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TOPICAL REVIEW

Endogenous bioelectrical networks store non-genetic patterning information during development and regeneration

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Abstract Pattern formation, as occurs during embryogenesis or regeneration, is the crucial link between genotype and the functions upon which selection operates. Even cancer and aging can be seen as challenges to the continuous physiological processes that orchestrate individual cell activities toward the anatomical needs of an organism. Thus, the origin and maintenance of complex biological shape is a fundamental question for cell, developmental, and evolutionary biology, as well as for biomedicine. It has long been recognized that slow bioelectrical gradients can control cell behaviors and morphogenesis. Here, I review recent molecular data that implicate endogenous spatio-temporal patterns of resting potentials among non-excitable cells as instructive cues in embryogenesis, regeneration, and cancer. Functional data have implicated gradients of resting potential in processes such as limb regeneration, eye induction, craniofacial patterning, and head-tail polarity, as well as in metastatic transformation and tumorigenesis. The genome is tightly linked to bioelectric signaling, via ion channel proteins that shape the gradients, downstream genes whose transcription is regulated by voltage, and transduction machinery that converts changes in bioelectric state to second-messenger cascades. However, the data clearly indicate that bioelectric signaling is an autonomous layer of control not reducible to a biochemical or genetic account of cell state. The real-time dynamics of bioelectric communication among cells are not fully captured by transcriptomic or proteomic analyses, and the necessary-and-sufficient triggers for specific changes in growth and form can be physiological states, while the underlying gene loci are free to diverge. The next steps in this exciting new field include the development of novel conceptual tools for understanding the anatomical semantics encoded in non-neural bioelectrical networks, and of improved biophysical tools for reading and writing electrical state information into somatic tissues. Cracking the bioelectric code will have transformative implications for developmental biology, regenerative medicine, and synthetic bioengineering.

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Embryogenesis enables genomes embedded in a single fertilized egg cell to produce the highly complex functional anatomies upon which selection operates. Thus, molecular insight into the dynamics by which biological pattern arises is fundamental to understanding the evolutionary process. Importantly, the processes of pattern formation extend beyond embryonic development. Regeneration, such as the complete restoration of amputated limbs, eyes and other organs in salamanders, or of the liver in mammals, plays a major role in shaping adaptive

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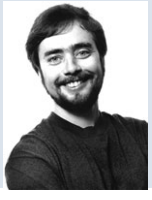

