regulatory proteins, such as the type 2 RyR protein variants, may play a role in antiapoptotic function associated with mild cognitive impairment and Alzheimer's disease Bruno et al. (2012).

The transient receptor potential (TRP) ion channel family has been found to play a significant role in mediating neurogenic inflammation and pain signaling. Members of this family are co-expressed in a large proportion of nociceptors, with at least 25% being found to have such co-expression Bautista et al. (2006). Specific members of the TRP family, such as TRPA1, have been shown to mediate the inflammatory actions of environmental irritants and analgesic agents and to enhance pain and inflammation Matta et al. (2008). Cognitive decline and neuroinflammation often occur together in the aging brain, with inflammatory molecules negatively impacting spatial memory Moore et al. (2009); Blalock et al. (2003).

The brain contains a significant number of non-neuronal cells such as glia, microglia, astrocytes, and oligodendrocytes which play important roles in maintaining brain Miranda-Negrón and García-Arrarás (2022) and neuronal ion homeostasis Allen and Lyons (2018), and providing protection as the first line of defense against inflammation. Microglia, in particular, act as the resident immune cells in the brain, responding to and propagating inflammatory signals by producing pro-inflammatory cytokines that can have cognitive consequences. Studies have shown that increased oxidative stress and inflammation are associated with brain aging Floyd and Hensley (2002). Furthermore, research has demonstrated that microglial activation is dependent on the expression of the $K_v1.5$ potassium channel, and that the β-amyloid peptide can

induce the expression of these channels in microglia Chung et al. (2001). This suggests that increased oxidative stress in aging could lead to inflammation by upregulating potassium channels in microglia and that changes in ion channels could be a potential cause of age-associated neuronal dysfunction.

3.2.4. Cancer

A wide variety of external factors (e.g. smoking, sun exposure) and internal factors (e.g. inherited genetic mutations, infections) have been implicated in cancer. Other work emphasizes cancer as a disorder of multicellular collective intelligence (reviewed in Levin 2021b; Chernet and Levin 2013; Sonnenschein and Soto 2016; Sonnenschein et al. 2014). While the incidence of cancer can vary widely among different populations and exposure profiles, the greatest risk factor for developing cancer is aging Finkel et al. (2007). Cancer has been proposed as fundamentally a morphostasis defect as well, resulting from the disconnection of cells from the signaling of the collective and its anatomical setpoints Rubin (1985); Needham (1936); Levin (2021b).

It is well-established that tumors have distinct bioelectric signatures and abnormal electrical connections compared to normal tissue Aasen et al. (2003); Chernet and Levin (2013); Loch-Caruso et al. (1985); Trosko et al. (1982); Bose et al. (2015), as well as an accumulation of excessive sodium Leslie et al. (2019). Additionally, the onset of tumorigenesis is associated with the bioelectric disconnection of cells from the larger somatic morphogenetic network. Metastatic melanoma can be induced experimentally by dysregulating bioelectric signaling between cells, in the absence of carcinogens or oncogenic mutations Blackiston et al. (2011); Morokuma et al. (2008). In addition, some experts have described cancer as a specific type of channelopathy, named oncochannelopathy Prevarskaya et al. (2018); Yang and Brackenbury (2013); Yang et al. (2012); Brackenbury (2012); Hutchings et al. (2020); Djamgoz et al. (2014); Payne et al. (2019); Oudin and Weaver (2016). However, it is important to note that while abnormal bioelectric states can certainly be caused by mutant ion channels, the dynamic nature of channel signaling allows for a wide range of other physiological events to induce these states without genetic mutations Mesnil et al. (1995).

Studies have begun targeting, and trying to reverse, the abnormal bioelectric states leading to carcinogenesis. Using neuroscience techniques such as optogenetics Chernet et al. (2016), hyperpolarization has been shown to produce cancer normalization even after tumors have formed, suggesting potent therapeutic potential for hyperpolarizing agents Chernet et al. (2015); Chernet and Levin (2014). Thus, hyperpolarization via pharmacological, genetic or light-based stimulation methods may be able to prevent or reverse tumors, and researchers are currently exploring the role of ion channels in tumor resistance Altamura et al. (2022). Gap junctions and connexins, which play a crucial role in spreading morphogenetic signals throughout the body, are being considered as potential therapeutic targets for cancer Kandouz and Batist (2010); Defamie et al. (2014). Overall, various types of ion channels are involved in cancer (see Table 1 for primary data). Recent research by Mathews et al. has demonstrated ion channel drug-induced suppression of the cancer phenotype in glioblastoma cell lines Mathews et al. (2022). Several different authors proposed ion channels as a target to suppress cancer Capatina et al. (2020); Djamgoz (2022); Rao et al. (2015).

3.2.5. Inflammaging

As people age,the balance of pro- and anti-inflammatory cytokines in the blood is disrupted, leading to three- or four-fold increase in pro-inflammatory cytokines in older adults. This is referred to as "inflammaging". Research has suggested that various age-related conditions such as muscle and bone loss, anemia, immune dysfunction, and cognitive decline are linked to this disruption in cytokine balance Morley and Baumgartner (2004); Reale (2014).

Inflammation can affect the expression and function of ion channels through various mechanisms. Cytokines, prostaglandins, leukotrienes, and reactive oxygen species (ROS) produced during inflammation can modulate ion channels through signaling pathways such as cyclic nucleotide, phosphoinositide, and mitogen-activated protein kinase (MAPK) signaling. Additionally, ion channels may be directly modified by molecules elevated in inflammation such as nitric oxide (NO), adenosine triphosphate (ATP), or protons. Inflammation can also disrupt the cytoskeleton in neuronal and epithelial cells, which can further alter ion channel function Eisenhut and Wallace (2011).

It has been shown that the inflammasome Guo et al. (2015), a multiprotein intracellular complex that forms in response to stress, is a key regulator of the cellular inflammatory response. It is activated in response to stressors, such as pathogenic microorganisms and non-infectious triggers, and leads to the release of the pro-inflammatory cytokines IL-1β and IL-18 Guo et al. (2015). Changes in potassium and chlorine levels and an influx of calcium affect the activation of the NLRP3 inflammasome Jo et al. (2016); Hafner-Bratkovič and Pelegrín (2018). One known activator of NLRP3, ATP, reduces potassium levels and alters other ionic contents within cells Jo et al. (2016), which is necessary for inflammasome activation in monocytes and macrophages Petrilli et al. (2007). Inflammasome activation can also impact potassium, chlorine, and calcium homeostasis within cells, leading to the release of cytokines in cells of the innate immune system Perregaux and Gabel (1994); Hafner-Bratkovič and Pelegrín (2018). NRLP3 activation has been linked to chronic inflammation, Alzheimer's disease, and metabolic disorders such as Type 2 diabetes Jo et al. (2016).

