BioSystems 164 (2018) 76–93

Contents lists available at ScienceDirect

BioSystems

journal homepage: www.elsevier.com/locate/biosystems

Review article

The bioelectric code: An ancient computational medium for dynamic control of growth and form

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ARTICLE INFO

Article history:
Received 14 July 2017
Received in revised form 20 August 2017
Accepted 22 August 2017
Available online 2 September 2017

Keywords:
Bioelectricity
Ion channels
Regeneration
Morphogenesis
Embryogenesis
Patterning
Primitive cognition
Dynamical system theory
Bayesian inference

ABSTRACT

What determines large-scale anatomy? DNA does not directly specify geometrical arrangements of tissues and organs, and a process of encoding and decoding for morphogenesis is required. Moreover, many species can regenerate and remodel their structure despite drastic injury. The ability to obtain the correct target morphology from a diversity of initial conditions reveals that the morphogenetic code implements a rich system of pattern-homeostatic processes. Here, we describe an important mechanism by which cellular networks implement pattern regulation and plasticity: bioelectricity. All cells, not only nerves and muscles, produce and sense electrical signals; *in vivo*, these processes form bioelectric circuits that harness individual cell behaviors toward specific anatomical endpoints. We review emerging progress in reading and re-writing anatomical information encoded in bioelectrical states, and discuss the approaches to this problem from the perspectives of information theory, dynamical systems, and computational neuroscience. Cracking the bioelectric code will enable much-improved control over biological patterning, advancing basic evolutionary developmental biology as well as enabling numerous applications in regenerative medicine and synthetic bioengineering.

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https://doi.org/10.1016/j.biosystems.2017.08.009
0303-2647/

1. Introduction

1.1. To be explained: adaptive pattern regulation

It has been recognized since ancient times that the egg of a given species gives rise to an individual with the appropriate anatomy of that species (Fig. 1A). How does this occur? What is responsible for the remarkable multi-scale complexity of metazoan organisms, from the distribution of cell types among tissues to the topological shape and arrangement of the body organs, and the geometric layout of the entire bodyplan? It is widely believed that the answer lies within the genome, but it is not that simple; DNA simply encodes specific proteins – there is no direct encoding of anatomical structure. Thus, it is clear from first principles that pattern control involves a code: the encoding of anatomical positions and structures within the egg or other cell type, and the progressive decoding of this information as cells implement invariant morphogenesis (Fig. 1B). It should be noted that the current understanding of these codes is in its infancy and many fundamental questions remain to be addressed. Despite the progress of genetics and molecular genomics, we are not yet able to predict the anatomical structure of an organism from its genomic sequence (other than by comparing it to genomes whose anatomy we already know), nor in general do we know how to encode instructions to cells to induce them to develop anatomical structures to a desired functional specification.

Indeed, the mystery is revealed to be even deeper than that of embryogenesis, in which the same initial starting condition (the egg) develops into the appropriate target morphology of a given species. Many types of animals exhibit extensive capacity for regeneration (Birnbaum and Alvarado, 2008) or remodeling (Farinella-Ferruzza, 1956); these organisms can restore complex body organs or appendages after dramatic morphological changes such as amputation. For example, planarian flatworms can rebuild any missing part of their body (including the head) (Lobo et al., 2012; Salo et al., 2009), while axolotls can regenerate eyes, limbs, tails, jaws, ovaries, and portions of the brain (Maden, 2008). Such examples reveal that living systems exhibit highly adaptive and context-sensitive pattern homeostasis. Individual cell behaviors are directed towards the maintenance and repair of a specific anatomical configuration. When the correct target morphology is achieved, large-scale remodeling and growth ceases.

1.2. Why do we need a code? representing homeostatic goal states in tissue properties

The current paradigm recognizes that different types of codes participate in pattern control. Examples include gradients of gene products that dictate positional information via chemical signals, such as HOX codes (Bondos, 2006), and epigenetic codes (Broccoli et al., 2015) that regulate transcriptional cascades via chromatin modification. However, the processes underlying embryogenesis are largely thought of as a 'feed-forward' system: the progressive unrolling of the genome in each cell results in specific cellular events which, integrated over large numbers of cellular agents over space and time, results in the emergence of a complex and highly organized forms. The mainstream consensus is that there is no overall encoding of the target morphology: the process is controlled by local events, and the resulting complex pattern is the result of emergence and self-organization.