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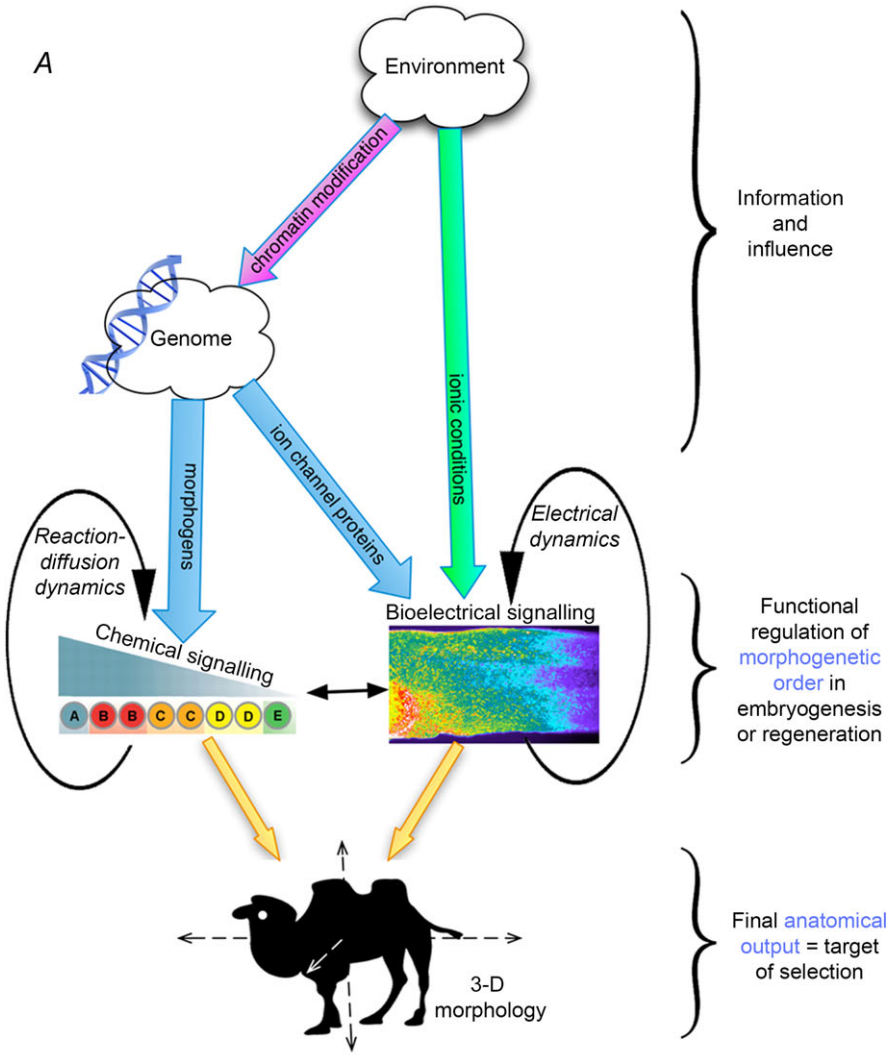
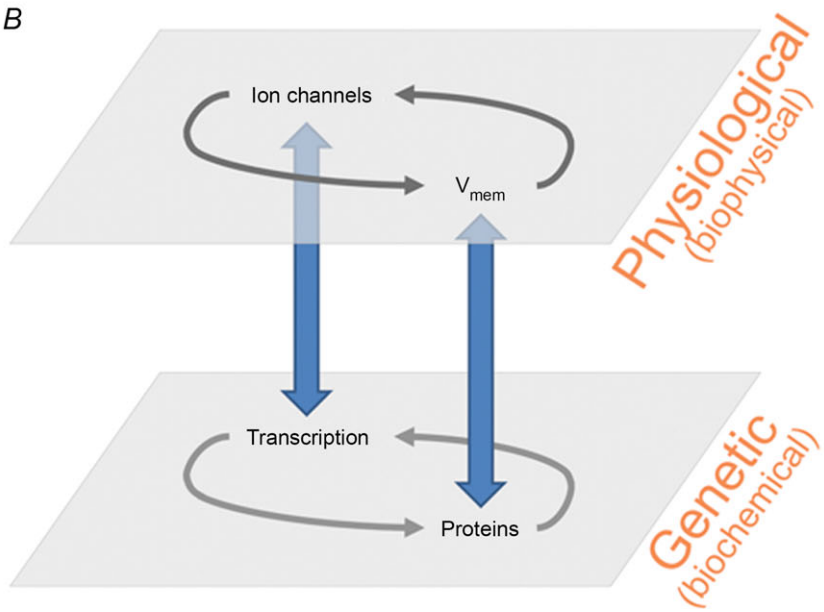
responses to injury (Sánchez Alvarado, 2000; Birnbaum & Sánchez Alvarado, 2008). This process requires animal bodies to be able to re-create specific anatomical structures during adulthood. Lastly, carcinogenesis can be seen as cellular defections from the correct target morphology – an inability of the normal field of patterning information to orchestrate individual cells' activities toward the evolutionary success of the body as a whole (Rubin, 1985; Tsonis, 1987; Dean, 1998). Thus, the instructive influences that establish, maintain, and correct large-scale pattern are of central importance to the evolutionary dynamics among organisms, to the tensions between the goals of cells and their hosts, and to the strategies of biomedicine (Levin, 2011, 2012*b*). Here, I briefly review exciting new data in developmental bioelectricity, and argue three main points. First, that bioelectric networks among all cells are an autonomous layer of instructive information that regulates complex pattern formation. Second, that the current gene-centric paradigm needs to be expanded with conceptual tools and new physiomic data, to fully understand the control of anatomy by bioelectricity and the evolutionary implications of its top-down causal efficacy. Third, that transformative changes in biomedicine and synthetic bioengineering will result from the functional taming of the unique properties of bioelectrical signalling.