Meta-analyses indicate that calcium-channel blockers have a potential protective effect against the development of Parkinson's disease, with some studies suggesting a risk reduction of up to 30% Lang et al. (2015). Additionally, blockers of the specific calcium channel $Ca_V1.3$, are being studied as a potential treatment for Parkinson's due to their ability to reduce mitochondrial impairment and neuroinflammation Swart and Hurley (2016). These blockers are currently in phase III clinical trials.

3.3. Bioelectricity and the hallmarks of aging

In this section, we review the links between bioelectricity and the remaining currently canonical hallmarks of aging López-Otín et al. (2023), proposing that bioelectricity is another layer relevant to aging that has not yet been captured by the existing hallmarks. Since experiments on instructive influence of bioelectrics in aging have not yet been performed, we highlight patterns in existing data and known mechanistic linkages that may help to guide subsequent functional testing of hypotheses about the roles of bioelectric signaling in longevity and healthspan.

In the previous section on bioelectricity, we described links between bioelectricity and seven of them: disabled macroautophagy, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, and inflammaging. In this section, we refine the links with bioelectricity by analyzing the five remaining ones: stem cell exhaustion, loss of proteostasis, telomere attrition, genomic instability and dysbiosis (see Fig. 4).

Stem cells and large-scale regeneration are controlled by developmental bioelectricity (reviewed in Levin 2021a; Harris 2021; Whited and Levin 2019; McLaughlin and Levin 2018). One mechanism linking bioelectric state to tissue outcomes and regeneration is via epigenetic chromatin modifications Tseng et al. (2010). In addition to its role in tail regeneration Tseng et al. (2010), voltage control of epigenetic state also plays a role in left-right asymmetry of development via the rightward electrophoretic transport of serotonin, which acts as a cofactor for histone deacetylases (HDACs) Carneiro et al. (2011). Furthermore, potassium chloride-induced membrane depolarization can trigger the demethylation of the BDNF promoter and subsequent dissociation of the MeCP2 transcription repressor complex, which facilitates BDNF expression Chen et al. (2003); Martinowich et al. (2003). Interestingly, HDACs have also been shown to be involved in regulation of gene

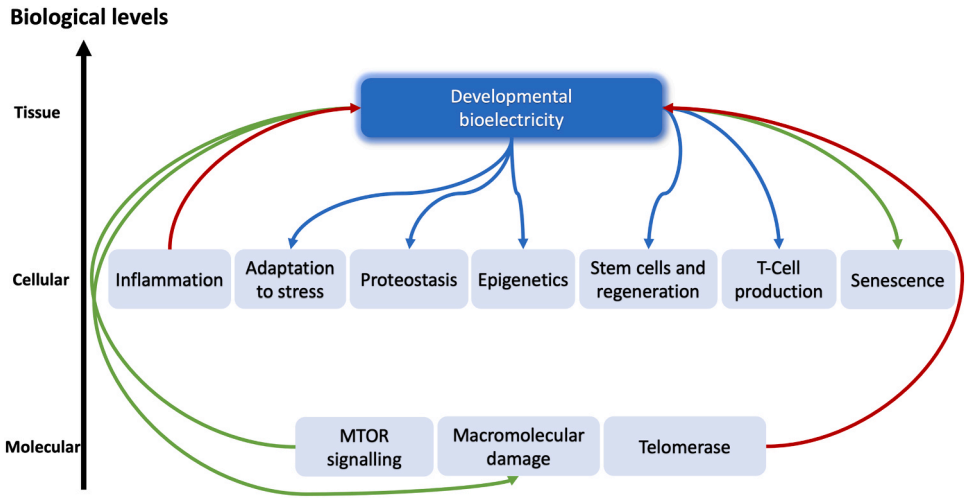

Fig. 4. Bioelectricity and the hallmarks of aging. This graph represents links between bioelectricity and cell- or molecular-level hallmarks of aging. Blue arrows show top-down unidirectional links, green arrows indicate bidirectional links and red arrows indicate bottom-up directional links from hallmarks of aging towards bioelectricity.

expression and its impact on various biological processes, including aging. For instance, sirtuin is an HDAC that has been linked to aging as it promotes longevity in yeast by deacetylating histone H4K16Ac de de de Lima Camillo and Quinlan (2021).

Lysosomal function plays a crucial role in regulating proteostasis, which is in turn modulated by ion channels Venkatachalam (2022). Various stress-regulated ion channels have been identifiedKnowles et al. (2013); Ramírez et al. (2016); additionally, damage to macromolecules may affect ion channels, leading to the disruption of the bioelectrical pattern necessary for maintaining the organism's structure. Ion channels and transporters are involved in regulating membrane excitability, Ca^{2+} homeostasis, mitochondrial and endolysosomal function, and the transduction of sensory signals, which in turn affect aging and longevity Venkatachalam (2022).

Telomerase has also been associated with ion channel defects in cardio-vascular diseases; genomic imbalances in key ion channel genes Banerjee and Hande (2013) and telomere shortening have been observed in sudden cardiac death victims Banerjee et al. (2008).

We were not able to find direct links between bioelectricity and genomic instability and dysbiosis.

Overall, a picture emerges where bioelectricity can affect a large number of the hallmarks of aging. But the opposite is also true: stress, cellular senescence, mTOR signaling and different macromolecular damage can affect the bioelectrical pattern. Developmental bioelectricity seems to stand between damage-based and programmatic theories de Magalhães (2011); Kirkwood and Melov (2011); de Magalhães (2023). As the bioelectrical pattern can control development and regeneration, it may control morphostasis during the aging process. A disruption of cellular information processing capabilities may lead to a drift in morphospace, either by reducing the capacity of cells to follow the bioelectrical pattern (or by being not able to maintain the appropriate V_{mem}) or by directly corrupting the bioelectrical pattern in charge of the morphostasis. Both ways result in aging or in other words a drifting in morphospace.

We emphasize that the above represent testable hypotheses suggested by existing literature. The causal relationship between bioelectrics and aging remains to be functionally demonstrated. In addition to investigating the mechanistic links between ion channel dysfunction and aging, it is crucial to explore the changes in bioelectric prepatterns during aging, in a wide range of tissues and organisms of diverse lifespan and healthspan. Furthermore, it is important to study the aging process in species such as planaria, which are apparently immortal, to gain insights into their remarkable regenerative capacity, cancer resistance, and lack of aging. The strong tissue-level morphogenetic control mechanisms in these species may be linked to the control of bioelectric patterns.