And yet, many of the examples of complex pattern regulation are challenging to explain as an open-loop, purely-emergent process (Fig. 1C,D). For example, embryos of many species can be cut in half or deformed at early stages and yet, can still achieve the morphology of a normal organism (e.g., monozygotic twins from embryo splitting). The ability to achieve the exact same end result from different starting configurations (e.g., a planarian or salamander limb cut at different positions) is highlighted especially starkly by the process of metamorphosis. Becoming a frog requires the tadpole to rearrange its face – the various craniofacial organs move to new positions during metamorphosis. This is normally a stereotypical process, but it was recently discovered that if "Picasso" tadpoles are created (where the eyes, nostrils, and other structures are in aberrant positions), the animals will still turn into largely normal frogs (Vandenberg et al., 2012): the organs move in new ways, but still achieve normal frog face target morphology (Fig. 1E). This means that genetics does not specify hardwired movements of the organs, but rather contribute to the function of a plastic system that enables diverse responses to abnormal starting states so that an invariant (and thus encoded) outcomes result.

While this kind of pattern memory is clearly stable, it is not read-only – it can be rewritten (Lobo et al., 2014). Modifications made to the shape (Yamaguchi, 1977) and size (Bryant et al., 2017) of limbs in crustacea and amphibians respectively are "learned" by the system, resulting in permanent changes to the target morphology (the pattern towards which regeneration builds) upon future rounds of regeneration. A most impressive example (Fig. 1F) is that of trophic memory in deer, in which some species shed and re-grow a consistent branching pattern of antlers (bone and innervation) each year (Bubenik and Pavlansky, 1965). It was observed that damage made to one point in the branched structure resulted in ectopic branches being produced at the same point in subsequent years of growth. This means that the growth plate in the scalp somehow 'remembers' the location of damage for months, as the whole antler rack falls off and is regenerated, and then triggers the cell behaviors needed to form an ectopic branch in just the right place. This type of spatial memory in remaining scalp cells (recalling events that occurred at significant distance in space and time) is especially difficult to reconcile with typical "molecular pathway" arrow models (or gene-regulatory networks) and strongly suggests a spatial encoding system.

Taken together, these examples strongly suggest a 'closed-loop' (feed-back based) pattern homeostatic process (Fig. 1G). Systems guided by pure emergence are notoriously difficult to control and study – knowing which low-level rule to perturb experimentally and how to alter it, in order to reach a desired large-scale outcome in a recurrent process is an extremely difficult inverse problem (imagine trying to determine how to modify a function such as $z = z^2 + c$ if one wants to add an extra geometric feature to its resulting fractal image). We have argued elsewhere (Lobo et al., 2014) that the highly robust regenerative capacity of living organisms suggests that evolution has found an easier way; moreover, scientists can capitalize on aspects of top-down control to achieve progress in regenerative medicine. If modular, representational information (i.e., the encoding of large-scale structure) exists, then re-writing the code to allow the cells to "build to spec" might enable much more efficient control of growth and form compared to approaches that by micromanage individual cell behaviors.

Much of the recent progress in biology has come from exploring the extent of complex outcomes that can result in the absence of a master plan (Davidson et al., 2010; Davies and Cachat, 2016; Deglincerti et al., 2016; Halley et al., 2012; Ishimatsu et al., 2010; Raspopovic et al., 2014). In its flight from vitalism and teleology, modern biology has preferred models of emergence and de-centralized control. However, explicitly represented goal states no longer need to be anathema to biology. Over the last 50+ years, cybernetics, control systems theory, and computer science have revealed frameworks for rigorous means of implementing mechanisms that store complex states and pursue them as homeostatic setpoints (thermostats and self-driving vehicles are examples). Many fields, from cognitive neuroscience to engineering routinely utilize goal-seeking and error-minimizing homeostatic control loops to understand and create complex adaptive functionality