The field of patterning information impinging on cells is most often thought of as mediated by chemical gradients. The mainstream emphasis is on these secreted signals (Niehrs, 2010; Ben-Zvi *et al.* 2011), the gene regulatory networks that couple to them (Huang *et al.* 2005; Geard & Willadsen, 2009; Gershenson, 2012), and mechanical forces (Beloussov & Grabovsky, 2006; Beloussov, 2008; Nelson, 2009; von Dassow & Davidson, 2011; Davidson, 2012), as the main drivers of patterning. However, this paradigm must now be expanded (Fig. 1*A*) to include a crucial new signalling modality that regulates cell behaviour and controls large-scale patterning of organisms: endogenous bioelectrical signalling (Levin, 2007, 2012*a*; Tseng & Levin, 2013). While it has been known for many decades that endogenous electric fields participate in embryogenesis and regeneration (Burr & Northrop, 1935; Lund, 1947; Jaffe & Nuccitelli, 1977; Nuccitelli *et al.* 1986; Borgens *et al.* 1989; Hotary & Robinson, 1992), recent data have revealed that gradients of resting potential across tissues provide instructive, functional cues that establish large-scale anatomical order (Robinson & Messerli, 1996; McCaig *et al.* 2005; Levin, 2013). The development of new molecular-level techniques has allowed a glimpse into the interplay of genetic and electrophysiological order, with many implications for evolutionary biology and biomedicine (Pullar, 2011; Levin, 2013; Tseng & Levin, 2013).

Bioelectricity refers to slowly changing ion flows emitted and sensed by all cell types (not rapid spiking in excitable cells nor external electromagnetic field exposure). I focus here not on the trans-epithelial electric fields known to regulate cell motility and wound healing (Shi & Borgens, 1995; McCaig *et al.* 2009; Zhao, 2009) or on nuclear envelope gradients (Mazzanti *et al.* 2001; Yamashita, 2011), but on V_{mem} (plasma membrane resting potential), which is now known to be much more than a housekeeping or permissive property. V_{mem} arises from the combined action of ion channels and ion pumps, as well as of gap junctions (GJs) – highly versatile aqueous connections between the cytoplasm of adjacent cells that allow voltage and current-mediated signals to be propagated and regionalized across cell groups. Cellular V_{mem} regulates cell-autonomous properties such as proliferation, differentiation and apoptosis (Blackiston *et al.* 2009; Sundelacruz *et al.* 2009; Aprea & Calegari, 2012), in mature somatic cells (Cone & Tongier, 1971; Stillwell *et al.* 1973) as well as stem cells (Stroh *et al.* 2011; Sundelacruz *et al.* 2013) and cancer cells (Yang & Brackenbury, 2013). Moreover, spatio-temporal patterns of differential V_{mem} levels across the body are now known to be instructive cues during embryogenesis, regeneration and cancer (Adams, 2008; Levin, 2012*a*; Tseng & Levin, 2013).

Modern tools include reagents such as fluorescent voltage-sensitive dyes (Adams & Levin, 2012*a*,*b*) and other sensor technologies (Reid *et al.* 2007; Tyner *et al.* 2007), and functional strategies using mis-expression, or pharmacological modulation, of specific ion translocator proteins to achieve predictable changes in cells' V_{mem} levels (Adams & Levin, 2006, 2013). Using such combinations of V_{mem} monitoring and selective depolarization and hyperpolarization, V_{mem} gradients have been shown to control left–right asymmetry (Levin *et al.* 2002; Adams *et al.* 2006; Bessodes *et al.* 2012), craniofacial morphogenesis (Bendahhou *et al.* 2003; Vandenberg *et al.* 2011), appendage regeneration (Adams *et al.* 2007; Tseng *et al.* 2010), head–tail polarity (Beane *et al.* 2011, 2013), size of regenerating appendages (Perathoner *et al.* 2014), and eye induction (Pai *et al.* 2012). Importantly, mechanistic links have now been forged between bioelectric controls and canonical biochemical pathways, as elegant genetic experiments revealed how ion flows couple to mainstream signalling pathways such as inositol-phospholipids (Zhao *et al.* 2006), Notch (Raya *et al.* 2004; Adams *et al.* 2007), and Bone Morphogenetic Protein (BMP) (Dahal *et al.* 2012). Recent data have also identified a number of mechanisms by which voltage changes are transduced into downstream transcriptional and epigenetic responses. V_{mem} gradients signal through the butyrate (Miyauchi *et al.* 2004; Chernet & Levin, 2013) and serotonin (Fukumoto *et al.* 2005; Blackiston *et al.* 2011) transporters, as well as voltage-sensitive phosphatases (Murata *et al.* 2005; Okamura & Dixon, 2011) and calcium channels (Holliday & Spitzer, 1990; Stewart *et al.* 1995; Chopra *et al.* 2010;





Pai *et al.* 2012), to regulate transcription (Langlois & Martyniuk, 2013) and epigenetic marking (He *et al.* 2011; Tseng & Levin, 2012) of downstream targets.