4. Broader implications: homologies between development, aging, cancer and regeneration

4.1. Same facets of the same problem: from anatomical homeostasis to morphological homeorhesis

Development and regeneration are both error-minimization schemes working towards reaching a target morphology. The concept of anatomical homeostasis during regenerative repair can be extended to the broader concept of morphological homeorhesis, in which developmental progression is a collection of regenerative repairs Pezzulo and Levin (2016). This concept suggests that each stage of development is essentially a "birth defect" from the viewpoint of the subsequent stage, and is repaired by a process of regulative development that minimizes system-level stress and moves toward a desired target morphology dictated by the bioelectric pattern Levin (2023b). Thus, development can be viewed as a collection of regenerative repairs towards an evolving target morphology Pezzulo and Levin (2016). This perspective is consistent with the data showing that bioelectric prepatterns precede and control subsequent transcriptional and anatomical changes Vandenberg et al. (2011); Pai et al. (2015), (2012): the bioelectric target pattern changes more quickly than the transcriptional and anatomical patterns, which are pulled along by error-minimizing loops that operating on metrics larger than individual cell stress states Yates (1994). As development progresses, maturation and adulthood occur when the bioelectric and biochemical prepatterns stop changing, and the anatomy catches up. From this point on, in the absence of injury or pathology, any subsequent changes are small-scale maintenance to preserve the already-achieved target anatomy, or in other words, morphostasis. The electric face Adams et al. (2016); Vandenberg et al. (2011) and the brain prepattern Pai et al. (2015) are specific examples of such an instructive prepatterns.

In this view, aging and cancer are both morphostasis defects, failures to maintain the target anatomy and function during adulthood and following morphological homeorhesis, they are both regenerative/developmental defects. Morphostasis is a key aspect of development, regeneration, and cancer suppression. Tissues regenerate, cells are replaced, molecules turn over rapidly, but the body/anatomy stays the same during the healthspan. Morphostasis may be seen as smaller-scale

anatomy changes compared to regeneration (of limbs for example) and development and as such it corresponds to smaller deviations from the trajectory in morphospace (see Fig. 8).

This viewpoint provides a research trajectory to investigate aging. If aging is a morphostasis defect, a developmental/regenerative defect like cancer and lack of regenerative ability, then the model systems, concepts, and approaches of regenerative biology should play a central role in the fight against aging. How can we capitalize on existing normalization Mintz and Illmensee (1975); Astigiano et al. (2005); Hendrix et al. (2007) and regenerative pathways Tsonis (1983); Tsonis and Eguchi (1981) to improve their efficacy over the lifespan?

4.2. Bioelectric signaling, regeneration and cancer resistance

4.2.1. Tumors as a morphostasis defect

The concept that cancer is a morphostasis/developmental defect has been around for a long time Soto and Sonnenschein (2011), (2005); Potter (2007); Rubin (1985); Moore et al. (2017); Levin (2021b). Needham and Waddington proposed the idea that tumors are a result of cells breaking free from the constraints of the morphogenetic field Needham (1936); Waddington (1935). According to this perspective, cancer develops when cells no longer follow the normal patterns of the body, leading to an "inexorable process in which the organism falls behind in its ceaseless effort to maintain order" Rubin (1985). This view emphasizes the role of the environment in shaping cell behavior and has gained renewed attention as an alternative to the mainstream gene-centric paradigm, which sees irreversible changes in DNA sequence or gene expression profiles as the driving force behind cancer stem cells. While some focus on the microenvironment Costa et al. (2009); Bissell and Hines (2011); Maffini et al. (2005), others have focused on long-range order on the scale of the entire organism Chernet and Levin (2014); Burr (1940).

An escape from the morphogenetic field can also be conceptualized as a shift in the scale of the target states maintained by the body components. The functional setpoints (specific regions of physiological or anatomical state space which cellular collectives normally work to occupy) can drop from the scale of an entire organ to that of a single cell (from complex anatomical setpoints to modest cell-level states); this loss of the collective computation of cell networks has been suggested to be an important part of the loss of homeodynamic cohesion seen in cancer (reviewed in Levin 2021b). From this point of view, the cells in a tissue cease working to minimize current distance from global (morphological and system-level physiological) setpoints and shift back to a smaller, more evolutionarily-ancient computational horizon limited to single cell goal Davies and Lineweaver (2011). This results in cells reverting to their primitive unicellular behavior and regarding the surrounding tissues as an external environment Levin (2021b); Rubin (1985); Davies and Lineweaver (2011). According to this perspective, cancer is caused by a disruption in the computational mechanism that usually coordinates cells cooperatively to work towards achieving organ-level morphogenetic objectives Levin (2019). This dysregulation of the "computational glue" that binds individual cells to a common navigation policy in anatomical morphospace Levin (2023a) can lead to uncontrolled growth and spread of abnormal cells, which is characteristic of cancer. Accumulating evidence suggests that bioelectric signaling is a key component of this cooperative computational mechanism Levin (2021b).

For many years, it has been known that tumors exhibit abnormal electrical properties, such as depolarized bioelectric signatures and disrupted electrical connectivity Aasen et al. (2003); Chernet and Levin (2013); Loch-Caruso et al. (1985); Trosko et al. (1982) (see Fig. 5), along with excessive sodium accumulation compared to normal tissue Quicke et al. (2022); Leslie et al. (2019); Jansson (1986). Tumorigenesis can start with the disconnection of cells from the larger morphogenetic network of the body Kandouz and Batist (2010); Moore et al. (2017). As noted above, cancer has been described by some researchers as a sub-type of channelopathy called onco-channelopathies Prevarskaya et al. (2018); Brackenbury (2012); Djamgoz et al. (2014). However, genetic changes are not required to induce abnormal bioelectric states: channel regulation is highly dynamic and can be altered by a range of physiological events that open or close channels post-translationally Mesnil et al. (1995).