By tracing the causal flow from the voltage change through the transduction machinery and down to the mRNA targets, numerous studies have now mechanistically linked ionic signalling with mainstream genetics. However, the most salient and unique aspects of bioelectric networks still remain to be integrated into the models and workflow of studies in this field. Counter to the prevalent idea that master regulators must be specific transcription factor proteins, the information-bearing signal (the necessary and sufficient trigger) for events such as eye induction, head determination, or tail regeneration via V_{mem} change is a *physiological state*, not a gene (Levin, 2013; Tseng & Levin, 2013). Studies reveal that the exact channel or pump used to trigger such morphological changes is often irrelevant – many sodium, potassium, chloride, or proton conductances can be used as long as the appropriate bioelectrical state is reached. This means that the cause of the given morphological change can be not a specific gene product (an ion channel protein) but rather a bioelectrical property not necessarily in 1:1 correspondence with a genetic locus (Fig. 1*B*). This is true not only for pattern formation, but also at the level of single cells: a recent breakthrough in somatic cell reprogramming showed that conversion to stem cell status was induced by both an acid bath and streptolysin O treatment (both of which can depolarize cells), in the absence of reprogramming transcriptional factors (Obokata *et al.* 2014).

Because channels and pumps are gated post-translationally, two cells expressing precisely the same mRNA and protein can be in extremely different bioelectrical states. A corollary is that rich patterns of bioelectrical gradients in a transcriptionally homogeneous tissue can be completely invisible to protein and mRNA profiling. Conversely, cells with very different channel and pump complements may have the same V_{mem}, since resting potential is an ensemble state (akin to the concept of 'pressure') that is a function of many different ion flows. The implication is that workhorse techniques of modern molecular developmental biology are insufficient to detect and characterize important biophysical determinants of morphogenesis.

Crucially, bioelectrical state can not only diverge from genetic information (Justet *et al.* 2013), but in a number of cases is dominant to it. One example is the guidance of cell motility: if a chemical gradient and an electric field are set up in opposite directions, the bioelectric vector trumps the chemical cue in directing cell movement (Zhao, 2009; Cao *et al.* 2011). Another example is the differentiation of human mesenchymal stem cells (hMSCs), which normally hyperpolarize as they differentiate; despite the presence of chemical inducers, hMSCs will not differentiate if kept artificially depolarized (Sundelacruz *et al.* 2008). The voltage state can even partially reverse the differentiation state, inducing plasticity in pre-differentiated hMSCs (Sundelacruz *et al.* 2013). A final example concerns cancer. It has recently been shown that a metastatic phenotype (overproliferation, matrix metalloprotease-dependent invasion of body tissues, and drastic arborization) can be imposed upon genetically normal melanocytes by depolarization (Blackiston *et al.* 2011; Lobikin *et al.* 2012). Conversely, the formation of tumours by human oncogenes such as p53 and KRAS mutations can be suppressed, despite the strong presence of oncogene protein within the cells, by artificially