In this view, cancer is not a special case of disease caused by accumulation of genetic damage similar to aging in the software design flaw theory de Magalhães (2023) but rather a bioelectric signaling disorder that extracts cells from the instructive morphogenetic field of the body. The comparison of tumors to wounds that fail to heal supports this idea that tumors are areas of disorganized cell growth lacking a proper goal

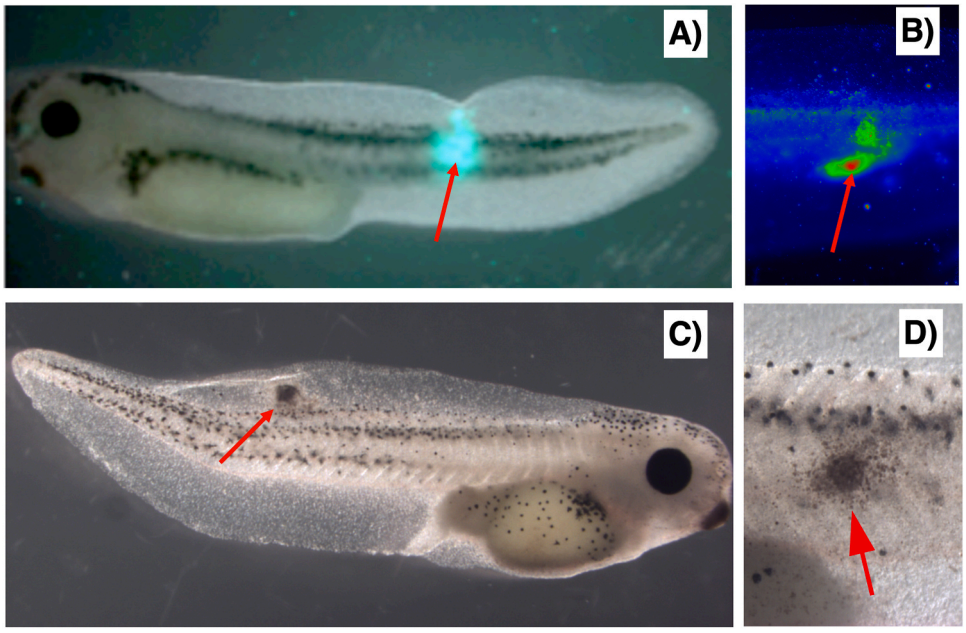

Fig. 5. Abnormal electrical signatures of tumors. **(A-B)** Depolarization of cancer cells can be observed in tadpoles using voltage-sensitive fluorescent dyes. **(C-D)** They reveal the locations of tumors. Figure used with permission from Levin (2021b).

state for patterning Pierce and Speers (1988); Riss et al. (2006) or a default morphogenetic field. This concept is also supported by molecular profiling studies that have shown similarities between the molecular signatures of tissue repair and carcinoma in the kidneys Riss et al. (2006).

4.2.2. Normalization of tumors during regeneration: the morphogenetic field as a suppressor of morphostasis defects

The hypothesis that cancer arises at the level of multicellular organization as a disruption of the morphogenetic field of the body is supported by experimental data. For instance, cells in a dispersed monolayer culture are much more susceptible to chemical carcinogenesis compared to organized tissues in vivo Parodi and Brambilla (1977). The development of tumors is not commonly seen in salamander species with high regenerative capabilities such as newts and axolotls, as reported by various studies Tsonis (1983). While exposure to carcinogens may lead to the formation of tumors in such species, it occurs only at high doses and over extended periods of time. When tumors do occur, they are normalized during the regenerative process Tsonis (1983); Tsonis and Eguchi (1981).

Studies have also shown that regenerating tissues, like limbs, are particularly resistant to the development of tumors Tsonis (1983); Tsonis and Eguchi (1981). In fact, malignant growths in these areas often regress, become incorporated into the regenerating tissue, or lead to the formation of duplicate body parts, rather than persisting as tumors in the regenerated structure. This is surprising as the process of regeneration shares many similarities with tumor development, including decreased activity of tumor suppressor genes (e.g., p53) Yun et al. (2013), (2014), increased activity of oncogenes (e.g., c-myc) Maki et al. (2009), and increased cell proliferation SubiranAdrados et al. (2021). Similarly, newt regeneration blastemas exposed to carcinogenic chemicals or ultraviolet radiation produce ectopic, but normal limbs or lenses, rather than tumors Breedis (1952); Butler and Blum (1955). Similarly, in the mammalian liver, one of the most regenerative tissues in mammals Enomoto and Farber (1982); Tatematsu et al. (1983), regeneration has been observed to counteract cancer. Early nodules induced by carcinogens were transformed into normal liver tissue Vogelstein and Kinzler (1993). Quantitatively, in carcinogen-induced tumors, more than 95% of these tumors were transformed into normal tissue by the liver Enomoto and Farber (1982); Tatematsu et al. (1983).

This demonstrates that in actively patterning tissues, regeneration can suppress tumorigenesis, suggesting that the induction of cancer and large-scale patterning disorganization are two points on a single axis. These findings support the notion that cancer is a result of the breakdown of multicellular organization, highlighting the importance of understanding the interactions between cells and their environment. These findings have ramifications at the bioelectrical level that are borne out in experimental findings. Injection of a hyperpolarizing ion channel significantly reduces tumor formation, even in the presence of potent human oncogenes such as Xrel3 or KRAS Chernet and Levin (2014); Chernet et al. (2016). Similarly, a recent study by Mathews et al. demonstrated that ion-channel drugs can inhibit the cancer phenotype in glioblastoma cell lines Mathews et al. (2022); Fukushiro-Lopes et al. (2020); Capatina et al. (2020); Frede et al. (2013).

Therefore, the morphogenetic field can be manipulated by bioelectricity and it disconnection can lead to cancer or normalization of tumorigenesis. This opens new avenues for aging viewed as a morphostasis defect as cancer.

4.3. Bioelectricity, regeneration and longevity: the morphogenetic field as a regulator of morphostasis?

4.3.1. Regeneration and longevity are intrinsically linked

Given the connections between large-scale anatomical order in regeneration, and its small-scale counterpart in cancer suppression and aging, it is interesting to consider animal model systems with increased regenerative abilities and/or long lifespans. Several organisms, including salamanders, the naked mole rat and the Brand's bat (Myotis brandtii), show high longevity associated with high regenerative/morphostatic capabilities Cayuela et al. (2019); Ruby et al. (2018); Seim et al. (2013).

The urodele species do not exhibit the typical signs of deterioration associated with aging in mammals and are therefore considered to have negligible senescence Cayuela et al. (2019); Finch (1994); Yun (2021). One of the key characteristics of salamander regeneration is its robustness. The regenerative ability does not deteriorate over time and is not affected by frequent regeneration events Yun (2015). A study by Eguchi et al. tracked the process of lens regeneration in Japanese newts over a period of 16 years, during which the lens was removed and regenerated 18 times Eguchi et al. (2011). The resulting lenses were found to be structurally identical to the original ones and expressed similar levels of lens-specific genes, indicating that the regenerative capacity of the newts remained unchanged. Additionally, the study found that the transcriptomes of young and old (19-times regenerated) lenses were nearly identical, demonstrating the robustness of newt lens regeneration Sousounis et al. (2015). The specimens used in the study were at least 30 years old, an advanced age for this species, further highlighting the exceptional regenerative abilities of salamanders.

As a salamander grows older, various changes occur in its tissues; however these do not affect regenerative potential, nor are they recognizable as signs of aging. These changes have been documented in the axolotl, and include an increase in overall size, a gradual replacement of cartilage in the skeleton with bone, a decrease in mobility, and a thickening of the dermal layer Vieira et al. (2020). It is important to note that the changes observed in axolotls as they age are probably specific to the species and the natural development of the organism, rather than being solely a result of aging. For instance, the growth in size is a feature that is specific to the axolotl, and is likely outcome of the organism's maturation process rather than aging itself. Additionally, species of salamanders that do not grow much as adults, such as *Notophthalmus viridescens*, do not exhibit a decline in their ability to regenerate as they age, thus continued growth is not required for maintained regenerative capacity. While an aging-related decrease in fertility has been reported in axolotls, this was based on anecdotal evidence and has not been observed in other salamander species or in other amphibian species Jones et al. (2014).

In addition to their impressive regenerative capabilities, salamanders also possess exceptional longevity, living much longer than other animals of similar size Sousounis et al. (2014). Salamanders break the rule of larger animals living longer, as they have a lifespan that is much longer than other animals of similar size. For example, axolotls, which have an average mass of 60–110 g, live over 20 years Warburg (2007), while P. walt newts, with an average mass of 25 g, live up to 20 years in the wild Warburg (2007). Japanese newts with an average mass of 8 g have a lifespan of 25 years Sousounis et al. (2015), while spotted salamanders with an average mass of 13 g can reach 30 years of age Voituron et al. (2011). Cave olms, with an average mass of 17 g, are the more extreme outlier, and can live more than 100 years Tacutu et al. (2018). These exceptional lifespans, despite their small size, makes salamanders outliers (see Fig. 6) and interesting subjects for studying aging and longevity. They match and in some cases exceed the longevity quotient found in other well-known outliers such as the naked mole rat Ruby et al. (2018) and Brandt's bat Seim et al. (2013). For a review on the links between the salamander and aging, we suggest Yun (2021).

However, despite the urodele's unflagging capacity for regeneration and their marked longevity, they do age. Other species, like the planaria and the jellyfish *Turritopsis dohrnii*, seem to be immortal Sahu et al. (2017); Lisenkova et al. (2017).

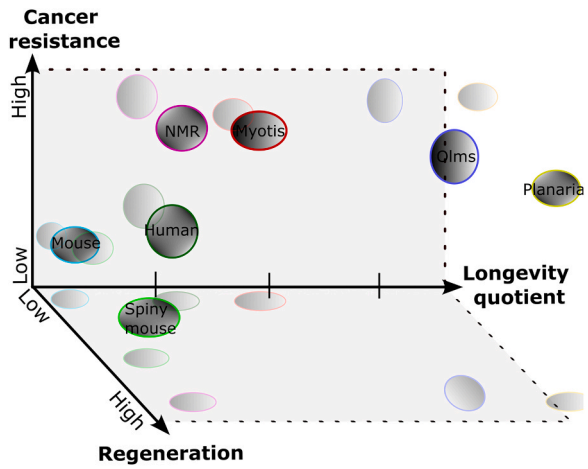

Fig. 6. Graph representing several organisms according to their lifespan, cancer resistance and regenerative capacities. The organisms with high regenerative capabilities form a cluster with long lifespan. Planaria is a complete outlier as it is immortal. Longevity quotients have been retrieved from Wilkinson and Adams (2019); Hulbert et al. (2007); Austad (2022). NMR stands for naked mole-rat, Myotis for *Myotis brandtii*.

4.3.2. The case of immortal species: the role of bioelectrical signaling in the remarkable features of planaria - regeneration, resistance to cancer, and immortality

Planarians are the kings of regeneration. This organism can be cut into at least 279 fragments and will regenerate as 279 identical worms Morgan (1898). Planarians not only exhibit remarkable regenerative abilities, but they also appear to be able to indefinitely avoid aging Cebrià et al. (2018); Sahu et al. (2017). Interestingly, because planaria often reproduce by fission, any mutation that does not kill the stem cell is carried into the next generation and expanded. These animals are therefore for some of them mixoploid chimeras (not every cell has the same chromosome number) with very messy genomes Levin et al. (2019a). Despite accumulating a high percentage of genetic changes, including large numbers of mutations, planarians can regenerate with 100% anatomical fidelity. Mutations have been found in protein-coding genes, including amino acid substitutions and non-synonymous SNPs, both within and outside gene-coding regions. Planaria can accumulate up to 74% mutations in protein-coding genes Nishimura et al. (2015) Furthermore, the genome of the planarian *Schmidtea mediterranea* appears to lack many essential genes, including components of core pathways for cell division, DNA repair, and metabolism Grohme et al. (2018). However, planarians can regenerate perfect anatomical structures each time under normal conditions, despite their messy genomes. How can these animals maintain accurate morphological control and escape aging despite their disorganized genomes and the accumulation of somatic mutations over hundreds of millions of years? It has been suggested Shreesha and Levin (2023) that this is due to an evolutionary ratchet that progressively emphasizes the capacity to create a normal animal despite hardware defects at the molecular level. Part of that algorithm may be the bioelectrical control system and the error-correcting codes that it implements in cellular collectives Fields and Levin (2019); Durant et al. (2016).

During the regeneration process in planaria, bioelectric gradients can be observed in fragments using fluorescent voltage reporter dyes, as reported by several studies Adams and Levin (2012a),b); Oviedo et al. (2008). By manipulating the ion conductances responsible for these gradients through pharmacological or RNAi methods, researchers can induce predictable changes in the anatomical structure of the regenerated planaria, resulting in forms with two heads or no heads that are still viable Beane et al. (2011). This works because the bioelectric pattern is natively used by cells to store the large-scale target morphology information about the number of heads Pezzulo et al. (2021); Durant et al. (2017); moreover, it also stores information about the shape of the heads. Specific manipulation can force a genetically wild-type worm to make head and brain shapes belonging to other species of flatworm 100–150 million years in evolutionary distance Sullivan et al. (2016); Emmons-Bell et al. (2015). The anatomical setpoint for the regenerative process is stored bioelectrically and is a true memory because it persists. Two-headed animals that are re-cut in plain water continue to demonstrate the 2-headed phenotype in perpetuity Oviedo et al. (2010).

Studies of the bioelectric prepatterns that keep information necessary for large-scale order in vivo are a primary target for aging research, as are the mechanisms that enable cells to detect deviation from those patterns, and mechanisms that enable cells to implement the changes needed to reduce error with respect to their states and the anatomical goal.