Figure 1. Bioelectric networks regulate pattern formation
A, selection acts upon the products of patterning processes such as development and regeneration. Biological patterning is controlled by not only gradients of secreted chemical products of gene regulatory networks, but also by gradients of cellular resting potential in all tissues. These bioelectric signals regulate cellular behaviours such as proliferation, differentiation and migration, and also set large-scale anatomical properties such as organ identity, axial polarity and symmetry. Both chemical and electrical layers exhibit their own internal dynamics driven by the laws of chemistry and physics, in addition to inputs from the genome and the environment. Bioelectric gradients are a systems-level, physiological, epigenetic instructive influence that helps drive large-scale patterning during embryogenesis, regenerative repair and cancer suppression. *B*, bioelectrical signalling operates in parallel to the widely studied gene regulatory networks. Ion channel and gap junction proteins are both regulated by, and themselves determine, resting potential (V_{mem}), thus implementing feedback loops with complex non-linear behaviour and self-organization of patterns. Networks of gap-junctionally coupled cells with slow V_{mem} changes have the capability of storing and processing information (as do neural networks). Because ion channels, pumps and gap junctions are gated post-translationally, bioelectrical dynamics in somatic cells is an autonomous layer of control without 1:1 correspondence to underlying transcriptional or proteomic state (differences in bioelectric states across tissues are not uniquely determined by, nor necessarily detectable by, tools that monitor, mRNA or protein profiles). Anatomical states are the results of stable attractors in bioelectrical state space. Bioelectric networks couple to biochemical signalling because V_{mem} changes can affect transcription and epigenetic marking, while itself being sculpted by transcriptional control of ion translocator protein expression within tissues. Together, these events form a continuous dynamic interplay of genetic and physiological order during the formation and maintenance of complex anatomical pattern. (Two-layer diagram drawn by Jessica Mustard, Tufts University, Biology dept.)

preventing the depolarization that occurs during oncogenic transformation (Chernet & Levin, 2013). The latter two examples reveal the potential dissociation between genetic state and disease outcome; an implication of these data is that the neoplastic state cannot be predicted from examination of the genome, transcriptome, or proteome. On the other hand, the functionally determinative voltage states cannot be seen in fixed tissue, stressing the importance of gathering real-time *in vivo* bioelectric information over and above analysis of mutations, mRNA profiles and protein levels.

Bioelectric patterns are clearly important drivers of cell behaviour and pattern formation, but how do these patterns originate? Diverse resting potentials across a tissue can arise from pre-existing differences in ion channel transcription; but that is not the whole story. Such regionalized patterns of V_{mem} can also form *de novo*, in transcriptionally and proteomically identical cells, because cells coupled by gap junctions (electrical synapses) form a (slow) electrically excitable medium; this is a particularly interesting aspect because such media are known to have powerful computational capabilities (Fenton *et al.* 1999; Gorgcki & Gorgcka, 2007; Adamatzky *et al.* 2011). Positive feedback loops implemented by elements such as voltage-gated ion channels, which both set and respond to V_{mem} changes, can drive spontaneous symmetry breaking and amplification of physiological noise. Considerable self-organization dynamics can take place without needing any pre-existing chemical prepattern (Schiffmann, 1991, 1997; Palacios-Prado & Bukauskas, 2009). This has been studied in nerve and muscle (Zykov, 1990; Chen *et al.* 1997; Boettiger *et al.* 2009; Boettiger & Oster, 2009), and Turing-type self-organization has long been appreciated in chemical signalling (Takagi & Kaneko, 2005; Müller *et al.* 2012; Sheth *et al.* 2012). However, models of self-organization of voltage patterns in groups of non-neural cells remain to be formally analysed. Quantitative analysis of *in silico* models of bioelectric dynamics will need to be integrated with deep new datasets from appropriate physiomic technologies, to fully understand and control developmental patterning *in vivo*.

One unexpected recent finding illustrates the storage of patterning information in physiological networks, and has significant implications for evolutionary dynamics. Planarian flatworms have the remarkable ability to regenerate completely from partial body fragments (Reddien & Sánchez Alvarado, 2004; Saló *et al.* 2009; Lobo *et al.* 2012). They are complex creatures, with a true brain, bilateral symmetry, a complex behavioural repertoire, and many body organs (Sarnat & Netsky, 1985; Gentile *et al.* 2011). Their capacity for self-repair serves as a paradigm case of dynamic morphostasis and continuous remodelling towards a specific target morphology. After a surgical bisection, the cells at one edge make a tail, while those at the other edge make a head, revealing that the adult stem cells which implement regeneration are not locally controlled (since the cells were direct neighbours until the scalpel separated them) but must communicate with the remaining tissue to decide what anatomical structures must be formed. It was shown recently that this long-range communication occurs via GJ-mediated electrical synapses (Scemes *et al.* 2007; Marder, 2009; Pereda *et al.* 2013), and works together with a bioelectric circuit that determines head *vs.* tail identity in each end's blastema (Beane *et al.* 2011, 2013). Importantly, it was shown that inhibition of this gap junction-mediated communication, using octanol, results in worm fragments forming heads at both ends (Nogi & Levin, 2005; Oviedo *et al.* 2010).

After this transient pharmacological treatment is complete (2 days of soaking in octanol), the octanol is completely gone within 24 h (as shown by HPLC analysis of worm lysate). What is remarkable (Fig. 2) is that weeks later, when these 2-headed animals have their heads and tails amputated again (in pure water, with no further perturbation), the same 2-headed phenotype results, and this is repeated upon subsequent amputations. A transient perturbation of physiological cell:cell communication via gap junctions has stably changed the pattern to which the animal regenerates upon damage! While epigenetic processes may be involved, standard chromatin modification mechanisms alone are not a sufficient explanation for this, since the ectopic heads (tissue which might be suggested to have been epigenetically reprogrammed into a head state from its original tail identity) are thrown away at each generation of cutting. What remains is a normal gut fragment, which somehow knows that it is to form two heads, not one, upon further cutting; the information about basic anatomical polarity and body organization must be stored in a distributed form throughout the animal. The involvement of electrical synapses and the holographic-like nature of the information suggest models in which the target morphology is actually stored (encoded) within the real-time current dynamics, perhaps akin to storage of spatial memory in neural networks or similar proposed processes of memory in non-neural tissues (McConnell *et al.* 1959; Turner *et al.* 2002; Zoghi, 2004; Levin, 2011, 2012*b*; Baluška & Mancuso, 2013; Shomrat & Levin, 2013).

Although there are no data suggesting that this 2-head phenotype persists through sexual reproduction, it is in fact inherited across these animals' most frequent natural mode of reproduction: fission. One can imagine that if such an animal were to be released into the wild and survived, an observer some decades later would find two 'species' of planaria – one with two heads and one with one head, having very different overall anatomies and behaviour. Seeking a genomic basis for this speciation event, the biologist would sequence its genome, and (since