5. Towards morphoceuticals for aging

Most molecular medicine currently approaches treatment of diseases by targeting the underlying biological hardware and attempting to push it into the desired biochemical state. This is typically done by making changes at the genetic level or by targeting specific protein activities - in other words, using a bottom-up approach. However, the anatomical homeostatic perspective we emphasize in this article suggests that it may be possible to achieve therapeutic outcomes by working top-down: rewriting the anatomical target or setpoint without altering the underlying morphogenetic machinery Mathews et al. (2023). This approach is analogous to the seismic shift that occurred in information technology in the 1950's and 60's, where the focus moved from hardware-based control to controls that exploit the reprogrammability of software and modular, top-down control. We suspect that learning to control complex morphogenesis top-down, without making individual molecular changes, can be similarly transformative for biomedicine Pio-Lopez and Levin (2023) with targets ranging from the learning abilities Csermely et al. (2020); Biswas et al. (2023); Watson et al. (2010) and novel problem-solving capacities of gene-regulatory networks and pathways, to bioelectric large-scale circuits that coordinate configurations in anatomical space Levin (2023a). Improving the ability of cellular collectives to work towards the correct target morphology at all scales, rather than trying to control a potentially very large set of molecular states, could represent a much more efficient way to achieve true shifts toward health that are maintained long after the intervention is removed.

Inspired by this perspective, a novel class of therapeutics called morphoceuticals has been developed to leverage the error-correcting capabilities of tissues rather than micromanaging molecular-level pathways Pio-Lopez and Levin (2023). These compounds are designed to target the high-level morphogenetic control machinery, and can be repurposed from existing drugs or can be newly discovered ones. The unique feature of morphoceuticals is that they aim to target computational mechanisms that assess and modify growth and form Pezzulo and Levin (2015), (2016). Morphoceuticals are designed on top-down control mechanisms Pezzulo and Levin (2016), 2015 and can be discovered through computational Churchill et al. (2019); Pio-Lopez and Levin (2023), pharmacological Sullivan and Levin (2016), (2018) or genetic screening George et al. (2019); Perathoner et al. (2014).

The concept of top-down control of biological modules and the allostatic capabilities of living systems Davies and Levin (2023) suggests that it may not be necessary to micromanage dosage and timing to address the defects that result in aging and cancer. Recent examples of inducing organ and appendage regeneration in vertebrate models have demonstrated that organ type, composition, shape, and size can be induced without precise timing or dosage regimes Durant et al. (2019); Murugan et al. (2022). This approach leverages the organism's modular, regulative control structure to achieve complex outcomes without knowing the molecular details.

Morphoceuticals have significant potential for addressing aging. Pai

et al. demonstrated that the brain developmental defects resulting from the mutation of neurogenesis genes, such as Notch, can be rescued by activating or misexpressing HCN2 (hyperpolarization-activated cyclic nucleotide-gated) channels Pai et al. (2015). HCN2 channels are voltage-regulated ion channels that enhance contrast, sharpening the differences in membrane voltage potential (V_{mem}) across compartment boundaries. They are context-sensitive and increase hyperpolarization in slightly polarized cells, but have no effect on depolarized cells. This makes them effective "contrast enhancers" that emphasize order in a fuzzy image, similar to how a Sharpen filter functions.

A computational model of the endogenous bioelectrical circuit that establishes the bioelectrical prepattern of the brain was developed by Pai et al Pai et al. (2018). This model employed HCN2 channels to reinforce voltage potential differences, which mark the boundaries of the developing brain. The model predicted that drugs that mimic the effect of HCN2 overexpression can rescue brain teratogenesis by repairing local and long-range bioelectric signals. This was tested experimentally using lamotrigine and gabapentin, which are approved for other human indications. Both drugs were found to rescue teratogen-induced defects in *Xenopus* embryos Pai et al. (2020); Pai and Levin (2022); Pai et al. (2020). This approach relies on an inherent modularity of morphogenesis and the computational capacity of tissues to use resident bioelectrical pattern as triggers and respond with complex modules containing transcriptional and biomechanical implementation machinery. These capabilities move cells towards the appropriate morphological target, without individual manipulation of gene levels, stem cell behavior, and localization. This methodology holds potential for repairing complex organ defects by systemic application of repurposed channel activators or blockers. Similarly, if, as we propose here, aging corresponds to a corruption of the bioelectrical pattern over time (see Fig. 8), this approach may correct it, helping the cell regenerate and counteracting the effects of aging on the bioelectrical pattern and subsequently on the body maintenance.

Many questions on the bioelectricity of aging remain to be solved; thus, the development of aging morphoceuticals will necessitate an iterative back and forth between computational modelling and experimentation. To identify potential targets for intervention in a specific tissue, transcriptomic databases such as EDEn Churchill et al. (2019) can be utilized (see Fig. 7). The next generation of aging morphoceuticals will require the development of tools that can extract relevant information on ion channels. Dynamic computational modeling will also play a crucial role in predicting the bioelectrical pattern resulting from opening or closing specific targeted channels with existing drugs. The predicted results can then be used to suggest specific in vivo experiments to assess specific morphoceutical potential for regeneration, repair or aging normalization.

A key question for the biomedical applications of morphoceuticals for aging is how the bioelectrical pattern is corrupted over time and if an enhancement/repair of it will lead to proper maintenance or rejuvenation. While the study of endogenous bioelectric patterns (i.e., physiomic profiling) is important for specific regenerative therapeutics, especially given the increased availability of machine learning and data mining tools Pio-Lopez and Levin (2023), a true anti-aging solution requires something different. A definitive aging intervention will not seek to micromanage specific bioelectric prepatterns, any more than it will try to enforce specific transcriptional profiles; rather, it will help cells maintain all of the multitude of required patterns and implement them despite the turnover of cells and materials over the organismal lifespan.