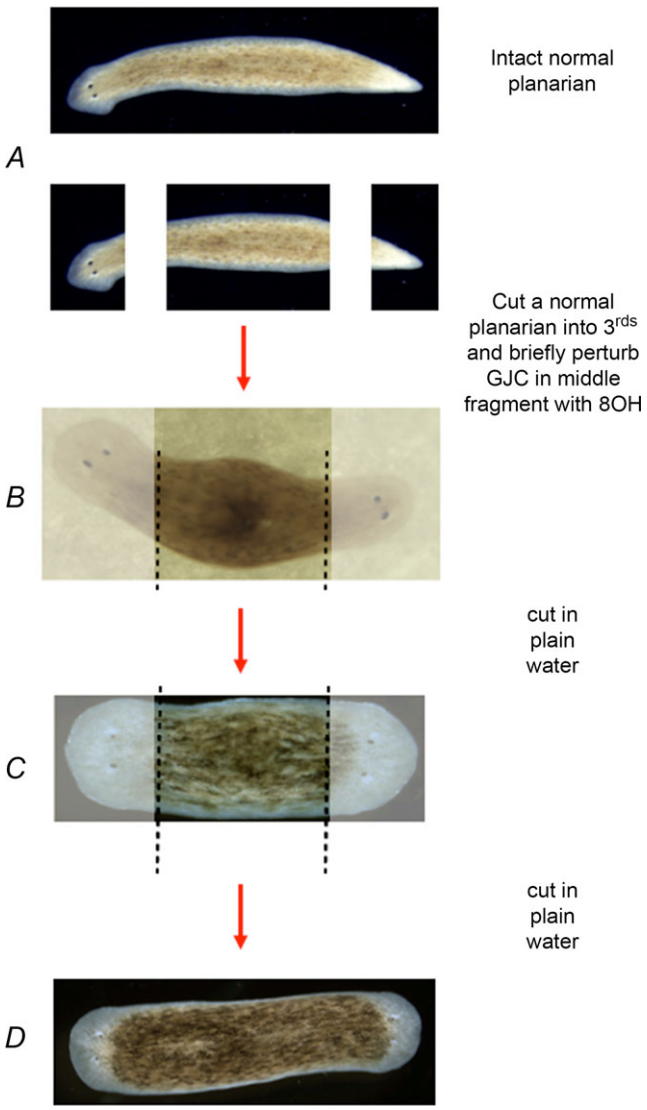


Figure 2. Stable inheritance of target morphology change after physiological perturbation
A normal planarian has a head and tail, and regenerates each at the appropriate end of an amputated fragment (*A*). When cut into thirds, and the middle fragment is briefly exposed to octanol, which temporarily blocks long-range bioelectrical signalling between the wound and mature tissues, a 2-headed worm results (*B*). GJC, gap-junctional communication. Remarkably, upon further rounds of cutting in plain water (long after the octanol has left the tissues, as confirmed by HPLC), the 2-headed form is recapitulated (*C* and *D*; images of 2-headed worms provided by Fallon Durant, Tufts University, Biology dept.). This change in the animal's target morphology (the shape to which it regenerates upon damage) appears to be permanent, and persists across the animal's normal reproductive mode (fissioning), despite the fact that the genomic sequence has not been altered. Chromatin modifications alone do not explain this, because the posterior wound cells, which could have been epigenetically reprogrammed to a head fate, are thrown away at each cut: the information encoding a bipolar 2-head animal is present even in the normal gut fragment – it is distributed throughout the body. We propose that this information is a kind of memory, encoded in electrical networks of somatic cells coupled by gap junctions, and is stored at the level of bioelectrical dynamics, not genetics.

octanol exposure was shown to not be genotoxic), would find no sequence differences accounting for this major change of body shape. The implications for evolutionary biology, and the role of physiological *vs.* genetic change in this process, are only beginning to be glimpsed and a number of open questions remain. First, it is not known whether the patterning change persists because of a permanent alteration of electrical connectivity (a stable change of gap-junctional states) as occurs in synaptic rewiring underlying learning in the CNS, or whether the GJ connection patterns go back to normal after octanol removal while the new target morphology state persists as a new attractor following the alteration of voltage states (more akin to intrinsic plasticity, Daoudal & Debanne, 2003; Debanne *et al.* 2003; Pulver & Griffith, 2010, or the way bits are stored in computer flip–flop circuits). It is also unclear what other aspects of the worm's morphology are encoded; at the moment, all that has been shown is that the bioelectric network stores a simple anatomical head–tail polarity dipole, and it is not known whether more subtle manipulations will reveal that it also contains rich information about detailed shape and layout of internal structures. Although it is unknown what role this mechanism has played in the evolution of planaria, this example of a non-genetic inheritance of large-scale bodyplan and behaviour change, as well as other poorly understood examples of physiological signals driving stable shape changes (Bubenik & Pavlansky, 1965; Seno & Shigemoto, 2006; Lobo *et al.* 2014), suggests that information encoded in physiological states could be an important driver of evolutionary change. While bioelectric circuits provide a flexible and robust mechanism for environmental signals to alter body shape, subsequent selection for changes in the gene networks governing ion channel expression could readily provide a way to canalize advantageous outcomes by a kind of Baldwin effect.

All of the recent data in a range of vertebrate and invertebrate systems show that information stored in bioelectrical states guides both single cell behaviour and large-scale morphogenesis. While this physiological layer of controls is autonomous, in that it has its own unique dynamics and is not determined 1:1 by genetic states, the bioelectric processes are tightly integrated with gene regulatory networks. The gradients are produced by genes encoding ion channels and pumps, and regulate expression of numerous downstream target genes – a circular causal chain implementing a cyclical dynamic system in which physiological and genetic processes continuously interplay. Thus, the question is not whether bioelectric or transcriptional cues are 'on top', but rather which events in this dynamical system represent optimal control points – master nodes that allow convenient and efficient control of the resulting shape outcomes. Such nodes are then particularly attractive targets for evolution as well as biomedical intervention. Interestingly, in a number of

cases, bioelectric signals are just such nodes. A very simple signal mediated by a single ion pump can initiate the whole cascade of tail, limb, or head formation (Adams *et al.* 2007; Beane *et al.* 2011; Tseng & Levin, 2013). Indeed, in some cases the bioelectric signal offers greater functional range than known biochemical triggers. For example, the eye 'master regulator' gene *Pax6* is unable to trigger eye formation anywhere but in the anterior neural field of vertebrate embryos, while induction of a specific V_{mem} range can reprogramme any tissue in the frog embryo to a complete eye, including gut endoderm and lateral plate mesoderm (Pai *et al.* 2012), revealing the ability of bioelectric cell state to switch fate across germ layers and induce the patterning of a complex multi-tissue organ. Because bioelectric signals are able to trigger complex downstream patterning cascades, it appears that such physiological states can act as master triggers for developmental modules – an organizational scheme that would clearly aid in the evolvability of complex adaptive structures.

In the examples discussed above, anatomical outcomes are triggered by specific bioelectrical states, such as V_{mem} ranges, which can be implemented by a plethora of different ion translocator proteins. One implication for evolution is that ion channel loci and their transcriptional controls would be free to diverge without consequence for the organism, as long as the necessary V_{mem} states remained in place (implemented by compensating or entirely different channels). And conversely, the patterning consequences of evolutionary changes in ion channel expression/function will not be readily understood without a consideration of the effects this has on the bioelectric dynamics within expressing cells. It appears that the bioelectric code maps systems-level physiological properties – not genes – onto some patterning events; for example, while $Na_V1.2$ is natively used by tadpoles to drive tail regeneration at early stages (Tseng *et al.* 2010), it is not 'a gene for tail regeneration', as many other channels can be used to achieve the same signal and outcome. An implication for biomedicine is that triggering desired patterning changes, such as limb regeneration cascades, could be accomplished by targeting any appropriate natively expressed channel (perhaps with existing ion channel drugs), not necessarily with one specific channel type that would require gene therapy for its introduction into the host. An implication for cancer biology is that while some ion channels' expression might be a useful marker (Wang, 2004; Fraser *et al.* 2005; Stühmer *et al.* 2006), there will also be many cases in which the transcriptional profile reveals nothing (because of signalling via post-translational gating of channel state), while drugs targeting a specific channel (Arcangeli *et al.* 2009, 2012) may have no effect (due to compensation and redundancy of channel types). If indeed cancer is augmented or induced by a depolarized bioelectric state (Binggeli & Weinstein, 1986; Olivotto *et al.* 1996; Yang & Brackenbury, 2013), we will have to think not only about individual ion channels as oncogenes (Pillozzi *et al.* 2002; Bennett *et al.* 2004; Lallet-Daher *et al.* 2013; Than *et al.* 2013) but more about how many channels contribute to a bioelectrical oncostate, to develop strategies for dominating the resting potential irrespective of native channel identity (Sharmeen *et al.* 2010; Chernet & Levin, 2013).

Molecular bioelectricity is a frontier field in which we have just begun to appreciate the richness of possibilities. Future progress will probably require the development of: (1) entirely new statistical dynamics models of voltage regulation of morphogenesis, (2) *in silico* simulations of self-organization dynamics in bioelectrical networks (perhaps with principles appropriated form neuroscience's study of memory), (3) expansion of tools like optogenetics to non-neural, non-excitable cells to read and write electrical state information to living tissues at will with high spatio-temporal resolution, and (4) deep physiomic datasets of pattern formation in model systems which can be mined to crack the bioelectric code. Existing data indicate that bioelectric networks in somatic tissues store and process instructive information that regulates the emergence of large-scale structures from individual cell behaviours. Learning to control the dynamics of these signals *in vivo* will enable highly effective top-down programming of shape, allowing control at the level of systems properties such as organ type, topology, size and large-scale arrangement – an important weapon in the uphill battle against the exponential complexity that hinders efforts to control 3–D shape at the level of individual molecular pathways. Harnessing this new set of inputs is a key step toward the ability to induce complex structures to be grown on-demand, as required for transformative applications in regenerative medicine and the synthetic biology of hybrid 'biobot' devices. As an important side-benefit for cognitive science, understanding the mapping of voltage gradients to tissue-level decision-making may significantly advance our nascent efforts to glean the semantics of electric states within the brain. Thus, the impact of these efforts will not only shed new light on a different kind of truly epi-genetic factor in evolution and embryogenesis, but will have transformative implications for our ability to rationally control growth and form in regenerative medicine and bioengineering applications.

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Additional information

Competing interests

None declared.

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