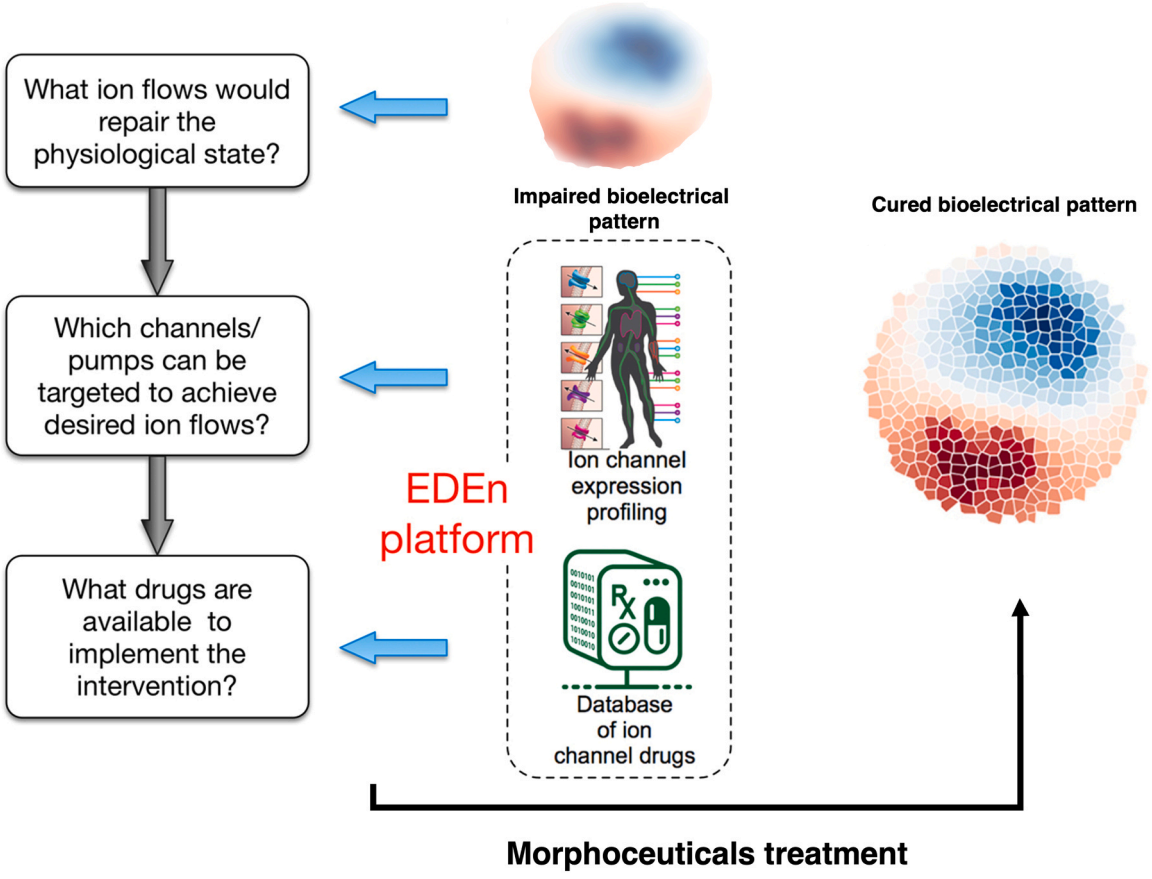

Fig. 7. Morphoceuticals discovery for aging. One possible approach to altering the bioelectrical patterns associated with diseases involves utilizing transcriptomic databases to identify potential ion channel targets within a particular tissue. This information can then be utilized as an input into a bioelectrical model to simulate the resulting bioelectrical pattern after intervention, which can be further analyzed to determine candidate drugs capable of moving the current bioelectrical state towards the desired pattern. Fig. reproduced and adapted with permission from Churchill et al. (2019).

6. Conclusion and perspectives

Here we have reviewed existing links between bioelectricity and aging, discussing how both current life extension strategies and known molecular or clinical characteristics of age-related diseases have connections to bioelectric signaling. We highlighted unidirectional and bidirectional links between bioelectricity and the physiological and molecular hallmarks of aging and accumulated evidence that bioelectricity provides the "computational glue" that links individual cells into larger-scale morphogenetic fields, enabling the cooperative collective action needed to reach morphogenetic goals. This naturally suggests hypotheses about the nature of aging as increasing bioelectric dysregulation. Building on these, we proposed the hypothesis that aging, along with its attendant diseases and dysfunctions, is a defect of morphostasis/regeneration due to a loss of morphostatic information, caused by disruption or degradation of the bioelectric patterns that connect individual cells into large-scale morphogenetic fields. Finally, we introduced the concept of morphoceuticals and discussed their potential power for treating aging. Many key questions remain open, providing a roadmap for future discovery in the bioelectricity of aging.

The link between development and aging has been pointed out by various authors de Magalhães (2023); Gems (2022). Very recently, Lu et al. developed a pan-mammalian clock and found that specific and conserved CpG sites related to development processes undergo consistent changes in methylation levels with age, implying that aging is a pseudo-programmed process intricately linked with mammalian development. As they point out, specific epigenetic aging effects are consistent across various mammalian species, providing valuable insights into shared and conserved aging processes. While still in its infancy, the study of the developmental bioelectricity as the physiological software of life strongly complements today's focus on the molecular hardware, and should be a highly valuable avenue of research to advance the understanding and treatment of the aging phenotype.

The bioelectrical pattern may become blurred over time (Fig. 8) but there are other ways it may be degraded. A noisy bioelectrical pattern, like a pixelated image, may imply a depolarization of some clusters of cells, a disconnection of these cells with the morphogenetic field that could lead to cancer or progressive failure of maintenance of the body via an inappropriate information transmission. Of course, there are other possible large-scale modalities encoding information that may be important for resisting aging, including long-range biochemical, biomechanical, or even photonic patterns Chang et al. (2002); Ingber (2008); Volodyaev and Beloussov (2015).

We presented the links between bioelectricity and the hallmarks of aging (see Fig. 4). However, an open question remains as to whether the links can be bi-directional or not. In addition, the field of aging focused recently on the epigenetics markers of aging de Magalhães (2023); Yang et al. (2023a). It is still not clear what the links between the bioelectrical pattern and the epigenetics are and how they influence each other. Interestingly, recently Yang et al. showed that partial reprogramming could be induced via chemicals Yang et al. (2023b). Several of them are know to be ion channels regulators including valproic acid Zanatta et al. (2019); Chateauvieux et al. (2010), forskolin Hoshi et al. (1988), sodium butyrate Baines et al. (1992); Roy et al. (2006), or retinoic acid de Hoog et al. (2018); Sidell and Schlichter (1986) to name a few. Overall, is some quantitative aspect of bioelectricity an accurate marker of aging similarly to the epigenetic clock? In all cases, conventional hallmarks alone are not likely to solve the problem, without addressing the bioelectric layer that is a driver of morphological change. Some of these changes may in fact be adaptive or due to physiological compensation during aging and could include signatures of homeodynamic adjustments of the system attempting to resist aging. The currently-available correlational data suggest the need for functional experiments to determine which bioelectric changes during aging have health impacts, and what comes first, loss of bioelectrical morphostatic information or the hallmarks of aging (or, if it is a feedback loop, which of these nodes is the most tractable for interventions).

Bioelectricity as a control layer for anatomy may be a bioelectrical marker of aging. We hypothesize here that the bioelectrical pattern is corrupted over time (Fig. 8) but it could lead to a progressive accumulation of damage still compatible with anatomical homeostasis. However, is this accumulation of damage the cause of a corruption of the bioelectrical pattern or is the corruption of the bioelectrical pattern the cause of this deficit of maintenance of the anatomy? In other words, do the cells lose the ability to follow the bioelectrical pattern or is it the corruption of the bioelectrical pattern that reduces their capability to maintain the body? These are not mutually exclusive - for example the corruption of the bioelectrical pattern may be also a cell-level problem where the cell can't maintain the appropriate V_{mem} pattern.

The causality likely flows in both directions - we have several bidirectional links between the different hallmarks of aging and bioelectricity (see Fig. 4), and more may be found in the future. But maybe the corruption of the bioelectrical pattern is programmed as the programmatic theory of aging is stating it, or perhaps it is the accumulation of damage in cells that will impair it. The Planarian model system, given its immortality, cancer resistance, and regeneration, all despite somatic inheritance of mutations, is likely to be a critical part of the roadmap Levin et al. (2019a); Shreesha and Levin (2023); Oviedo and Beane (2009); Sahu et al. (2017).

While most of the above discussion focuses on cell-level bioelectric properties, it must be remembered that subcellular bioelectric states also exist, as well as compartmentation of ions inside cells Head et al. (2014); Martens et al. (2004); Dart (2010). This compartmentation can result from the integration of ions in vesicles Aw et al. (2008) or mitochondria, or due to the non-uniform distribution of the ion channels on the membrane, whether in lipid rafts Head et al. (2014); Martens et al. (2004); Dart (2010) or due to planar polarity Aw et al. (2008); Hermle et al. (2010). The golgi and other organelles Giulian and Diacumakos (1977), notably the nucleus Loewenstein and Kanno (1962); Mazzanti et al. (2001); Bustamante et al. (2000), (1995), (1994), possess their own voltage patterns distinct from that of the entire cell and its plasma membrane. Even microtubules have an electrical dimension which may allow them to perform computations and other biophysical functions Tuszynski et al. (2020); Kalra et al. (2020); Cantero et al. (2018); Friesen et al. (2015); Cifra et al. (2010). This allows ion-specific pathways to be tightly regulated and potentially allows ion populations to act directly on the DNA Dart (2010); Hermle et al. (2010) and second messenger cascades. Interestingly, this cellular bioelectrical pattern mediated by localized ion populations may act on a much faster timescale than the tissue-level bioelectrical pattern that needs time to be spatiotemporally integrated. This, and other effects on intracellular organelles and pathways related to repair, metabolism, and DNA damage response, could readily impact the many facets of aging Hermle et al. (2010). Overall, localized ion populations and resulting nano-scale voltage gradients could be interpreted as discrete signals providing a much richer, multiscale bioelectrical interface than event that afforded by the plasma membrane bioelectric potentials.

One other key question is whether aging morphoceuticals will simply allow better maintenance of existing tissues tissues (maintain status quo), or allow true rejuvenation. In other words, does the bioelectrical pattern represents the anatomy at age t once development is over, or will its enhancement/repair will allow a rejuvenation of the body or 'reverse' development Schmich et al. (2003)? The details of the relationship between bioelectricity and aging are currently unknown and represent an exciting avenue for investigation using existing and emerging tools. We think it likely that bioelectricity - the signaling layer that mediates global order in embryogenesis and large-scale repair - offers a clinically impactful roadmap for addressing the progressive deterioration of target morphology we call aging.

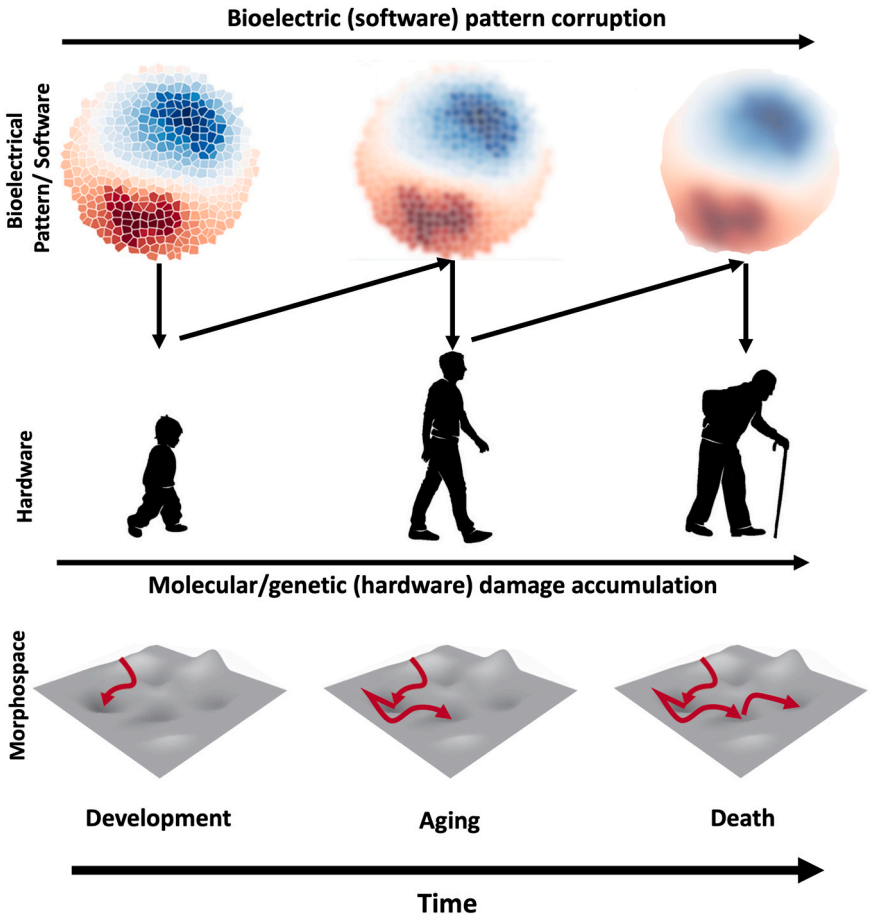

Fig. 8. Aging as a drift in morphospace. By accumulation of molecular and cell damage, the bioelectrical pattern in charge of the maintenance of the anatomy is corrupted over time or the cell gradually loses the ability to follow the bioelectrical pattern, resulting in a gradual loss of anatomical homeostasis leading to aging and ultimately death.

Declaration of Competing Interest

M.L. is a scientfic co-founder of Morphoceuticals Inc., which does research in the field of bioelectrically induced organ regeneration. M.L. is also a scientific co-founder of Astonishing Labs, which does research in the field of aging.

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